Telaprevir 375-mg Film-Coated Tablet

for the Treatment of Genotype 1 Chronic Hepatitis C

Antiviral Drugs Advisory Committee

April 28, 2011

Briefing Document

NDA 201-917

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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1 EXECUTIVE SUMMARY

Indication for telaprevir:

Telaprevir, in combination with pegylated interferon (Peg-IFN; Pegasys® or PegIntron®) and ribavirin (RBV; Copegus® or Rebetol®), is proposed for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease (including cirrhosis or scarring of the liver) who are new to treatment ("treatment-naïve") or those who have previously been treated with interferon-alfa (pegylated or non-pegylated) alone or in combination with RBV but did not achieve sustained viral response (SVR or viral cure) ("treatment failure"), including all major sub-groups: prior relapsers, partial responders, and null responders. (Note: definitions of types of patients as in Draft Guidance for Industry: Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Agents for Treatment. Sept 2010).[1]

Telaprevir must not be administered as monotherapy and must only be prescribed with both Peg-IFN and RBV. The recommended dose of telaprevir tablets is 750 mg (two 375-mg tablets) taken orally 3 times a day (7-9 hours apart) with food. The total daily dose is 6 tablets (2,250 mg). The recommended treatment duration is 12 weeks of telaprevir in combination with Peg-IFN and RBV, plus an additional 12 or 36 weeks of Peg-IFN/RBV alone, depending on the patient's treatment history and their antiviral response to treatment during telaprevir dosing.

Hepatitis C is a widespread global disease with significant public health consequences.

Hepatitis C virus (HCV) infection affects 130 to 170 million people globally, with approximately 3 to 4 million persons newly infected each year.[2,3] In the United States, 3.9 million people are estimated to be living with hepatitis C, which is approximately 4 times that for people living with HIV (1.1 million infected) or HBV (1.4 million infected).[4]

Overall, 55% to 85% of primary HCV infections become chronic, and chronic hepatitis C can lead to serious liver disease.[5] More than 50,000 deaths annually are directly attributable to HCV, with an additional 300,000 deaths due to liver cancer caused by HCV, and almost 800,000 deaths due to cirrhosis.[6] Hepatitis C is the leading cause of liver transplantation in the United States.

Chronic HCV infection is curable, unlike HIV and hepatitis B infection. However, 50% of people with genotype 1 chronic hepatitis C are not cured with currently available medicines.

Multiple HCV genotypes exist (1, 2, 3, and 4), however, genotype 1 HCV accounts for most infections globally. In the United States and Europe, more than 70% of people with chronic hepatitis C are infected with HCV genotype 1.[7-9] Genotype 1 has a lower cure rate than other HCV genotypes using the current standard treatment for chronic hepatitis C of 48 weeks Peg-IFN plus RBV. As evaluated by sustained virologic response (SVR [undetectable serum HCV RNA 24 weeks after end-of-treatment]), 48 weeks of Peg-IFN/RBV therapy results in a SVR in only about 50% of treatment-naive patients with genotype 1 chronic hepatitis C, compared with 70% to 80% of patients with genotypes 2 and 3.[10-13]

Other factors, including high baseline HCV RNA levels, cirrhosis or bridging fibrosis, and black or Latino ethnicity, can also contribute to decreased SVR rates with standard Peg-IFN/RBV treatment.

There are no effective re-treatment options for patients who do not achieve a viral cure after treatment with 48 weeks of Peg-IFN/RBV therapy.

Re-treatment with an additional 48 weeks of Peg-IFN/RBV results in SVR in only 5% to 20% of patients. Consequently, there is a clear need for more effective therapies to enable more patients to achieve a viral cure, ideally with shorter treatment durations.

Telaprevir provides a new treatment option for patients with genotype 1 chronic hepatitis C.

Telaprevir is a direct acting antiviral agent with specific antiviral activity against HCV genotype 1 that aims to inhibit the HCV NS3•4A protease, an enzyme essential for the virus to replicate.

The Phase 3 clinical study program for telaprevir was designed to assess the efficacy and safety of treatment with telaprevir in combination with Peg-IFN/RBV in all major groups of patients with genotype 1 chronic hepatitis C.

The Phase 3 telaprevir studies enrolled treatment-naive and prior-treatment failure patients who had varying degrees of liver disease, including clinically compensated cirrhosis. Furthermore, enrollment also included patients from various geographic regions, and diverse racial/ethnic backgrounds.

The primary endpoint of all phase 3 studies was the proportion of patients with SVR24

SVR is an important indicator of the success of chronic hepatitis C treatment that is tantamount to a cure, and correlates with improved clinical outcomes, including reduced incidence of hepatic carcinoma (liver cancer), fibrosis, and hepatic events, as well as prolonged survival[14-21]

Key design features of the telaprevir Phase 3 studies included:

- **Treatment naive patients.** Study 108 (ADVANCE) was a pivotal phase 3 study designed to establish the superiority of a telaprevir/Peg-IFN/RBV regimen to Peg-IFN/RBV in patients who had not been previously treated for HCV. Two additional key features of this study were:
  - Response-guided therapy. Patients with undetectable HCV RNA after week 4 and 12 of treatment (extended rapid viral response, eRVR) received a total of 24 weeks of Peg-IFN/RBV treatment, and all others patients received a total of 48 weeks of treatment
  - Evaluation of 8-week and 12-week telaprevir treatment durations.
- **Prior treatment-failure patients.** Study C216 (REALIZE) was a pivotal Phase 3 study designed to establish the superiority of a telaprevir/Peg-IFN/RBV regimen to standard Peg-IFN/RBV treatment in a well characterized population that had received prior treatment with Peg-IFN/RBV but did not achieve SVR. This population consisted three sub-groups of patients: relapsers, partial responders and null responders to prior treatment. The total treatment duration was 12 weeks with telaprevir or placebo concurrent with 48 weeks Peg-IFN/RBV for all patients in the study.

  - Lead-in Peg-IFN/RBV dosing. Study C216 also evaluated the effect of a 4-week lead-in period with Peg-IFN/RBV before the telaprevir-treatment phase.

- **Confirmation of response-guided therapy**. Study 111 (ILLUMINATE) was a confirmatory Phase 3 study comparing the SVR rates of 12 weeks telaprevir treatment concurrent with 24-weeks or 48-weeks Peg-IFN/RBV treatment in treatment-naive patients who achieved eRVR.

Clinical Pharmacology

The pharmacokinetic and pharmacokinetic/pharmacodynamic characteristics of telaprevir have been studied since the start of the clinical development program.

Telaprevir is orally bioavailable and should be administered with food for improved exposure. After a single dose, the terminal elimination half-life is approximately 4 hours, and at steady state, the effective half life is about 9 to 11 hours. Exposure-response relationships in Phase 2/3 showed that dosing at 750 mg q8h in a T12/PR regimen (12 weeks of telaprevir [T12] with Peg-IFN/RBV [PR]) provides a good balance between safety and efficacy.

Viral dynamic modeling and clinical results in Phase 2/3 indicate that increasing the telaprevir duration beyond 12 weeks does not increase SVR rates for either treatment naive or prior-treatment failure patients, and that T12/PR regimens with and without response-guided PR duration (T12/PR24 for patients with eRVR and T12/PR48 for patients without eRVR, versus T12/PR48 for all patients) resulted in similar SVR in treatment-naive patients and in prior relapsers.

Hepatic metabolism plays a major role in the elimination of telaprevir, and renal elimination is negligible. Telaprevir is a substrate of CYP3A and P-gp, and an inhibitor of CYP3A.

An extensive drug interaction program was carried out to examine interactions with model drugs and with drugs commonly prescribed to patients with chronic hepatitis C, including drugs used for oral contraception, treatment of anxiety/insomnia, depression, hypertension, elevated cholesterol, ulcers, opioid addiction, HIV coinfection, and in preventing rejection after organ transplantation.

Efficacy

Telaprevir-based therapy demonstrated significantly higher SVR rates than Peg-IFN/RBV alone

- Among treatment-naive patients, rates of SVR24 were 72% to 79% in the telaprevir groups compared with 46% in the placebo group ($P < 0.0001$)
- Among the prior relapse population, rates of SVR24 were 84% to 88% in the telaprevir groups compared with 22% in the placebo group ($P < 0.0001$)
- Among the prior partial responder population, rates of SVR24 were 56% to 61% in the telaprevir groups compared with 15% in the placebo group ($P < 0.001$)
- Among the prior null responder population, rates of SVR24 were 31% to 33% in the telaprevir groups compared with 5% in the placebo group ($P < 0.001$)

Majority of treatment naive patients were eligible to receive 24 weeks of treatment using response-guided therapy, which is half the duration of currently available treatments; significantly higher SVR rates were observed after 24 weeks of telaprevir-based therapy in patients with eRVR compared to Peg-IFN/RBV alone.

Overall, 58.4% of patients in Study 108, and 65.2% of patients in Study 111 achieved eRVR and were eligible for 24 weeks of total treatment, instead of 48 weeks standard treatment. Approximately 90% of patients with eRVR achieved SVR after 24 weeks of therapy. Lead-in treatment for 4 weeks with Peg-IFN/RBV before telaprevir treatment in a prior treatment-failure population did not improve SVR rates over a simultaneous start.

SVR rates were similar among a broad range of subgroups

Substantial clinical benefit, compared to standard therapy, was achieved in treatment-naïve patients who were black, Hispanic or Latino, had cirrhosis or bridging fibrosis, or had high baseline levels of HCV RNA, and in patients who did not achieve SVR with a prior course of Peg-IFN/RBV. The responses in the control groups were comparable to those reported in the literature for Peg-IFN/RBV for the relevant populations

The efficacy data support a response-guided regimen of 12 weeks telaprevir plus 24 weeks PEG-IFN/RBV for treatment-naive patients. Additionally, a response-guided regimen of 12 weeks telaprevir plus 24 weeks PEG-IFN/RBV for patients who relapsed after prior Peg-IFN and RBV treatment and who achieve an eRVR on a telaprevir/Peg-IFN/RBV regimen is recommended. A dose regimen of 12 weeks telaprevir plus 48 weeks PEG-IFN/RBV is recommended for all other patients.

Virology

In a regimen of telaprevir, Peg-IFN, and RBV, the primary role of telaprevir is to inhibit wild-type virus and variants with lower-levels of resistance to telaprevir. The primary and complementary role of Peg-IFN and RBV is to clear any remaining telaprevir-resistant variants.

Clinical virology results from clinical studies of telaprevir in combination with Peg-IFN and RBV have shown a clear and consistent resistance profile across HCV genotype 1 patient populations (treatment-naive and prior Peg-IFN/RBV treatment-failure). Sequence analyses in patients not achieving an SVR with a telaprevir-based regimen consistently identified amino acid substitutions at 4 positions in the NS3•4A protease region that were associated with decreased sensitivity to telaprevir, consistent with the mechanism of action for telaprevir: V36A/M, T54A/S, R155K/T, A156S/T/V, and V36M+R155K. Phenotypic characterization of these HCV NS3 variants determined that lower-level resistance to telaprevir (3- to 25-fold decrease in IC50 to telaprevir in a replicon-based assay) was conferred by V36A/M, T54A/S, R155K/T, and A156S, and higher-level resistance to telaprevir (>25-fold decrease in replicon IC50) was conferred by A156T/V and V36M+R155K. Telaprevir-resistant variants are less fit than wild-type virus and are sensitive to Peg-IFN, RBV, and polymerase inhibitors in vitro.

Predominant baseline resistance to telaprevir is rare (< 1% to 2.7%) and does not necessarily preclude achieving an SVR with a T/PR regimen. On-treatment virologic failure during telaprevir treatment is associated with higher-level telaprevir-resistant variants, and occurs more frequently in genotype 1a compared to 1b. On-treatment virologic failure rates on T/PR

are low in treatment-naive patients, and prior relapser patients, but are higher for prior nonresponders patients. Relapse is generally associated with wild-type or lower-level resistant variants. Overall, TVR-resistant variants were observed in 12% of treatment-naïve patients (Study 108; T12/PR arm) and 22% of treatment-experienced patients, after therapy with a telaprevir-containing regimen. Resistant variants were observed in the majority of subjects who did not achieve an SVR. Resistant variants tend to be replaced by wild-type virus over time in the absence of telaprevir selective pressure.

Safety

The safety profile of telaprevir is based on the data from 43 clinical studies, including 5 completed Phase 2 studies and 3 completed Phase 3 studies that were conducted in patients with genotype 1 chronic hepatitis C.

In the 5 pooled placebo-controlled Phase 2-3 studies, upon which the majority of safety analyses have been conducted, 2,012 patients received at least one dose of telaprevir.

From these 5 placebo-controlled studies, a total of 1346 patients randomized to receive telaprevir for 12 weeks in combination with Peg-IFN/RBV for 24-48 weeks (T12/PR group, the proposed regimen) and a total of 764 patients randomized to receive placebo in combination with Peg-IFN/RBV (Pbo/PR group). The majority of safety data in this document focus on telaprevir/placebo treatment phase since that period from 0 to 12 weeks provides a direct comparison between the telaprevir and placebo arms. Other safety data poolings (including a pooling of the 3 Phase 3 studies) are qualitatively comparable to this primary safety pooling.

A total of 73.0% of patients in the T12/PR group and 49.1% of patients in the Pbo/PR group completed the intended total treatment duration with at least 1 study drug in their treatment regimen.

The most frequently occurring adverse events (AEs; > 20.0%) in the T12/PR group for which rates were higher than in the Pbo/PR group were pruritus, nausea, rash, anemia and diarrhea.

AEs known to be associated with Peg-IFN/RBV treatment (fatigue, headache, influenza-like illness, insomnia, and pyrexia) were also frequently reported with comparable incidence in both treatment groups. Among AEs reported in 5.0% to 20.0% of patients, hemorrhoids, anorectal discomfort, anal pruritus, dysgeusia, and generalized pruritus occurred more frequently in the T12/PR than in the Pbo/PR group.

Most AEs began in the first 4 weeks of treatment in both the T12/PR and Pbo/PR groups. Many AEs resolved within the first 24 weeks of treatment as evidenced by the lower prevalence of these AEs thereafter. AEs associated with Peg-IFN and RBV therapy persisted in patients who remained on treatment after Week 24 and the prevalence remained stable.

AEs of grade 3 or higher and AEs leading to permanent discontinuation of telaprevir/placebo, which occurred more frequently in the T12/PR group than in the Pbo/PR group, included anemia and rash, the most clinically significant AEs associated with telaprevir.

Grade 3 AEs, serious AEs, and AEs that led to treatment discontinuation that occurred more frequently in the T12/PR group than in the Pbo/PR group were anemia and rash.

- **Anemia**

Anemia led to discontinuation of telaprevir/placebo in 2.7% of patients in the T12/PR group and 0.5% of patients in the Pbo/PR group.

Mean hemoglobin levels decreased rapidly during the first 4 weeks in both the T12/PR and Pbo/PR groups and continued to decrease thereafter, but with a larger decrease in the T12/PR group.

Between weeks 12 and 14, hemoglobin nadir values below 10.0 g/dL were observed in 33.7% and 13.6% of patients in the T12/PR and Pbo/PR groups, respectively. Hemoglobin nadir values below 8.5 g/dL were observed in 8.3% and 2.3% of patients in the T12/PR group and Pbo/PR groups, respectively.

Anemia was generally managed using RBV dose reduction; erythropoietin stimulating agents were rarely used. In the placebo-controlled studies, RBV dose reduction occurred in 21.6% of patients in the T12/PR group and 9.4% of patients in the Pbo/PR group and resulted in full regimen discontinuation in less than 1% of patients in both the T12/PR and Pbo/PR groups, respectively.

During the telaprevir clinical program, hemoglobin was monitored and RBV reduced in accordance with PEG-IFN/RBV prescribing information. If ribavirin was permanently discontinued for the management of anemia, telaprevir was also to be permanently discontinued. If telaprevir was discontinued for anemia, patients may have continued treatment with peginterferon alfa and ribavirin. Ribavirin could be restarted per the dosing modification guidelines for ribavirin. The dose of telaprevir could not be reduced and telaprevir could not be restarted if discontinued. Erythropoietin stimulating agent (ESA) use was generally prohibited.

- **Rash**

First onset of rash occurred at any time after start of telaprevir but the majority of rash events began during the first 4 weeks of treatment. Progression of rash severity was reported for less than 10% of the cases, and many rash events resolved during the first 24 weeks of treatment.

Rash special search category (SSC) events were observed in 55.4% and 32.7% of patients in the T12/PR and Pbo/PR groups, respectively. Serious rash SSC events were reported in 1.7% of patients in the T12/PR group and no patients in the Pbo/PR group. Rash SSC events resulted in full regimen discontinuation in 2.6% of patients in the T12/PR group, and no patients in the Pbo/PR group.

A Dermatology Expert Panel (DEP) concluded that the visual appearance of the rash observed in people who received a telaprevir-based regimen was virtually indistinguishable from the Peg-IFN/RBV rash. The DEP noted that some observed rashes in people who received telaprevir were greater in severity and occurred on a greater extent of the body surface area (BSA) and were also similar in visual appearance to the Peg-IFN/RBV regimen rash. Furthermore, the DEP found that almost all rashes involved < 30% BSA, and that rashes were primarily pruritic and eczematous, although some had an additional maculopapular component; these rashes were not consistent with a typical hypersensitivity.

The DEP identified 3 cases suggestive of Stevens-Johnson syndrome (SJS). Of these three cases, one was considered definite by the DEP. This case was not drug related as it occurred 11 weeks after the last dose of telaprevir. SJS has been reported in patients taking Peg-

IFN/RBV. The DEP identified 11 cases suggestive of drug reaction with eosinophilia with systemic symptoms (DRESS); organ involvement was not suspected in 9 of the cases.

Several investigations were undertaken to understand rash mechanism; however, none has been identified to date.

Rash was managed in the majority of patients with antihistamines and topical corticosteroids. Severe eczematous rash required discontinuation of telaprevir; if rash did not improve in 7 days, sequential or simultaneous interruption or discontinuation of RBV and/or Peg-IFN was to be considered by the investigator. Any rash that was associated with significant systemic symptoms, mucous membrane ulceration, target lesions, epidermal detachment, vesicles, or bullae constitutes a severe skin reaction and required immediate and permanent discontinuation of telaprevir, peginterferon alfa, and ribavirin.

Safety analyses were also conducted using a dataset of pooled Phase 3 studies (Studies 108 and C216 were placebo-controlled; Study 111 was open-label); this pooling included 1797 patients that received at least one dose of telaprevir and 493 patients that received placebo, both in combination with Peg-IFN and RBV.

A pooling of the three Phase 3 studies was conducted during the NDA review period after discussion with the Division, and key results from this pooling are included in this briefing document. The safety results from this pooling are comparable to the results from the Phase 2 and 3 pooling of five placebo-controlled studies; there were small quantitative differences in the frequencies of some adverse events, but no qualitative differences, and no change in the overall conclusions of the safety evaluation.

Benefit-Risk Assessment

The principal benefits of treatment with a telaprevir-containing regimen over standard Peg-IFN/RBV treatment are significantly higher SVR rates in all populations studied (e.g. among treatment-naive patients, rates of SVR24 were 72% to 79% in the telaprevir groups compared with 46% in the placebo group) and 6-month shorter treatment duration for the approximately two-thirds of treatment-naive patients who achieve eRVR (HCV RNA undetectable at Weeks 4 and 12).

The key risks of treatment with telaprevir are adverse events (notably rash and anemia), potential risks associated with viral resistance to telaprevir, including absence of data on the management of patients who have failed a telaprevir containing regimen, and the potential but avoidable risks associated with drug-drug interactions.

Most patients who failed treatment with T/PR had telaprevir-resistant variants.

Although telaprevir-resistant variants are replaced with wild-type virus over time, there are no data on re-treatment of patients who have failed a telaprevir-containing regimen with a direct acting antiviral agent such as telaprevir.

Achievement of an SVR is a significant measure of the benefit of chronic hepatitis C treatment associated with reduced incidence of liver cancer, hepatic events, and fibrosis, and prolonged survival.[14-22]

Reduction in hepatic inflammation with regression of hepatic fibrosis has been demonstrated to improve quality of life, and reduce the risks of complications of portal hypertension

(ascites, gastroesophageal varices, and portal systemic encephalopathy), hepatic decompensation and hepatocellular carcinoma.

A recent study of more than 1,000 prospectively followed patients with HCV-associated advanced hepatic fibrosis reported a 10-fold reduction in death/liver transplantation (2.2% versus 21.3%) and of liver-related mortality (2.7% versus 27.2%) in patients who achieved SVR compared to patients who failed combination therapy with Peg-IFN and RBV.

The significantly higher SVR rate of telaprevir compared with Peg-IFN/RBV therapy in all subject categories has the potential to offer many more patients the benefits of eradicating HCV and achieving a viral cure. These data support the use of telaprevir in combination with Peg-IFN/RBV as first-line therapy in adult patients with compensated liver disease (including cirrhosis) who are treatment-naive or did not achieve SVR with prior treatment.

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ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition and Notes
ADME	absorption, distribution, metabolism, and elimination
ADR	adverse drug reaction
AE	adverse event
AGEP	acute generalized exanthematous pustulosis
ALT	alanine aminotransferase
ART	Anti-retroviral therapy
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{8h}	AUC from the time of dosing to 8 hours
AUC_{∞}	AUC from the time of dosing extrapolated to infinity
BMI	body mass index
bpm	beats per minute
$C_{avg,ss}$	average concentration during a dosing interval at steady state
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
CHC	chronic hepatitis C
CI	confidence interval
CL/F	apparent clearance
CrCl	creatinine clearance
CUI	clinical utility index
CYP	cytochrome P450
DBP	diastolic blood pressure
DEP	dermatology expert panel
DDI	drug-drug interaction
DNA	deoxyribonucleic acid
DRESS	drug reaction with eosinophilia with systemic symptoms
ED_{50}	median effective dose
EE	ethinyl estradiol
EOT	end of treatment
eRVR	extended rapid virologic response
EVR	early virologic response
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HAART	highly active antiretroviral therapy
HCP	health care provider
HCV	hepatitis C virus
Hgb	hemoglobin
HIV	human immunodeficiency virus
HLA	Human leukocyte antigen
IC_{50}	concentration that inhibits 50%
IFN	interferon
IU	International Unit
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
Pbo	placebo

Abbreviation	Definition and Notes
Pbo/PR48	control group with total treatment duration of 48 weeks
PCP	primary care physician
PD	pharmacodynamic
Peg-IFN	pegylated interferon
Peg-IFN-alfa-2a	pegylated interferon-alfa-2a (Pegasys®)
Peg-IFN-alfa-2b	pegylated interferon-alfa-2b (PegIntron®)
P-gp	P-glycoprotein
PK	pharmacokinetic
PR	pegylated interferon-alfa-2a and ribavirin (used in reference to treatment groups)
q8h	every 8 hours
q12h	every 12 hours
RBC	red blood cell
RBV	ribavirin
RNA	Ribonucleic acid
RT-PCR	Reverse transcription polymerase chain reaction
RVR	rapid virologic response
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SCAR	serious cutaneous adverse reactions
SCS	summary of clinical safety
SD	standard deviation
SJS	Stevens-Johnson syndrome
SSC	special search category
SVR	sustained virologic response
$SVR24_{planned}$	sustained virologic response 24 weeks after the last planned dose of study drug
$t_{½}$	terminal elimination half-life
TDF	tenofovir disoproxil fumarate
TEN	toxic epidermal necrolysis
T/Pbo	telaprevir/placebo
T/PR	telaprevir, pegylated interferon-alfa, and ribavirin
VBT	viral breakthrough
V/F	apparent volume of distribution
WBC	white blood cell

DEFINITION OF TERMS

Abbreviation	Definition and Notes
EVR (early virologic response)	≥ 2-$\log_{10}$ decrease in HCV RNA at Week 12 of treatment compared to baseline HCV RNA level
RVR (rapid virologic response)	Undetectable HCV RNA at Week 4 of treatment
eRVR (extended RVR)	Undetectable HCV RNA at Weeks 4 and 12 of treatment
Prior treatment failure	Subjects who previously received Peg-IFN/RBV, but who did not achieve SVR
Prior relapser	Subject who had undetectable HCV RNA at the end of prior treatment followed by detectable HCV RNA after the end of prior treatment
Prior nonresponders:	Subjects who never had undetectable HCV RNA during prior treatment. This includes prior partial responders and prior null responders
- Prior partial responder	- Subject who had ≥ 2-$\log_{10}$ decrease in HCV RNA at Week 12 of prior treatment compared to baseline HCV RNA level, but who never achieved undetectable HCV RNA levels during prior treatment
- Prior null responder	- Subject who had < 2-$\log_{10}$ decrease in HCV RNA at Week 12 of prior treatment compared to baseline HCV RNA level during prior treatment
Relapse	Undetectable HCV RNA at the end of treatment followed by detectable HCV RNA after the end of treatment
SVR (sustained virologic response)	Undetectable HCV RNA 24 weeks after the last dose of treatment
Viral breakthrough (Phase 3 studies)	Undetectable HCV RNA followed by confirmed > 100 IU/mL HCV RNA during treatment, or, for subjects who did not have undetectable HCV RNA, > 1-$\log_{10}$ increase in HCV RNA over nadir during treatment
On-treatment virologic failure	Discontinued due to meeting a virologic stopping rule and/or having detectable HCV RNA at the end of treatment with viral breakthrough

2 BACKGROUND AND SCIENTIFIC RATIONALE

2.1 Prevalence and Consequences of Chronic Hepatitis C

Globally, 170 million people are estimated to be infected with HCV, which induces liver necrosis and inflammation and increases the risk of progressive liver scarring, portal hypertension, liver failure, and liver cancer.[23] Three to four million new infections occur annually, including a mean 21,500 cases in the United States from 2003 to 2008, of which 70% will lead to chronic HCV infection.[23,24] The prevalence of chronic HCV infection in the United States (3.9 million infected) is approximately 4 times that of HIV (1.1 million infected) or HBV (1.4 million infected). Moreover, a larger proportion of chronically HCV-infected individuals (75%) remain undiagnosed compared with individuals infected with HIV (21%) or HBV (65%).[4]

These issues present a major public policy challenge that needs to be addressed in parallel with the introduction of increasingly effective antiviral therapy.

Approximately 20% of subjects with chronic hepatitis C (CHC) develop cirrhosis within 20 years of infection. Cirrhosis increases risk of liver cancer and the possibility of future liver decompensation. Although some subjects progress more slowly or are ultimately spared from advanced liver disease, all subjects with CHC are at risk for morbidity and early mortality from HCV infection and, therefore, are in need of effective treatment.

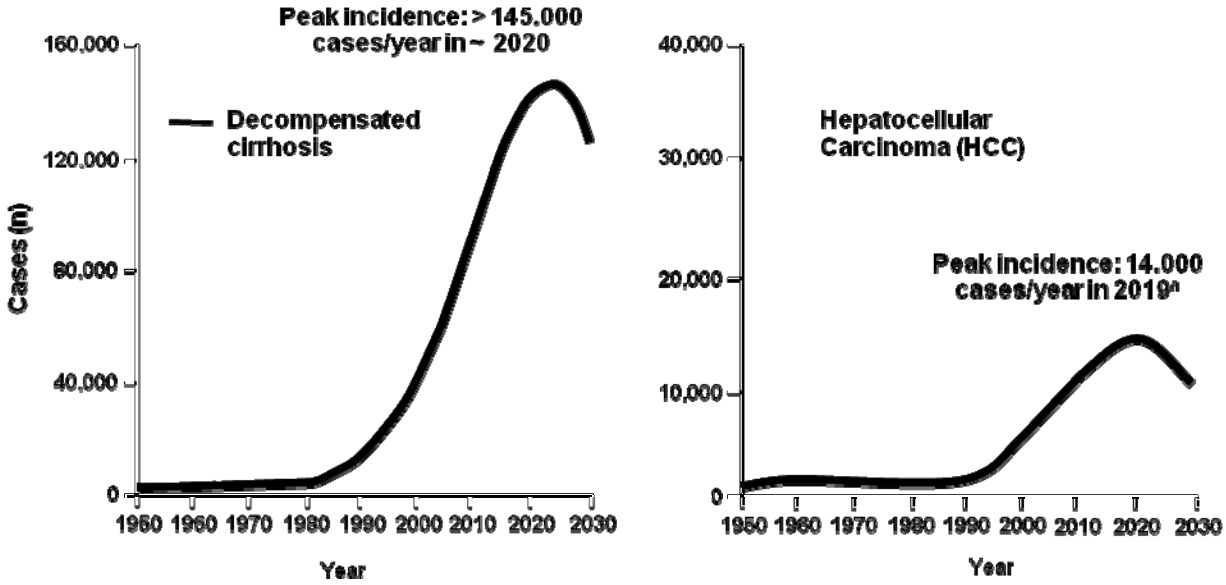
Cirrhosis in subjects with CHC frequently leads to symptoms such as fatigue, weight loss, depression, muscle wasting, and impaired cognition, which may be disabling and decrease quality of life. Clinical complications associated with advanced liver disease include gastrointestinal bleeding, ascites, bacterial infections, encephalopathy, and liver cancer. Chronic HCV infection is the most frequent indication for liver transplantation in the United States, and recurrent HCV, which occurs universally after liver transplant, is associated with a greater likelihood of rapidly progressive liver disease in transplant recipients.

The mortality attributable to HCV in the U.S. is substantial and expected to grow.

The prevalence of decompensated cirrhosis associated with chronic HCV infection began to increase after 1995 and is currently estimated to represent 11.7% of cases of cirrhosis in the United States.[25] The number of cases of decompensated cirrhosis is predicted to continue to increase through 2020-2030.[25] In the absence of more effective treatments, the proportion of subjects with advanced liver disease will continue to increase, and the absolute number of cirrhotic subjects will increase from the current level of 800,000 to over a million in 2020 (Figure 1).[25]

Similarly, the number of hepatocellular carcinoma cases from 1990-1999 (37,697) increased from 2000-2009 (86,765), and are projected to increase even more from 2010-2019 (130,366).[25] Assuming the risk of HCC in individuals with HCV infection and advanced fibrosis remain unchanged, the incidence of CHC-associated HCC is projected to peak in 2019 at about 14,000 cases per year (Figure 1).[25]

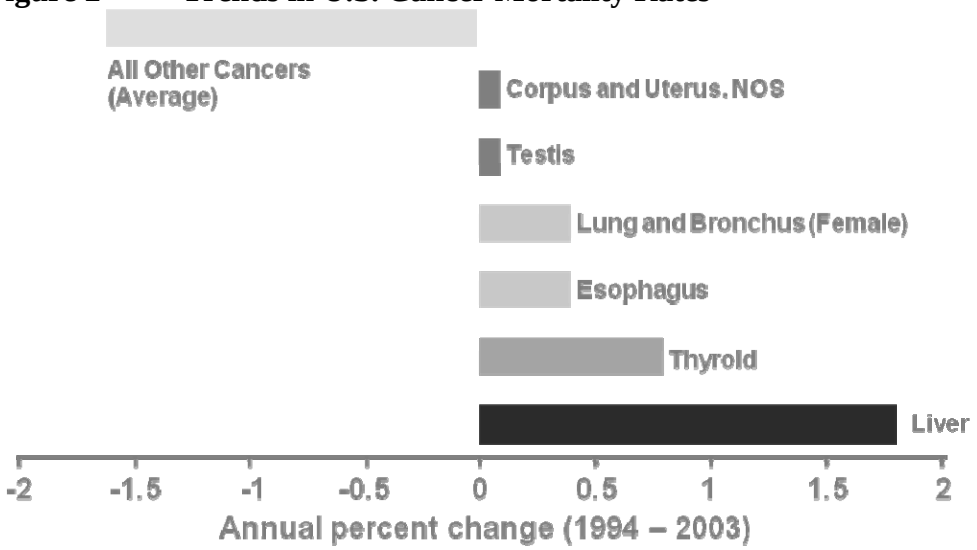
Figure 1 Actual and Projected U.S. Incidence of Decompensated Cirrhosis and Hepatocellular Carcinoma



[a] Assuming HCC risk in HCV-infected individuals with fibrosis does not change.
Source: Davis GL, et al. *Gastroenterology.* 2010;138(2):513-521.

The rising magnitude of liver cancer as a major public health problem is illustrated by the fact that hepatocellular carcinoma has the fastest growing death rate in the United States of all cancers (Figure 2).[26] An analysis of trends in HCC risk factors reported a larger increase in HCV-associated HCC, compared with HBV and alcoholic liver disease. Moreover, in a large, U.S.-based, multicenter, cross-sectional study examining risk factors in individuals with HCC, a larger number of subjects had concomitant HCV (47%) compared with HBV (15%), both HCV and HBV (5%), or neither virus (33%).

Figure 2 Trends in U.S. Cancer Mortality Rates



Source: National Cancer Institute. SEER Summary Figures and Tables 2011.

2.2 Differences Between HCV and HBV or HIV

There are fundamental biological differences between HCV and HBV or HIV, most notably a presumed lack of an archival form of the RNA genome of HCV. An important implication of this distinction is that eradication of HCV should be possible with a finite course of therapy, unlike HBV and HIV, which are currently incurable and require long-term therapy to maintain viral suppression. The durable nature of a sustained virologic response (SVR) has, in fact, been demonstrated consistently in long term observations from HCV therapeutic studies.

These considerations underscore the potential for widespread adoption of an effective HCV treatment regimen with an acceptable tolerability profile and the shortest possible duration.

Another important aspect of the biological distinction among the viruses is related to the anticipated impact of resistant mutations. Variants with single or double resistant mutations likely pre-exist before treatment, and therefore all direct-acting antiviral drugs carry the risk of selecting resistant variants. With viruses like HIV or HBV, the potential to archive resistant variants has major implications for the future use of the drug that selected for resistance or other drugs in the same class with similar resistance profiles. With HCV, it may be possible for the levels of resistant variants to decline over time in the absence of drug, because of their low replicative fitness, and ultimately be replaced by the viral population that predominated before treatment since HCV is not archived. This may mitigate concerns for long-term clinical implications of HCV resistance. Ultimately, future clinical studies retreating subjects who failed therapy with a direct-acting antiviral drug will be needed to fully understand the clinical impact of resistance.

2.3 SVR is Essentially Equivalent to a Cure

The goal of HCV therapy is SVR, traditionally defined as HCV RNA undetectability 6 months after stopping treatment. It is worth re-emphasizing that SVR is considered tantamount to virologic cure based a wealth of cumulative experience and supported by

studies showing rates of durable absence of detectable HCV RNA in more than 99% of subjects.

Subjects who achieve SVR demonstrate multiple benefits, including a reduction in critical outcomes measures, such as decompensation, de novo varices formation, hepatocellular carcinoma, and actual mortality.

Several studies support the contention that SVR actually improves outcomes in subjects with HCV. The NIH-supported Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) Study was a multicenter study of 1,145 subjects with advanced chronic HCV who were nonresponders to previous IFN-based treatment. They received a lead-in phase of full combination therapy with PR prior to the maintenance phase. In subjects achieving SVR on this regimen, rates of HCV-associated complications were significantly lower than in nonresponders with respect to several critical parameters including decompensated liver disease, liver transplantation, HCC, and liver-related death.

A recent study also demonstrated that SVR after HCV therapy improves long-term survival. In this comprehensive Veterans Affairs study of subjects who received treatment between June 2007 and June 2008, among the cohort of 16,864 subjects with a post-treatment HCV RNA test, SVR rates were 35% (GT1), 72% (GT2), 62% (GT3). Multivariate modeling accounting for a wide variety of comorbidities demonstrated an association between SVR and a highly significant reduction in all-cause mortality across hepatitis C virus (HCV) genotypes.

2.4 Limitations of Current Standard of Care for Treatment of CHC Infection

Numerous factors affect the likelihood of response to interferon-based therapy in subjects with CHC. Subjects with high viral load of genotype 1 HCV have notably lower rates of cure than subjects with low genotype 1 viral load or other viral genotypes, and comprise the majority of HCV subjects in the United States.[27] Subjects with advanced liver scarring, older age, increased BMI, or insulin resistance also have impaired response rate to interferon-based therapy. Likewise, African Americans are consistently reported to have substantially lower rates of SVR with standard therapy than subjects in other ethnic groups. This latter observation may be explained in part by a higher prevalence of the "T" allele in the polymorphic IL28B gene in African American (i.e., black) subjects. This polymorphism has been shown to correlate with nonresponse to interferon-based treatment, independent of the ethnicity of the subject.

With current standard therapy, 40% to 52% of subjects with CHC are cured (i.e., achieve SVR). Cure rates at the lower end of this range predominate in the United States whereas cure rates at the higher end of this range are generally seen in Europe. Subjects with chronic genotype 1 HCV usually require a full 48 weeks of therapy to maximize the likelihood of achieving SVR, although subjects with a low baseline viral load who achieve a rapid virologic response (RVR) after 4 weeks of treatment may benefit from a shorter duration of treatment. In contrast, subjects who are HCV-positive at Week 12 and HCV-negative at Week 24 (slow responders) may need 72 weeks of Peg-IFN/RBV therapy to decrease the risk of relapse. An extended treatment course may not be tolerable to all subjects given the established safety profile of Peg-IFN/RBV therapy that includes a number of adverse events. Consequently, there is a significant unmet need for effective treatment options that provided

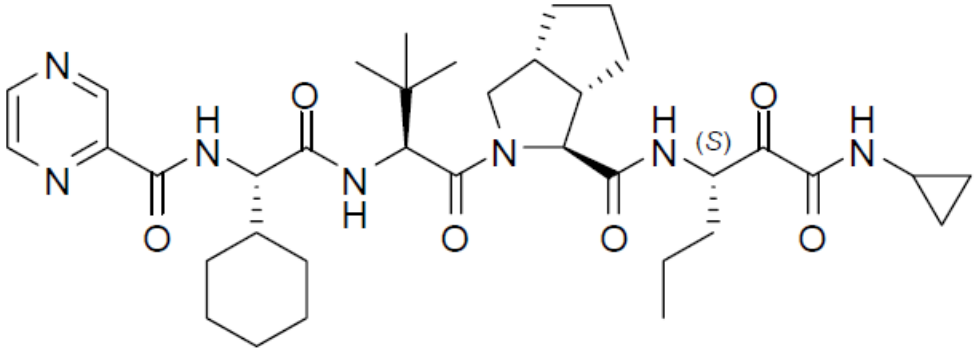
a reduced length therapy in a greater number of subjects than is possible with current standard treatment.

There are limited options for subjects who have previously failed to respond to standard Peg-IFN/RBV therapy. Retreatment with Peg-IFN/RBV is associated with a 6% to 11% SVR rate, or up to 16% SVR rate with 72 weeks of retreatment. Likewise, two-thirds of subjects who relapse after standard treatment do not achieve SVR after retreatment.

2.5 Rationale for Development of Telaprevir

Telaprevir is a member of a new class of direct-acting antiviral agents, the HCV NS3•4A protease inhibitors. Telaprevir is a potent, reversible, selective, linear peptidomimetic inhibitor of the virally encoded NS3•4A serine protease, which is essential for the replication of HCV (Figure 3). Currently, no drugs in this pharmacological class or any other HCV direct-acting antiviral agents are marketed.

Figure 3 Chemical Structure of Telaprevir



MW 679.85

Telaprevir has additive antiviral activity when combined with Peg-IFN/RBV. In subjects with genotype 1 CHC, 12 weeks treatment with telaprevir combined with Peg-IFN/RBV for 24 or 48 weeks, resulted in significantly higher SVR rates than treatment with 48 weeks of Peg-IFN/RBV alone. This efficacy benefit was achieved in both treatment-naive and prior treatment-failure populations and across a broad range of subjects, including populations that historically have a low SVR rate when treated with standard Peg-IFN/RBV therapy: subjects who are black, Hispanic or Latino, have cirrhosis, high baseline levels of HCV RNA, or had null or partial response to prior treatment with Peg-IFN/RBV.

2.6 Proposed Indication

Telaprevir, in combination with Peg-IFN (Pegasys® or PegIntron®) and RBV (Copegus® or Rebetol®), is proposed for the treatment of genotype 1 CHC infection in adult subjects with compensated liver disease (including cirrhosis) who are treatment-naive or who have previously been treated with interferon-alfa (pegylated or non-pegylated) alone or in combination with RBV, including prior relapsers, partial responders, and null responders.

2.7 Recommended Dosage and Administration

Telaprevir must not be administered as monotherapy and must only be prescribed with both Peg-IFN and RBV. The recommended dose of telaprevir tablets is 750 mg (two 375-mg

tablets) taken orally 3 times a day (7-9 hours apart) with food. The total daily dose is 6 tablets (2,250 mg). The recommended treatment duration is 12 weeks of telaprevir in combination with Peg-IFN and RBV, plus an additional 12 or 36 weeks of Peg-IFN/RBV alone, depending on the subject's treatment history and response to treatment.

2.7.1 Duration of Treatment in Treatment-Naive Subjects

In subjects who have had no previous treatment for HCV (treatment-naive), treatment with telaprevir must be initiated in combination with Peg-IFN and RBV and administered for 12 weeks.

- Subjects with undetectable HCV RNA at Weeks 4 and 12 receive an additional 12 weeks of Peg-IFN and RBV alone for a total treatment duration of 24 weeks
- Subjects with detectable HCV RNA at either Weeks 4 or 12 receive an additional 36 weeks of Peg-IFN and RBV alone for a total treatment duration of 48 weeks

HCV-RNA levels should be monitored at Weeks 4 and 12 to determine treatment duration. Treatment with telaprevir should be discontinued in subjects who do not have an adequate viral response during treatment.

2.7.2 Duration of Treatment—Previously Treated Subjects

In subjects who have had previous treatment for HCV, treatment with telaprevir must be initiated in combination with Peg-IFN and RBV and administered for 12 weeks. Subjects who had a partial response to previous treatment (partial responders) or minimal response (null responders) to Peg-IFN plus RBV receive an additional 36 weeks of Peg-IFN and RBV treatment alone for a total treatment duration of 48 weeks.

In subjects who had relapse after previous treatment to Peg-IFN plus RBV, a response-guided regimen is recommended.

- Subjects with undetectable HCV RNA at Weeks 4 and 12 of telaprevir-based treatment receive an additional 12 weeks of Peg-IFN and RBV alone for a total treatment duration of 24 weeks
- Subjects with detectable HCV RNA at either Weeks 4 or 12 of telaprevir-based treatment receive an additional 36 weeks of Peg-IFN and RBV alone for a total treatment duration of 48 weeks

Telaprevir must be dosed with Peg-IFN and RBV to prevent treatment failure.

3 NON-CLINICAL DEVELOPMENT

A series of nonclinical studies establishing the pharmacology, pharmacokinetic, and toxicity profile of telaprevir provided the foundation for clinical development:

- Primary pharmacology studies were conducted to establish the antiviral potential of telaprevir
- Safety pharmacology studies were conducted in a variety of test systems to explore and assess the effects of telaprevir on vital organ systems and to detect potential for adverse pharmacodynamic effects
- Single-dose toxicity, repeat-dose toxicity (up to 9 months in duration), genetic toxicity, reproductive and developmental toxicity, and local tolerance studies, as well as other specific toxicity studies were conducted to establish the toxic potential of telaprevir

3.1 Pharmacology

3.1.1 Mechanism of Action

Telaprevir is a potent, slow-binding peptidomimetic ketoamide inhibitor that was designed using structure-based drug design. The interaction of telaprevir with the HCV NS3•4A protease occurs in 2 steps, with formation of a weaker complex with an apparent K_i of 44 nM, followed by rearrangement to the tightly bound form with a potency (K_i*) of 7-10 nM. Once the tightly bound HCV NS3 protease/telaprevir complex is formed, it remains inhibited with a $t_{1/2}$ of ~58 min. Because the HCV replication cycle takes about 2.7 hours, this long half-life offers the possibility of having a prolonged inhibitory effect on the essential NS3•4A protease for a substantial portion of the HCV replication cycle and may translate into enhanced therapeutic efficacy.

Telaprevir inhibited HCV replication with an IC_{50} of 0.28 μM in a genotype 1a HCV infectious virus assay and an IC_{50} of 0.354 μM in a genotype 1b HCV replicon assay. At a concentration of 7 μM, telaprevir reduced levels of HCV replicon RNA by > 3.5-$\log_{10}$. In HCV replicon assay cells, the CC_{50} of telaprevir was 83 μM, resulting in an in vitro selectivity index (CC_{50}/IC_{50}) of 234.

An HCV protease mouse model was developed to evaluate in vivo inhibition of HCV protease activity in the target organ (liver) following oral administration. Telaprevir inhibited HCV protease activity in the liver with an ED_{50} of < 0.3 mg/kg, and pharmacokinetic (PK) analyses established a 6- to 16-fold higher liver-to-plasma exposure ratio 1 hour after dosing. These results are consistent with the liver-targeting feature of the telaprevir structure-based drug design program.

The current standard treatment of HCV infection is a combination of Peg-IFN and RBV. When studied in combination in the HCV replicon assay, the activity of telaprevir was additive to moderately synergistic with IFN-α and additive with RBV.

3.1.2 Resistance

Phenotypic studies (enzymatic and replicon-based) were performed to characterize substitutions identified in the HCV NS3 protease domain that were observed after treatment failure in clinical studies of telaprevir. A lower-level of resistance to telaprevir (3- to 25-fold increase in IC_{50} from wild-type was conferred by single substitutions at V36A/M, T54A/S, R155K/T, and A156S. A higher-level of resistance to telaprevir (> 25-fold increase in IC_{50} from wild-type) was conferred by A156T/V and the double variant V36M+R155K. The in vitro replication capacity of all telaprevir-resistant variants was lower than that of wild-type in the replicon system.

3.1.3 Cross-Resistance

Telaprevir-resistant variants were tested for cross-resistance against representative linear (boceprevir) and macrocyclic HCV protease inhibitors (ciluprevir, danoprevir, TMC-435350 and vaniprevir). Substitutions at positions 36 and 54 conferred lower-levels of cross-resistance to linear inhibitors, and no significant resistance to macrocyclic inhibitors. Substitutions at position 155, 156, or double variants with substitutions at residues 36 and 155 showed cross-resistance to all NS3 protease inhibitors tested with a wide range of sensitivities. All telaprevir-resistant variants remained fully sensitive to IFN-α, RBV, and representative HCV nucleoside and non-nucleoside polymerase inhibitors.

3.1.4 Secondary Pharmacology

Telaprevir had no activity in a HIV-1 protease enzyme and cell-based HIV 1/IIIB and HBV replication assays. Likewise, telaprevir lacked activity against a representative panel of serine proteases in relevant-pathways of mammalian biochemistry and exhibited a low potential for pharmacologically-mediated off-target toxicities for a range of receptors and ion channels, with the exception of an apparent species-specific binding displacement for the rat testosterone receptor.

3.1.5 Safety Pharmacology

A series of GLP-compliant safety pharmacology studies were conducted to assess telaprevir's effects on major organ systems. Overall, and when combined with results from non-GLP secondary pharmacodynamic screening and selectivity studies (described above), and with clinical observations and ECG evaluations performed in the repeat-dose toxicity studies, nonclinical evaluations suggest telaprevir has no significant effects on vital function.

3.2 Pharmacokinetics

Pharmacokinetic data revealed high transepithelial intestinal permeability of telaprevir. Telaprevir is a substrate for efflux pump protein P-glycoprotein (P-gp) but not an inhibitor (at concentrations up to 10 μM). After oral administration of telaprevir formulated as an SDD suspension, peak plasma concentrations were generally reached rapidly, followed by a rapid decline (half-lives from 0.8 to 1.5 hours in rats, rabbits, and dogs). Telaprevir was moderately bound to plasma proteins in all species. No concentration-dependent binding was noted in rat or dog plasma, whereas a mild concentration-dependent decrease in binding was evident in mouse and human plasma. In rats, radioactivity was widely distributed throughout the entire body. In pregnant mice and rats, the placenta presents a partial barrier for ^{14}C-

telaprevir. No unique human metabolites were observed, and the human profile of metabolites was reflected in the nonclinical species tested. The animal PK data in general reflected the clinical data. The elimination of telaprevir is mainly metabolic via the liver, resulting in fecal excretion of metabolites.

3.3 Toxicology

The comprehensive toxicology program evaluating telaprevir demonstrated a low potential for acute oral toxicity and identified dose- and duration-related target organ toxicities following repeated administration that, in most cases, are clinically monitorable and reversible post-cessation of treatment. With the exception of effects on the hematopoietic system (decreased erythrocytic parameters), these toxicities are considered species-specific or considered to lack a clinical correlate.

Telaprevir and its epimer were demonstrated to be non-genotoxic, and no pre-neoplastic or proliferative lesions were noted in chronic repeat-dose toxicity studies in rats and dogs. As a result of these findings and combined with the proposed clinical treatment duration of 12 weeks, carcinogenicity studies were not required.

Telaprevir had no effects on mating and fertility index in rats; however, reversible effects on male fertility parameters and a slight increase in pre-implantation loss and/or an increase in non-viable conceptuses were noted in the fertility and early embryonic development study. These findings were likely associated with degenerative testicular effects noted in this species which were not observed in dogs. Telaprevir has no teratogenic potential and should not be regarded as a developmental toxicant in rats and mice. 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.

Telaprevir is a non-irritant from both the dermal and ocular perspectives and was concluded to be negative for skin sensitizing potential.

4 CLINICAL DEVELOPMENT PROGRAM

Vertex Pharmaceuticals Incorporated began the clinical development of telaprevir for use in the United States, Canada, and Mexico. Vertex partnered with Mitsubishi Tanabe Pharma Corporation for development in Southeast Asia, China, and Japan, and the Johnson & Johnson companies Janssen, Pharmaceutica, and Tibotec to develop telaprevir for use in the rest of the world.

Vertex and Tibotec have collaborated in the telaprevir development program, and have conducted a total of 40 completed clinical studies in subjects with genotype 1 CHC, and 3 ongoing studies. These clinical studies were performed in the United States and Europe in full compliance with Good Clinical Practice (GCP) and are the focus of the findings presented in this submission. In addition, Mitsubishi has conducted 8 studies with healthy or CHC-infected subjects in Japan for which serious adverse event (SAE) data and rash cases reviewed by the dermatology expert panel (DEP, Section 8.2.1.1) are included in the safety analyses presented in this submission.

4.1 Study Design, Guidelines, and Regulatory Input

In total, 5 Phase 2 studies (104, 104EU, 106, 107, C208) and 3 Phase 3 studies (108, 111, C216) have been completed by Vertex or Tibotec in treatment-naive (108, 111, 104, 104EU, C208) or prior treatment-failure (C216, 106, 107) subjects with genotype 1 CHC (Table 2). Treatment-naive subjects were defined as those who had not been previously treated for hepatitis C, whereas prior-treatment failure subjects are defined by quantitative analysis of serum HCV RNA levels (Table 1).

Table 1 Subcategories of Prior Treatment Response

Study	Subcategory	Definition
Prior nonresponse[a]		Never had undetectable HCV RNA during prior treatment
	Prior null response	Study 107: <1-$\log_{10}$ decrease in HCV RNA at Week 4 or <2-$\log_{10}$ decrease in HCV RNA at Week 12
		Study C216: <2-$\log_{10}$ decrease in HCV RNA at Week 12
	Prior partial response	≥2-$\log_{10}$ decrease in HCV RNA at Week 12
Prior viral breakthrough[b]		Undetectable HCV RNA followed by detectable HCV RNA during prior treatment
Prior relapse		Undetectable HCV RNA at the end of prior treatment followed by detectable HCV RNA after the end of prior treatment

[a] Type of prior nonresponse (null or partial) was not determined for subjects in Study 106.
[b] Subjects with prior viral breakthrough were not enrolled in Study C216.

The telaprevir Phase 3 program was based on several learnings from Phase 1 and Phase 2 studies:

- Phase 1 studies demonstrated that 2 weeks of telaprevir monotherapy resulted in a more than 4-$\log_{10}$ decline in plasma HCV RNA levels, but was associated with the emergence of telaprevir-resistant HCV variants and viral breakthrough in some subjects.
- Phase 2 studies established that the combination of telaprevir with Peg-IFN/RBV provided greater antiviral efficacy compared with telaprevir monotherapy or Peg-IFN/RBV alone, and thus established the need for RBV in the regimen.
- Phase 2 studies also evaluated varying durations of Peg-IFN/RBV, leading to the response-guided therapy recommendations that were tested in Phase 3 studies with treatment-naive subjects.

4.1.1 Phase 3 Study Design and Primary Endpoints

Overall, the telaprevir clinical development program was designed taking into account the advice from health authorities globally, and the program is in line with the recently issued draft FDA guidance for the development of direct-acting antiviral agents intended for treatment of CHC (September 2010).[1]

Studies 108 and C216 were pivotal Phase 3 studies, whereas Study 111 is a supportive study. Critical design features shared by the three Phase 3 studies included (Table 2):

- All Phase 3 studies were designed to assess the efficacy and safety of 12 weeks of treatment with telaprevir 750 mg every 8 hours (q8h) in combination with 24 or 48 weeks of treatment with Peg-IFN/RBV in a broad range of subjects with genotype 1 CHC and compensated cirrhosis
- The primary endpoint of all Phase 3 studies was the proportion of subjects achieving SVR, demonstrated by having undetectable HCV RNA 24 weeks after last planned dose of study drug
- Subjects enrolled in the Phase 3 studies had varying degrees of liver disease (including clinically compensated cirrhosis), were from various geographic regions, and had diverse racial/ethnic backgrounds

Each of the Phase 3 studies also had unique features that were designed to address issues vital to the recommended treatment protocol, including response guided therapy, lead in dosing:

- Study 108 was designed to establish the superiority of a telaprevir/Peg-IFN/RBV regimen compared to a standard Peg-IFN/RBV regimen in treatment-naive subjects
  - Response-guided therapy: Subjects with undetectable HCV RNA at Weeks 4 and 12 (extended rapid viral response [eRVR]) received a total of 24 weeks of Peg-IFN/RBV treatment, whereas all other subjects received a total of 48 weeks of treatment.
  - Evaluation of 2 telaprevir treatment durations (8 weeks and 12 weeks): The 8-week arm was included to determine whether a shorter duration of telaprevir treatment might provide the same efficacy as 12 weeks duration, with a reduction in the occurrence of severe rash.

- Study C216 was designed to establish the superiority of a telaprevir/Peg-IFN/RBV regimen to standard Peg-IFN/RBV treatment in a prior treatment-failure population (prior relapsers, prior partial responders, and prior null responders). The total treatment duration was 48 weeks in both the telaprevir (T12/PR48) and the placebo (Pbo/PR48) groups
  - The study was also designed to test the effect of a 4-week lead in of Peg-IFN/RBV treatment before beginning telaprevir treatment.
- Study 111 was designed to determine whether a total treatment duration of 24 weeks was non-inferior to a total treatment duration of 48-weeks in treatment-naive subjects with eRVR.

Table 2 Tabular Listing of Phase 2 and Phase 3 Clinical Studies

Study Number	Type	Phase	Study Design	Drug Regimen	Number of Subjects	Status
Phase 2						
104	Efficacy, safety, and PK	2	Randomized, placebo-controlled, double-blind, parallel-group, multiple dose	**T12/PR12 Group** T: 12 weeks Peg-IFN/RBV:12 weeks **T12/PR24 Group** T:12 weeks Peg-IFN/RBV: 24 weeks **T12/PR48 Group** T: 12 weeks Peg-IFN/RBV: 48 weeks **Pbo/PR48 Group** T placebo: 12 weeks Peg-IFN/RBV: 48 weeks	250 treatment-naive subjects with genotype 1 CHC	Complete
104EU	Efficacy, safety, and PK	2b	Randomized, partially placebo-controlled, partially double-blind, parallel-group, multiple dose	**T12/P12 Group** T: 12 weeks Peg-IFN: 12 weeks **T12/PR12 Group** T: 12 weeks Peg-IFN/RBV: 12 weeks **T12/PR24 Group** T: 12 weeks Peg-IFN/RBV: 24 weeks **Pbo/PR48 Group** T placebo: 12 weeks Peg-IFN/RBV: 48 weeks	323 treatment-naive subjects with genotype 1 CHC	Complete

Table 2 Tabular Listing of Phase 2 and Phase 3 Clinical Studies

Study Number	Type	Phase	Study Design	Drug Regimen	Number of Subjects	Status
106	Efficacy, safety, and PK	2	Randomized, partially placebo-controlled, partially double-blind, parallel-group, multiple dose	**T24/PR48 Group** T: 24 weeks Peg-IFN/RBV: 48 weeks **T24/P24 Group** T: 24 weeks Peg-IFN: 24 weeks **T24/PR24 Group** T: 12 weeks Peg-IFN/RBV: 24 weeks **Pbo/PR48 Group** T placebo: 24 weeks Peg-IFN/RBV: 48 weeks	453 subjects with genotype 1 CHC who were nonresponsive to prior treatment with Peg IFN and RBV	Complete
C208	Efficacy, PK, PD, and safety	2a	Randomized, open-label, multiple dose	**T12(q8h)/P(2a)R Group** T 750mg q8h: 12 weeks Peg-IFN/RBV: ≤ 48 weeks **T12(q8h)/P(2b)R Group** T 750mg q8h: 12 weeks Peg-IFN/RBV(Rebetol): ≤ 48 weeks **T12(q12h)/P(2a)R Group** T 1,125 mg q12h: 12 weeks Peg-IFN/RBV: ≤ 48 weeks **T12(q12h)/P(2b)R Group** T 1,125 mg q8h: 12 weeks Peg-IFN/RBV(Rebetol): ≤ 48 weeks	161 treatment-naive subjects with genotype 1 CHC	Complete

Table 2 Tabular Listing of Phase 2 and Phase 3 Clinical Studies

Study Number	Type	Phase	Study Design	Drug Regimen	Number of Subjects	Status
107	Efficacy and safety	2	Nonrandomized, open-label, multiple dose	**T12/PR Group** **Prior null responders:** T: 12 weeks Peg-IFN/RBV: 48 weeks **Prior partial responders w/ relapse and viral breakthrough:** T: 12 weeks Peg-IFN/RBV: 24 or 48 weeks	117 subjects who were enrolled in the control arms of Studies 106, 104, or 104EU and discontinued treatment due to an inadequate response	Complete
Phase 3						
108	Efficacy	3	Randomized, placebo-controlled, double-blind, parallel-group, multiple dose	**T8/PR Group** T: 8 weeks Peg-IFN/RBV: 24 or 48 weeks **T12/PR Group** T: 12 weeks Peg-IFN/RBV: 24 or 48 weeks **Pbo/PR48 Group** T placebo: 12 weeks Peg-IFN/RBV: 48 weeks	1,088 treatment-naive subjects with genotype 1 CHC	Complete
111	Efficacy	3	Randomized, open-label, multiple dose	**T12/PR Group** T: 12 weeks Peg-IFN/RBV: 24 or 48 weeks	540 treatment-naive subjects with genotype 1 CHC	Complete

Table 2 Tabular Listing of Phase 2 and Phase 3 Clinical Studies

Study Number	Type	Phase	Study Design	Drug Regimen	Number of Subjects	Status
C216	Efficacy, PK, PD, and safety	3	Randomized, placebo-controlled, double-blind, multiple dose	**T12/PR48 Group** T: 12 weeks Peg-IFN/RBV: 48 weeks **T12(LI)/PR48 Group** T placebo: 4 weeks; then T: 12 weeks Peg-IFN/RBV: 48 weeks **Pbo/PR48 Group** T placebo: 16 weeks Peg-IFN/RBV: 48 weeks	662 treatment-failure subjects with genotype 1 CHC	Complete
Ongoing Studies						
112	3-Year Virology Follow-up	XX	Non-randomized follow-up		**Cohort A:** 123 subjects who achieved an SVR in a previous study (Study 104, 104EU, 106, 107, 108, 111, or C216) **Cohort B:** 79 subjects who did not achieve SVR in a previous study (Study 104, 104EU, 106, 107, 108, 111, or C216)	Ongoing
110	Efficacy, PK, PD, and Safety	2a	Randomized, placebo-controlled, double-blind, parallel-group, multiple dose	Telaprevir or telaprevir placebo for 12 weeks in combination with Peg-IFN-alfa-2a/RBV for 48 weeks	**Part A:** 8 treatment-naive subjects with genotype 1 CHC and HIV-1 co-infection who are not receiving a HAART regimen **Part B:** 13 treatment-naive subjects with genotype 1 CHC and HIV-1 co-infection who are receiving a HAART regimen	Ongoing

Table 2 Tabular Listing of Phase 2 and Phase 3 Clinical Studies

Study Number	Type	Phase	Study Design	Drug Regimen	Number of Subjects	Status
C219	Efficacy, Safety, and PK	3b	Nonrandomized, open-label, multiple dose	Telaprevir for 12 weeks in combination with Peg-IFN-alfa-2a/RBV for 48 weeks	23 subjects with genotype 1 CHC who were randomized to the control group in Study C216 and who failed therapy for virologic reasons, and subjects from Studies 101 and 103 who had not achieved SVR	Ongoing

5 CLINICAL PHARMACOLOGY

The PK and PK/pharmacodynamic (PD) characteristics of telaprevir in human subjects have been thoroughly studied throughout the clinical development program. Studies in healthy subjects were conducted to evaluate the following: dose-proportionality, food-effect, bioavailability of different formulations, absorption, distribution, metabolism, excretion (ADME), effect of hepatic impairment, and effect of renal impairment. Based on the results of in vitro studies, several additional studies were conducted in healthy human subjects to examine the drug-drug interaction (DDI) potential of telaprevir as a substrate and inhibitor of CYP3A, and as a substrate of P-gp, using both model drugs and drugs that are commonly prescribed to subjects with HCV. Because HCV coinfection is relatively common in subjects with HIV, studies were also conducted to examine the potential DDIs between telaprevir and commonly used HIV medications (i.e., ritonavir-boosted HIV protease inhibitors, tenofovir disoproxil fumarate, and efavirenz).

Data were collected from four Phase 2 studies and three Phase 3 studies to assess the effects of subject demographic characteristics and other covariates on telaprevir PK, and to characterize the exposure-response relationships for efficacy and safety.

Formulation development for telaprevir progressed from suspensions through 250-mg tablets to 375-mg tablets. The proposed commercial formulation is a 375-mg film-coated tablet. Physiochemical properties suggest that telaprevir is a Biopharmaceutics Classification System Class II (low solubility/high permeability) compound.

5.1 Absorption, Distribution, Metabolism, Excretion

Telaprevir is orally bioavailable and likely to be absorbed in the small intestine, with no evidence for absorption in the colon. It is a substrate of P-gp. In vitro studies demonstrated a lack of P-gp inhibition by telaprevir at concentrations of up to 10 μM (~ 6,800 ng/mL). A clinical drug interaction study with digoxin demonstrated increased digoxin plasma concentrations upon coadministration with telaprevir in the absence of an effect on renal clearance of digoxin, indicating that telaprevir may inhibit and/or saturate P-gp at relatively high local concentrations in the gut, whereas significant systemic P-gp inhibition by telaprevir is unlikely.

Telaprevir is approximately 59% to 76% bound to plasma proteins (mainly alpha-1-acid glycoprotein and albumin) and has a large apparent volume of distribution (V/F). The V/F of telaprevir was estimated from population PK analyses of Phase 2/3 studies to be 252 L, with inter-individual variability estimated to be 72.2%.

Telaprevir is extensively metabolized via hydrolysis, oxidation, and reduction. The major cytochrome P-450 isozyme involved in the metabolism of telaprevir is CYP3A. However, the structures of the metabolites (via reduction and/or hydrolysis) of telaprevir also suggest the involvement of non-CYP pathways. After repeated oral administration of telaprevir in combination with Peg-IFN/RBV in subjects with CHC, the predominant metabolites of telaprevir were VRT-127394 (R-diastereomer of telaprevir, 30-fold less active), pyrazinoic acid (not active), and VRT-0922061 (M3 isomer metabolite, reduction at the α-ketoamide bond of telaprevir, not active).

Because telaprevir is both a substrate and inhibitor of CYP3A, there is a potential for DDIs between telaprevir and substrates, inducers, and inhibitors of CYP3A. In vitro studies suggest that telaprevir has a low potential to induce CYP2C, CYP3A, or CYP1A and is therefore unlikely to demonstrate induction when coadministered with corresponding substrates. Time- and concentration-dependent inhibition of CYP3A by telaprevir was observed in human liver microsomes. No inhibition by telaprevir of CYP1A2, CYP2C9, CYP2C19, or CYP2D6 isozymes was observed in vitro.

Telaprevir is predominantly eliminated in the feces, suggesting that biliary excretion plays a role in the disposition of telaprevir (as seen in animal studies). Following administration of a single oral dose of 750 mg ^{14}C-telaprevir in healthy subjects, the median recovery of the administered radioactive dose was approximately 82% in feces, 9% in exhaled air (as CO_2), and 1% in urine. Apparent clearance (CL/F) of telaprevir was estimated from population PK analyses of Phase 2/3 studies to be 32.4 L/hr, with inter-individual variability estimated to be 27.2%.

5.2 Pharmacokinetics

Dose proportionality

After a single dose (range 375 to 1875 mg) in healthy subjects (Study 017), the AUC and C_{max} of telaprevir generally increased slightly greater than proportional to dose.

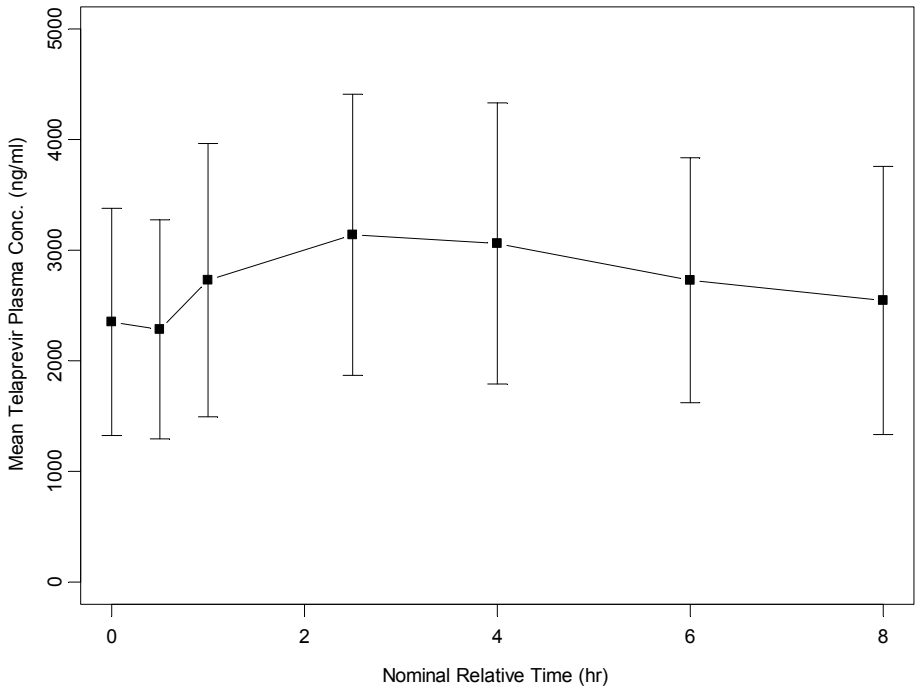
However, in a multiple-dose 5-day study in healthy subjects (Study C136), an increase in dose from 750 mg q8h to 1875 mg q8h resulted in less than proportional increase in exposure (i.e., a dose increase of 2.5-fold resulted in C_{min}, C_{max}, and AUC_{8h} increases of approximately 40%).

Multiple Dose PK

In monotherapy studies, telaprevir C_{max} and AUC increase after multiple dosing compared with the first dose. When telaprevir was dosed as 750 mg q8h, steady state was reached after 3 to 7 days with an accumulation ratio of approximately 2.2 to 2.5, which is greater than expected based on single-dose half-life. After a single dose, the terminal elimination half-life ($t_{1/2}$) is approximately 4 hours. At steady state, the effective half-life is approximately 9 to 11 hours.

Based on population pharmacokinetic analysis, following multiple doses of telaprevir (750 mg q8h) in combination with Peg-IFN/ RBV in treatment-naive subjects with genotype 1 CHC (Study 108), mean (SD) C_{max} is 3,260 (946) ng/mL, C_{min} is 2,690 (827) ng/mL, and AUC_{8h} is 24,400 (7,180) ng.h/mL. The mean telaprevir plasma concentration versus time profile was determined in a PK substudy of Study 108 (Figure 4).

Figure 4 Mean Telaprevir Plasma Concentration Versus Time Profile at Steady-State



Note: Mean (error bars are SD) telaprevir concentration versus sampling time after dose during the intensive PK sampling visit.

Coadministration of Peg-IFN and RBV

In subjects with chronic HCV infection, coadministration with Peg-IFN resulted in a telaprevir $C_{max,ss}$ 43% higher and an AUC 38% higher than telaprevir monotherapy; RBV coadministration did not affect telaprevir exposure. Similar telaprevir exposures were obtained regardless of whether the coadministered treatment was PEG-Intron/Rebetol or Pegasys/Copegus. Peg-IFN or RBV levels were not affected by the coadministration of telaprevir

Healthy Subjects Versus Subjects With Chronic HCV Infection

Comparison of telaprevir exposure and the elimination half-life in healthy subjects and subjects with chronic HCV infection revealed similar results after single- or multiple-dose administration of telaprevir as monotherapy.

Population PK Analyses

Results from pooled analyses of Phase 2/3 studies indicated that subject age and race, within the range of values available in the analysis, did not have a clinically relevant impact on the average steady-state exposure to telaprevir. Subject weight (highly correlated with subject BMI as well as subject gender) was found to be an influential covariate, with lower exposures in subjects with greater weight. However, the inter-individual variability in telaprevir exposure is only reduced from 29% to 27% when subject weight was accounted for in the population PK model suggesting that the variability in telaprevir exposure due to subject weight is small compared to the overall variability in exposure. Based on exposure-

response analyses (see Section 5.4), the magnitude of the effect of weight on telaprevir exposure is not expected to be clinically relevant. Comparison of individual exposure estimates from the population PK analysis further showed no clinically relevant effects on telaprevir exposure based on subject age (up to 70 years), race, gender, or weight/BMI.

5.3 Food Effect

To achieve optimal exposure, telaprevir should be taken with food. In a Phase 1 study, when compared with administration following a standard normal caloric meal (21 g fat, 533 kcal), exposures (AUC) decreased by an average of 73% when telaprevir was taken in the fasted state, by 39% following a low-calorie low-fat meal (3.6 g fat, 249 kcal), and by 26% following a low-calorie high-protein meal (9 g fat, 260 kcal). The exposure to telaprevir was increased by 20% when taken following a high-fat caloric meal (56 g fat, 928 kcal) compared with an intake following a standard normal caloric meal.

In Phase 2/3 studies, subjects were advised to consume a regular meal or snack (high fat was not required) within 30 minutes prior to dosing with telaprevir. Based on its prescribing information, RBV is also to be dosed with food. Since RBV is administered twice a day and has a long half-life, it was administered with 2 of the 3 daily telaprevir doses in the Phase 2/ 3 studies.

5.4 Rationale for Dose Selection

As a consequence of its high replicative rate and its error-prone polymerase, HCV exists as a quasispecies. In most subjects, the quasispecies consists predominantly of wild-type virus and minority populations of viral variants with varying levels of resistance to direct-acting antiviral agents, including HCV protease inhibitors such as telaprevir. These variants may have lower level (< 25-fold increase in IC_{50}) or higher level telaprevir resistance. The HCV variants usually exist at a low frequency before the start of treatment because they are less fit (have lower replicative capacity) than wild-type virus.

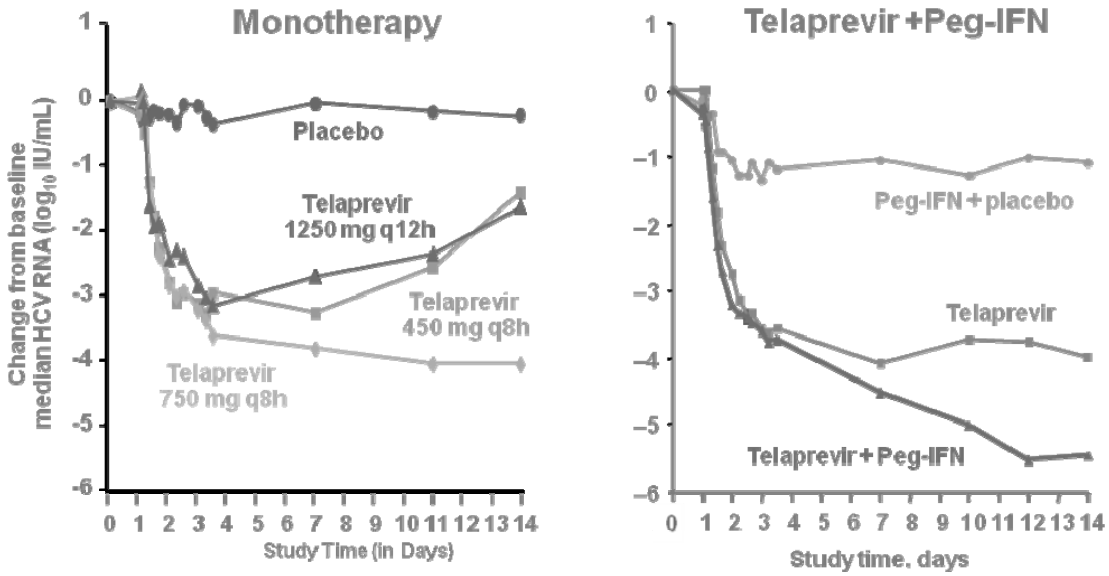
Two main goals of antiviral therapy applied to the development of telaprevir were (1) to achieve a high enough exposure to inhibit replication of wild-type and lower level resistant variants within an acceptable safety margin, and (2) to maintain this dose for a duration needed to eliminate wild-type and lower level resistant variants in combination with Peg-IFN/RBV treatment. The primary role of telaprevir in a T/PR regimen is to eradicate wild-type and lower level resistant variants, leaving the complementary role of PR to eradicate higher level resistant variants and any remaining lower level resistant variants. Susceptibility of HCV to telaprevir in both treatment-naive subjects and in subjects who have previously failed treatment with Peg-IFN/RBV therapy is expected to be the same.

The antiviral activity of different dosages of telaprevir, administered as a suspension formulation, was evaluated in subjects with genotype 1 CHC (Study 101). The antiviral response was evaluated after administration of telaprevir monotherapy administered for 14 days at 450 mg q8h, 750 mg q8h, or 1250 mg q12h (Figure 5A). The greatest reduction in HCV RNA was observed with the 750 mg q8h regimen, which corresponded to the highest exposure to telaprevir. Because no clinically relevant differences were observed in the safety profile of the 3 dose regimens, the 750 mg q8h regimen was further explored in 2 subsequent short-term studies using a tablet formulation with about 1.5- to 2-fold improved exposure to telaprevir (Studies 102 and 103). In these studies, telaprevir 750 mg q8h coadministered with

Peg-IFN or Peg-IFN/RBV resulted in further increase in telaprevir exposures and greater HCV RNA reduction compared with telaprevir monotherapy (Figure 5B), as well as suppression of telaprevir-resistant HCV variants. Because the telaprevir 750 mg q8h dose was generally well tolerated and not associated with any SAEs or discontinuations due to AEs, and the short-term efficacy was favorable (all 12 subjects achieved undetectable HCV RNA at Week 4 in Study 102), this regimen was selected for further clinical development, and no further dose-ranging studies were performed.

Figure 5 Median Change From Baseline HCV RNA: Monotherapy (Study 101) and in Combination with Peg-IFN (Study 103)

A. B.



In Panel A (monotherapy), telaprevir doses of 450 mg q8h, 750 mg q8h, and 1250 mg q12h were administered. In Panel B (telaprevir + Peg-IFN), telaprevir 750 mg q8h was administered.

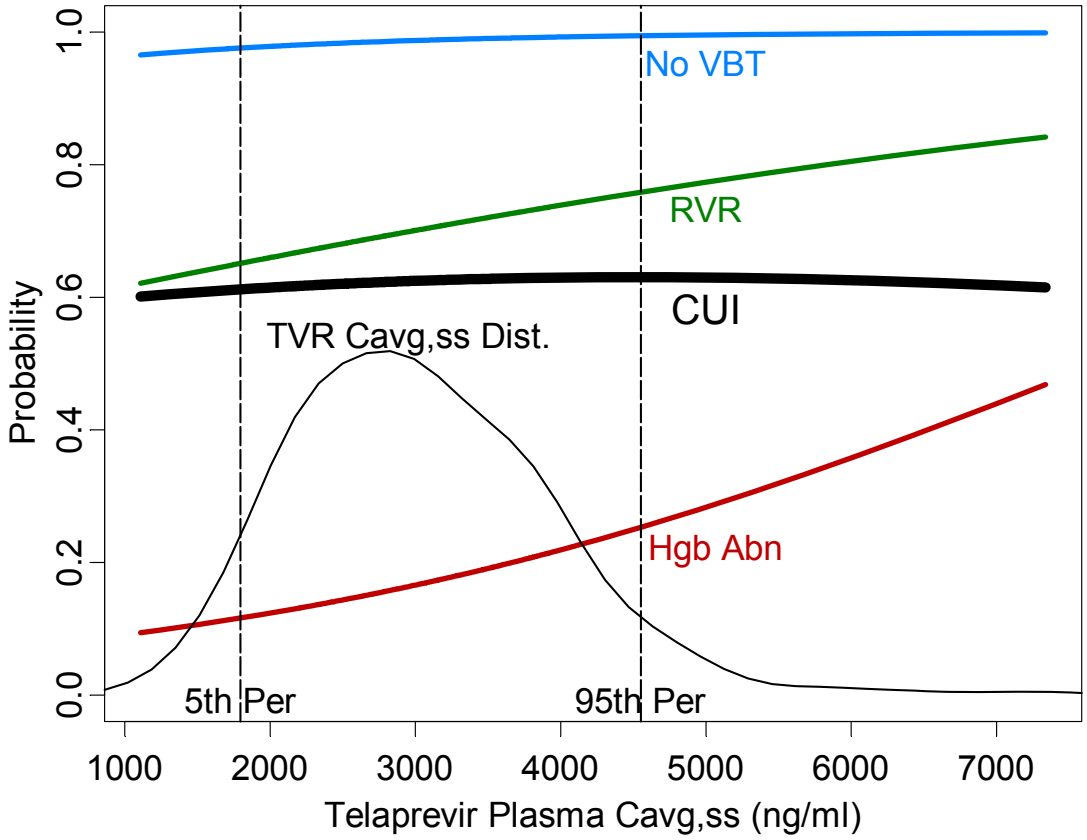
Exposure-response analyses, including clinical utility analyses[28,29], conducted on data from the Phase 2/3 development programs confirmed that the 750 mg q8h dose and the regimen of telaprevir in combination with Peg-IFN/RBV results in telaprevir exposures that provided a good balance between efficacy and safety.

The clinical utility index (CUI) represents a composite of the exposure-response relationships for both safety and efficacy endpoints by defining the probability of clinical success as the difference between the probability of clinical efficacy and the probability of clinical safety over a range of drug exposures. The CUI from Study 108 represents a composite of the probability of achieving a RVR, preventing viral breakthrough (no VBT), and incurring a Grade 2 or greater hemoglobin decrease (Hgb abnormalities), as a function of model-predicted telaprevir exposure (Figure 6). During the construction of the CUI, the probability of RVR and no VBT are weighted by the percentage of subjects who meet these endpoints and go on to achieve SVR (81% for RVR and 77% for no VBT). The probability of the Hgb abnormalities is weighted by the percentage of subjects that meet this endpoint and fail to achieve SVR (24%). This weighting scheme was implemented to objectively scale the

individual endpoint probability curves by their relative importance on the probability of clinical success.

The distribution of telaprevir exposures (plotted as the population PK model-predicted average plasma concentrations), are included with the 5th and the 95th percentiles marked as dotted vertical lines. The resulting plot shows a relatively flat CUI indicating that the exposure range of telaprevir obtained from the 750 mg q8h dose in combination with Peg-IFN/RBV results in a good balance between efficacy and safety (Figure 6).

Figure 6 Clinical Utility Index for Telaprevir in the Treatment-Naive Population in Study 108

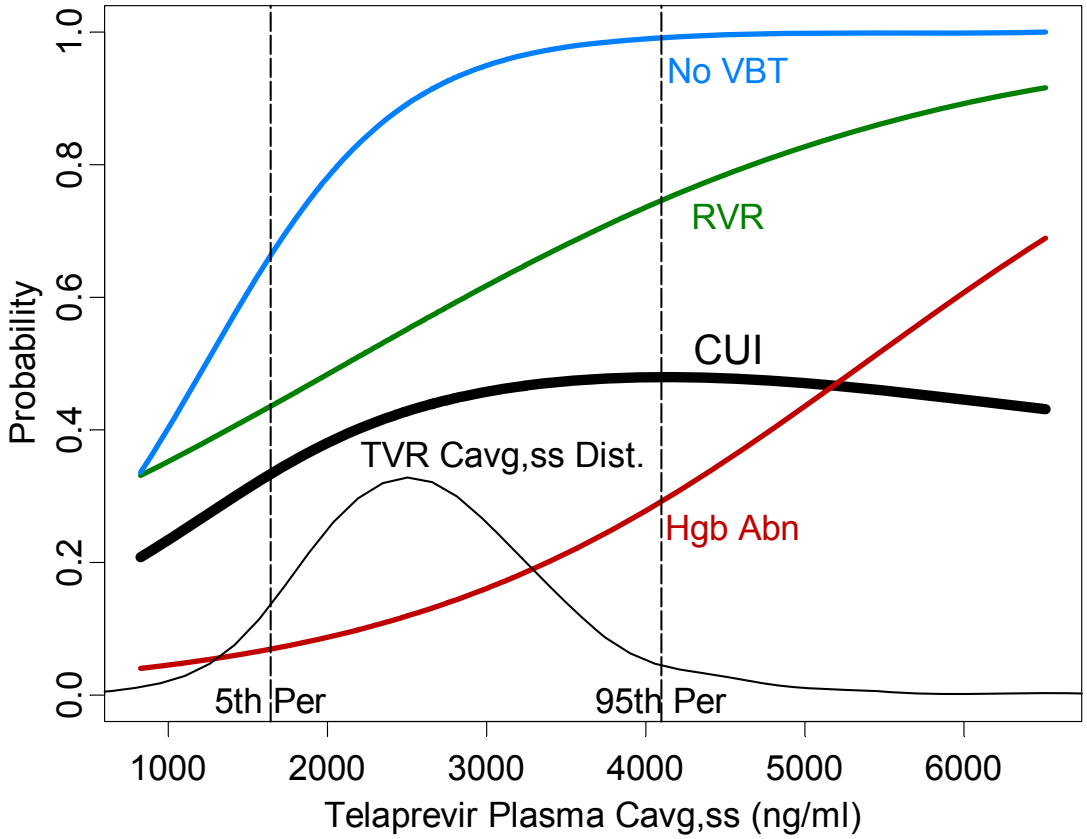


Probability of rapid viral response (RVR), no viral breakthrough (No VBT), grade 2 or higher hemoglobin abnormalities (Hgb Abn) and the resulting clinical utility index (CUI = ((0.81×P(RVR)+0.77×P(No VBT))/2) – 0.24×P(Hgb)) as predicted by logistic regression modeling as a function of model-predicted telaprevir $C_{avg,ss}$. The probabilities for RVR and no VBT were conditioned with the median Day 29 Peg-IFN-alfa-2a serum concentration. The probability for hemoglobin abnormalities was conditioned around the median Day 29 Peg-IFN-alfa-2a serum concentration and median Day 29 RBV plasma concentration. The distribution of model-predicted telaprevir $C_{avg,ss}$ is also included, with the 5th and 95th percentiles indicated by the dashed vertical lines. Note: The number of subjects in this analysis means that there are very few subjects below the 5th and above the 95th percentiles, which means that the curves in these areas should be interpreted with caution.

The exposure-response relationship for subjects with prior treatment failure from Study 106 showed that the clinical utility index weighted by SVR is relatively flat between the 5th and the 95th percentiles of telaprevir exposure (Figure 7). Furthermore, Phase 3 studies have

confirmed that this dose of telaprevir used in combination with Peg-IFN/RBV therapy provides superior SVR rates over those seen with Peg-IFN/RBV therapy alone.

Figure 7 Clinical Utility Index for Telaprevir in the Prior Treatment-Failure Population in Study 106

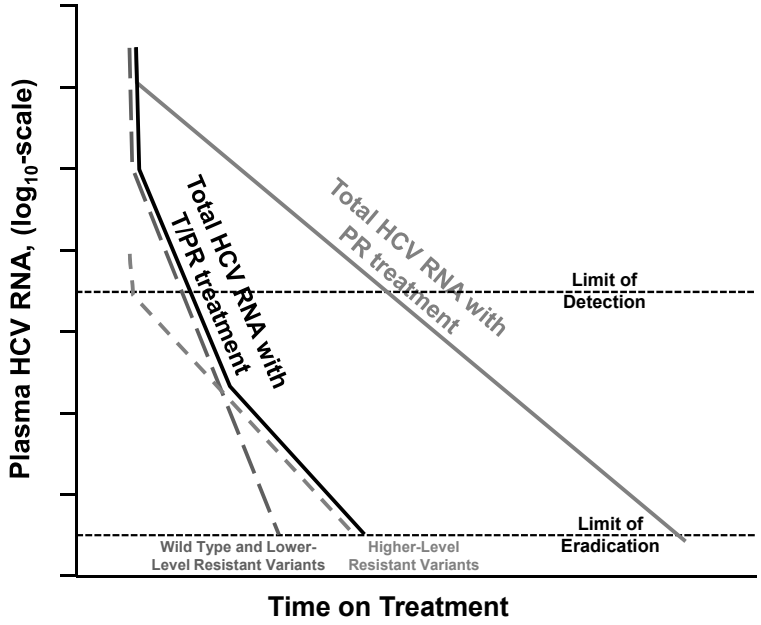


Probability of RVR, no viral breakthrough (No VBT), Grade 2 or higher hemoglobin abnormalities (Hgb Abn), and the resulting clinical utility index (CUI = ((0.74×P(RVR)+0.58×P(No VBT))/2) – 0.29×P(Hgb)) as predicted by logistic regression modeling as a function of model-predicted telaprevir $C_{avg,ss}$ The probabilities for RVR and no VBT were conditioned with the median Day 29 Peg-IFN-alfa-2a serum concentration. The probability for Hgb abnormalities was conditioned around the median Day 29 Peg-IFN-alfa-2a serum concentration and median Day 29 RBV plasma concentration. The distribution of model-predicted telaprevir $C_{min,ss}$ is also included, with the 5th and 95th percentiles indicated by the dashed vertical lines.
Note: The number of subjects in this analysis means that there are very few subjects below the 5th and above the 95th percentiles, which means that the curves in these areas should be interpreted with caution.

5.5 Rationale for Treatment Duration

An optimized T/PR regimen should have a telaprevir treatment duration that is sufficient to eradicate wild-type and lower level resistant variants, and Peg-IFN/RBV treatment duration sufficient to eradicate any remaining variants, including higher level resistant variants (Figure 8). Because higher level resistant variants have lower replicative fitness and pre-exist at lower prevalence, some subjects may achieve viral eradication with a shorter duration of Peg-IFN/RBV.

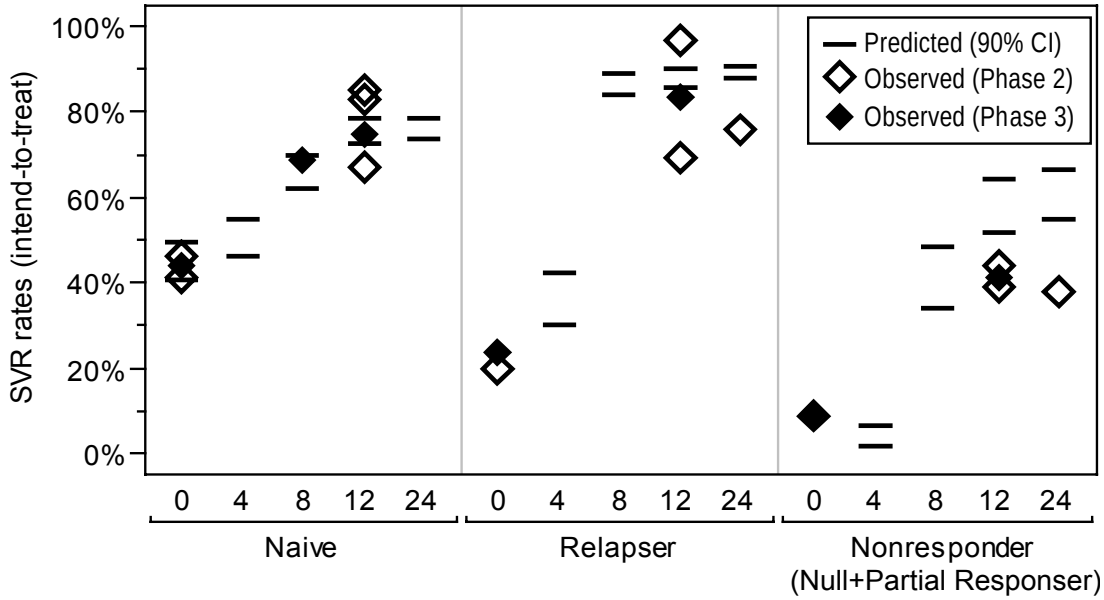
Figure 8 Schematic of Relative Treatment Duration Required for SVR in a Quasispecies Consisting of Wild-type Virus and Telaprevir-Resistant Variants



A viral dynamic model of T/PR treatment was developed using in vitro and clinical data from early studies obtained from 28 subjects treated with 2 weeks of telaprevir monotherapy and 478 treatment-naive subjects treated with PR and T/PR regimens (Studies 104 and 104EU). Model predictions were evaluated from the outcome data of 2,380 subjects in subsequent studies. The model prediction capability was verified by comparing predicted SVR rates against the observed values in clinical studies, with accurate predictions observed in treatment-naive and prior relapser populations, but predictions were less accurate in the prior nonresponder population.

For a regimen with 12 weeks of telaprevir and 24 or 48 weeks of Peg-IFN/RBV treatment ($T12/PR_{24-48}$) in a treatment-naive population, the model predicted 75% SVR (90% CI: 72%, 79%; Figure 9). Shortening the telaprevir duration (to 4 or 8 weeks) was predicted to reduce SVR rates (by 25% or 9%, respectively) and was associated with an increase in virologic failure during PR treatment with telaprevir-sensitive variants. Increasing the telaprevir duration from 12 to 24 weeks was predicted to result in similar SVR rates. These predictions were consistent with the observed SVR rates and sequencing analysis in Phase 2/3 studies. Similar results were obtained in the prior nonresponder and relapser populations (although the predicted SVR rates were lower for nonresponders).For details on efficacy results, see Section 6.

Figure 9 Predicted and Observed SVR Rates by Telaprevir Treatment Duration



Assumptions in model predictions: (1) The disposition of treatment discontinuations was assumed to be similar to that in Study 108; some of the studies have different dispositions than the assumed disposition, resulting in differences between predicted and observed SVR rates. (2) Definition of prior PR response followed standard definition; (3) PR durations: T4, 48 weeks; T8-T24, 24 weeks for subjects with eRVR and 48 weeks for subjects without eRVR; (4) Treatment adherence rate was 100%; (4) Genotype 1a:1b ratio was 1:1.
Note: Predicted SVR rate for PR48-treatment failures is zero by definition because the simulated subjects used in the treatment-failure predictions were subjects who would not reach SVR when treated with PR48.

The model predicted that the difference in SVR rates between T12/PR regimens with and without response-guided PR duration (T12/PR24 for subjects with eRVR and T12/PR48 for subjects without eRVR, versus T12/PR48 for all subjects) was 1% to 2% in both treatment-naive and in prior relapser populations. The predictions were also consistent with the observed SVR rates by PR duration in Phase 2/3 studies.

Clinical data support response-guided treatment durations in patients with eRVR.

In Study 108, subjects in the T8/PR and T12/PR treatment groups with eRVR had a planned treatment duration of 24 weeks. The majority of subjects in the T/PR groups had eRVR; therefore, more than half of the telaprevir-treated subjects were assigned to a 24-week treatment duration. SVR rates were 89.2% in the T12/PR group among subjects who had eRVR and had a planned treatment duration of 24 weeks. Relapse rates were low among subjects who had eRVR and completed treatment (6.4% in the T12/PR group). These results suggest that 24 weeks of treatment was sufficient in most subjects with eRVR. Treatment with telaprevir markedly increased the rapid antiviral response, which likely contributed in large measure to its increased efficacy and permitted the majority of subjects to achieve SVR with a shorter duration of therapy.

In Study 111, response-guided therapy was further evaluated by randomization at Week 20 of subjects with eRVR to either the T12/PR24 or T12/PR48 group. SVR rates were 92.0% in the T12/PR24 group and 87.5% in the T12/PR48 group among subjects with eRVR.

Statistical analyses of the SVR rates in Study 111 demonstrated that the T12/PR24 treatment regimen was non-inferior to the T12/PR48 treatment regimen, as the lower limit of the 95% CI (-2.1%) was entirely to the right of the pre-defined non-inferiority margin of -10.5%. There was no evident advantage in extending treatment for 48 weeks compared to 24 weeks in subjects with eRVR.

Therefore, Peg-IFN/RBV treatment duration of 24 weeks is recommended in treatment-naïve patients with eRVR; 48 weeks of Peg-IFN/RBV treatment is recommended in treatment-naïve patients who do not have eRVR.

Certain populations that have lower SVR rates with standard therapy, including patients with cirrhosis, subjects with high baseline HCV RNA levels, and subjects who are Black, were less likely to have eRVR with T/PR treatment. Therefore, although many patients in these categories will benefit from response-guided therapy, these patient populations are more likely to need 48 weeks of treatment than the general population of treatment-naïve patients. The majority of patients in the overall treatment-naïve population will likely meet the response-guided therapy criteria for a shorter total treatment duration of 24 weeks.

Response-guided therapy was not evaluated in Phase 3 clinical studies in the treatment-failure population. However, data from the Phase 2 and Phase 3 studies indicate that the treatment-failure population is not uniform. The prior relapse population and the prior nonresponse population are quite distinct, and the prior relapse population appears to have more similarities to the treatment-naïve population than to the prior nonresponse population, based on rapidity of the antiviral response and on SVR rates.

Baseline characteristics in each prior relapse population in Studies 106, 107, and C216 and each treatment-naive population with eRVR are summarized in Table 3. Baseline characteristics in the prior relapse population were similar to those in the treatment-naive population with eRVR, further demonstrating the similarities between these 2 groups.

Table 3 Demographic and Baseline Disease Characteristics in Prior Relapse Populations (Total) and Treatment-Naïve Populations (eRVR+), FA Set

	Prior Relapse			Treatment-Naïve (eRVR+)	
	Study 106	Study 107	Study C216	Study 108	Study 111
Variable	T12/PR24 N = 42	T12/PR24 N = 25	T12/PR48 N = 145	T12/PR N = 212	T12/PR24 N = 162
Male, n (%)	29 (69.0)	15 (60.0)	98 (67.6)	130 (61.3)	104 (64.2)
Caucasian, n (%)	39 (92.9)	22 (88.0)	132 (91.0)	193 (91.0)	135 (83.3)
Black, n (%)	2 (4.8)	2 (8.0)	7 (4.8)	9 (4.2)	17 (10.5)
Hispanic, n (%)	2 (4.8)	2 (8.0)	17 (11.7)	18 (8.5)	18 (11.1)
Age, mean (SD) years	51.2 (7.9)	49.3 (7.8)	51.1 (8.5)	45.8 (10.6)	48.6 (8.9)
BMI, mean (SD) kg/m^2	28.3 (5.2)	25.9 (4.94)	27.6 (4.86)	26.3 (4.7)	28.7 (5.6)
BMI ≥ 25 kg/m^2, n (%)	NA	12 (48.0)	100 (68.9)	124 (58.5)	117 (72.2)
Genotype 1a, n (%)	26 (61.9)	15 (60.0)	65 (45.8)	126 (59.4)	114 (70.4)
HCV RNA ≥ 800000 IU/mL, n (%)	37 (88.1)	16 (64.0)	124 (85.5)	158 (74.5)	124 (76.5)
Cirrhosis, n (%)	10 (23.8)	1 (4.0)	28 (19.3)	9 (4.2)	18 (11.1)

The following data analyses indicate that patients with prior relapse and eRVR are likely to benefit from response-guided therapy:

- In Study 111, the SVR rate in treatment-naïve subjects with eRVR was 92.0% in the T12/PR24 group and 87.5% in the T24/PR48 group.
- In Study 106, the SVR rate was 69.0% in subjects with prior relapse in the T12/PR24 group. Among subjects with prior relapse in this treatment group who had eRVR, the SVR rate was 89.3%.
- In Study 107, the SVR rate was 96.0% in subjects with prior relapse in the T12/PR24 group. Among subjects with prior relapse in this treatment group who had eRVR, the SVR rate was 100%.
- In Study 108, the SVR rate was 74.7% in treatment-naïve subjects in the T12/PR group; among subjects in this treatment group who had eRVR and were assigned to a Peg-IFN/RBV treatment duration of 24 weeks, the SVR rate was 89.2%.
- In Study C216, the SVR rate was 83.4% in subjects with prior relapse in the T12/PR48 group. Among subjects with prior relapse in this treatment group who had eRVR, the SVR rate was 95.8%.
- Relapse was rare in subjects with prior relapse in the T12/PR24 groups who had eRVR.

A shortened duration of therapy from 48 weeks to 24 weeks is likely to have a safety benefit as a result of reduced exposure to Peg-IFN/RBV, as shown in Study 111.

A summary of SVR and relapse in subjects with eRVR is provided in Table 4.

Table 4 SVR and Relapse Rates in Treatment-Naive and Prior Relapse Subjects With eRVR, Full Analysis Set

Parameter	Subject Population/ Study	T12/PR24[a] % (N[b])	T12/PR48 % (N)
SVR Rates	**Treatment-naive**		
	Study 108	89.2 (212)	NA
	Study 111	92.0 (162)	87.5 (160)
	Prior Relapse		
	Study 106	89.3 (28)	NA
	Study 107	100 (24)	NA
	Study C216	NA	95.8 (95)
Relapse Rates[c]	**Treatment-naive**		
	Study 108	6.6 (210)	NA
	Study 111	5.6 (162)	2.5 (156)
	Prior Relapse		
	Study 106	7.1 (28)	NA
	Study 107	0 (24)	NA
	Study C216	NA	3.2 (95)

Abbreviations: NA: not applicable
[a] In Study 108, the treatment group was T12/PR, and subjects with eRVR were assigned to receive 24 weeks of treatment.
[b] Denominator is subjects with eRVR.
[c] N for relapse differs from N for relapse described in previous sections (in this analysis, N = FA Set; in previous sections, N = undetectable HCV RNA at end of treatment)

In summary, response-guided therapy is recommended in patients with prior relapse for the following reasons.

- SVR rates in subjects with prior relapse are comparable to or higher than those in treatment-naïve subjects
- SVR rates are greater than 89% in subjects with prior relapse who had eRVR and were treated for 24 weeks
- Relapse rates are low in subjects with prior relapse who had eRVR and were treated for 24 weeks
- Results from Study 111 demonstrated a lack of additional benefit of a 48-week regimen compared to a 24-week regimen in treatment-naïve subjects who had eRVR.

Therefore, Peg-IFN/RBV treatment duration of 24 weeks is recommended in patients with prior relapse with eRVR; Peg-IFN/RBV treatment duration of 48 weeks is recommended in all other patients in the treatment-failure population.

Additional clinical pharmacology studies can be found in the following sections: DDI interactions (Section 7), and Hepatic and Renal Impairment (Section 8.5.1).

6 CLINICAL EFFICACY

6.1 Phase 3 Clinical Study Program

The rationale for the selection of treatment regimens studied in the Phase 3 program was based on efficacy, safety, viral sequencing, viral dynamic modeling, and PK/PD analyses (see Sections 5.4 and 5.5).

6.1.1 Inclusion and Exclusion Criteria

Eligible subjects were 18 to 70 years of age and had genotype 1 CHC. Subjects were also seronegative for hepatitis B surface antigen and antibodies against HIV types 1 and 2. Subjects with cirrhosis were permitted if there was no evidence of hepatic decompensation. Subjects were excluded if they had hepatocellular carcinoma, another cause of liver disease in addition to hepatitis C, or poorly controlled diabetes.

6.1.2 Efficacy Endpoints

Following submission of the NDA and discussion with FDA during the review period, an updated analysis was applied to the HCV RNA data for defining virologic outcome, as described below:

Virologic outcome was updated based on the HCV RNA assessment in a visit window defined below:

- For subjects assigned total treatment duration of 24 weeks, the visit window was Week 32 to Week 78.
- For subjects assigned total treatment duration of 48 weeks, the visit window was Week 56 to Week 78.

In addition, LLOQ of 25 IU/mL was used to update the analysis of the virologic response in the follow-up period in the visit window.

Treatment success was defined as subjects who had HCV RNA <25 IU/mL at the last visit in the defined visit window. Relapse was defined as subjects who had HCV RNA <25 IU/mL at the end of treatment and ≥25 IU/mL at the last visit in the defined visit window.

6.1.3 Treatment Regimen

In all treatment groups, the dose of telaprevir was 750 mg q8h. Peg-IFN and RBV doses were in accordance with the package inserts for each drug.

6.1.4 Response Guided Therapy

In Studies 108 and 111, the total treatment duration for subjects in the telaprevir treatment groups was based on each subject's individual on-treatment virologic response (Table 5). In Study C216, the total treatment duration was 48 weeks.

Table 5 Virologic Response Criteria for Total Treatment Duration

Study	Treatment Group/Virologic Response Criteria	Peg-IFN/RBV Treatment Duration
Treatment-naive population		
Phase 3 studies		
Study 108	**Telaprevir treatment groups**	
	Undetectable HCV RNA at Weeks 4 and 12	24 weeks
	All other subjects	48 weeks
Study 111	**All subjects**	
	Undetectable HCV RNA at Weeks 4 and 12	24 or 48 weeks (randomized)
	All other subjects	48 weeks
Treatment-failure population		
Phase 3 study		
Study C216	NA	48 weeks

NA: not applicable

6.1.5 Detection and Quantitative Analysis of HCV RNA

Quantitative analysis of HCV RNA was performed using highly sensitive RT-PCR-based assays. Plasma HCV RNA levels were determined using the Roche COBAS TaqMan HCV/HPS assay (Version 2.0 for Phase 3 Studies). The lower limit of quantitation (LLOQ) was 25 IU/mL for the Version 2.0 assay. If HCV RNA values were < LLOQ, they were reported as either < 25 IU/mL, detected or < 25 IU/mL, undetected. When the term "undetectable" is used, this means the result was "< 25, undetected."

6.2 Pivotal Phase 3 Clinical Studies in Treatment Naive Subjects and Prior Treatment Nonresponders with Genotype 1 CHC

6.2.1 Study 108: A Phase 3 Study of 2 Dose Regimens of Telaprevir in Combination With Peg-interferon Alfa-2a (Pegasys®) and Ribavirin (Copegus®) in Treatment Naive Subjects with Genotype 1 CHC

6.2.1.1 Study Summary

- This study demonstrated the clinical benefit of telaprevir with an absolute, significant difference of 26% and 33% in SVR rates for the 8-week and 12-week T/PR regimens compared to standard Peg-IFN/RBV treatment.
- Clinical benefit was achieved across a broad range of subject subgroups, including some groups that traditionally have a worse outcome with the standard Peg-IFN/RBV treatment
- Subjects treated with a T/PR regimen who had eRVR and therefore had a 24-week planned treatment duration had a high SVR rate and low relapse rate, suggesting that a 24-week treatment duration was sufficient for subjects with eRVR

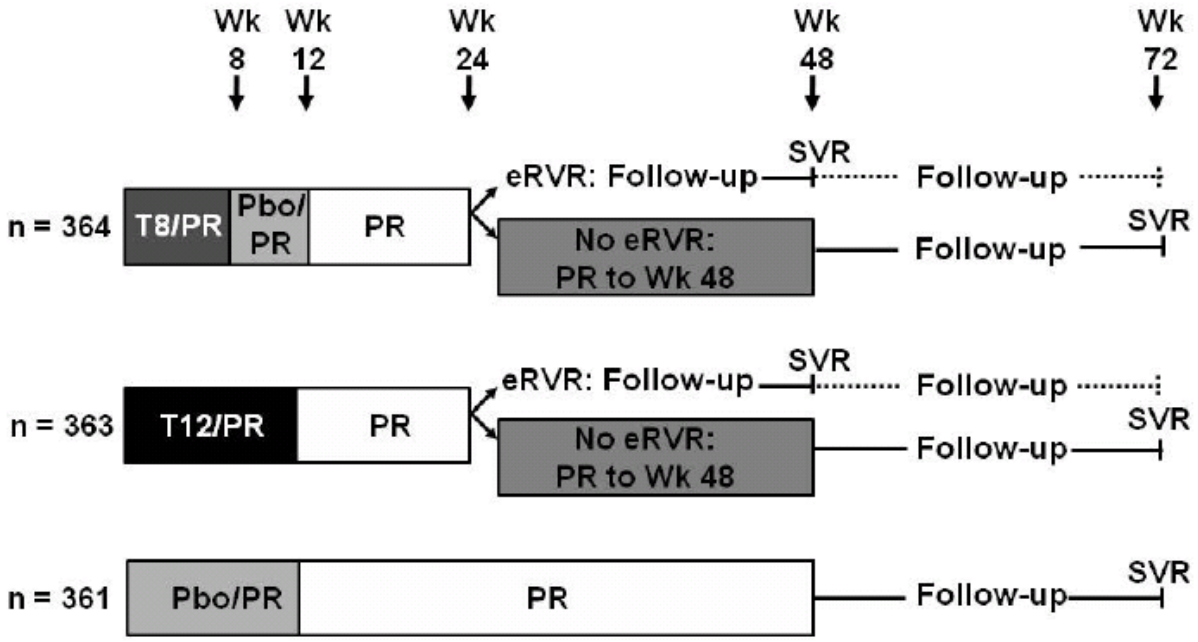
6.2.1.2 Study Design

Study 108 was a randomized, double-blind, placebo-controlled, multinational, multicenter study conducted in treatment-naive subjects with genotype 1 CHC. Subjects were enrolled at

study centers in Argentina, Austria, Australia, Canada, France, Germany, Israel, Italy, Poland, Spain, the United Kingdom, and the United States.

The study was designed to assess the superior efficacy of telaprevir dosed with Peg-IFN and RBV against standard treatment, Peg-IFN and RBV in treatment-naive subjects with CHC (Figure 10). Subjects were randomized to 1 of 3 treatment groups in a 1:1:1 ratio stratified by HCV genotype and baseline viral load.

Figure 10 Study 108 Design



eRVR = extended rapid viral response (undetectable HCV RNA at Week 4 AND Week 12.

6.2.1.3 Duration of Treatment

The telaprevir regimens were 24 or 48 weeks in duration, with telaprevir given in combination with Peg-IFN and RBV for either the first 8 weeks (T8/PR) or the first 12 weeks (T12/PR). For subjects who had undetectable HCV RNA at Week 4 and Week 12 (extended rapid virologic response [eRVR]), Peg-IFN and RBV were dosed for a total of 24 weeks. For subjects who did not achieve eRVR, Peg-IFN and RBV were dosed for a total of 48 weeks.

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

6.2.1.4 Endpoints and Statistical Considerations

The primary efficacy endpoint was SVR24. A key secondary efficacy endpoint was the proportion of subjects with SVR24 who received 24 total weeks of treatment because they had an eRVR compared to subjects who received 48 total weeks of treatment because they did not have an eRVR.

The primary analysis was a comparison of SVR rates in each of the T8/PR and T12/PR groups with the Pbo/PR group, using a logistic regression analysis model with SVR as dependent variable and treatment, HCV genotype subtype (1a, 1b, 1 unknown), and baseline HCV RNA plasma level as factors. *P* values and 95% CI were calculated to compare SVR rates between the Pbo/PR48 group and each telaprevir treatment group.

Virologic outcome was updated based on the HCV RNA assessment in a visit window defined below:

- For subjects assigned total treatment duration of 24 weeks, the visit window was Week 32 to Week 78.
- For subjects assigned total treatment duration of 48 weeks, the visit window was Week 56 to Week 78.

In addition, LLOQ of 25 IU/mL was used to update the analysis of the virologic response in the follow-up period in the visit window.

Treatment success was defined as subjects who had HCV RNA <25 IU/mL at the last visit in the defined visit window. Relapse was defined as subjects who had HCV RNA <25 IU/mL at the end of treatment and ≥25 IU/mL at the last visit in the defined visit window.

6.2.1.5 Demographics and Baseline Disease Characteristics

Demographics and baseline characteristics were well balanced among treatment groups (Table 6). Most subjects were male (58.5%), white (88.1%), and from North America (60.2%). The larger number of black and Hispanic subjects in T8/PR compared with T12/PR and Pbo/PR48 may have been because of increased randomization of subjects from North America to this group. Baseline disease characteristics were also similar among treatment groups.

Table 6 Study 108 Baseline Demographics and Disease Characteristics

	T12PR n = 363	T8PR n = 364	PR n = 361
Male gender, n (%)	214 (59)	211 (58)	211 (58)
Race[a], n(%)			
White	325 (90)	315 (87)	318 (88)
Black	26 (7)	40 (11)	28 (8)
Ethnicity, n (%)			
Hispanic/Latino	35 (10)	44 (12)	38 (11)
Median age, years (range)	49 (19 - 69)	49 (19 - 68)	49 (18 - 69)
Median BMI, kg/m2 (range)	26 (18 - 47)	26 (17 - 46)	26 (17 - 48)
HCV RNA ≥ 800,000 IU/mL[b], n (%)	281 (77)	279 (77)	279 (77)
HCV genotype subtype[c], n (%)			
1a	213 (59)	210 (58)	208 (58)
1b	149 (41)	151 (41)	151 (42)
1, unknown	1 (< 1)	3 (1)	2 (1)
Stage of fibrosis or cirrhosis, n (%)			
Bridging fibrosis	52 (14)	59 (16)	52 (14)
Cirrhosis	21 (6)	26 (7)	21 (6)

[a] Race and ethnicity were self-reported and not mutually exclusive; [b] Roche TaqMan® v2 LLOQ of 25 IU/mL; [c] 5'NC INNO-LiPA assay.

6.2.1.6 Subject Disposition

A total of 1,095 subjects were enrolled and randomized, of whom 7 discontinued before receiving their first dose of study drug. Therefore, the full analysis set included 1,088 subjects (Table 7). The majority of subjects (88.6%) completed the study, and most subjects who did not complete the study discontinued before their last planned dose of study drug. Of the 1,088 subjects who received at least 1 dose of study drug, 730 subjects completed assigned treatment. More subjects in the T8/PR and T12/PR telaprevir groups completed the assigned treatment than in the Pbo/PR group. The primary reason for the difference in treatment completion between the telaprevir groups and Pbo/PR48 group was the higher rate of discontinuation due to virologic failure in the Pbo/PR group.

Table 7 Study 108 Subject Disposition

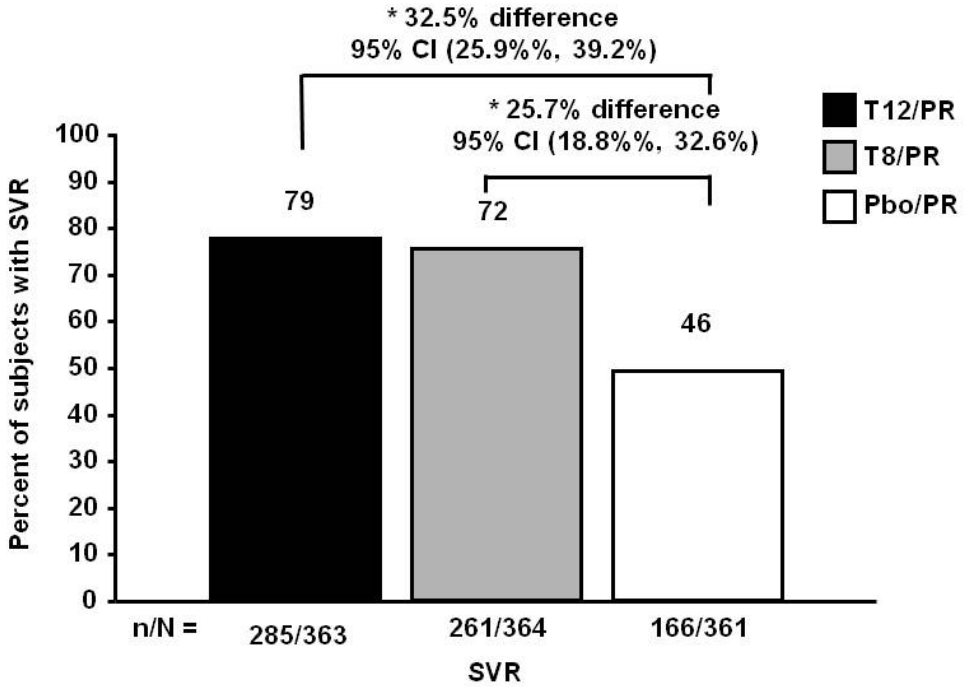
	Subjects, n (%) N = 1,088		
	T12/PR n = 363	**T8/PR n = 364**	**Pbo/PR n = 361**
Assigned to 24 wk	210 (58)	207 (57)	—
Assigned to 48 wk	153 (42)	157 (43)	—
Completed study	328 (90)	311 (85)	325 (90)
Completed treatment	268 (74)	260 (71)	202 (56)
Discontinued treatment	95 (26)	104 (29)	159 (44)
AEs	36 (10)	37 (10)	26 (7)
Virologic failure	39 (11)	40 (11)	118 (33)
Lost to follow-up	4 (1)	3 (1)	4 (1)
Other[a]	17 (5)	24 (7)	11 (3)

[a]The "Other" category includes subjects who discontinued due to noncompliance with study drug, other noncompliance, refused further treatment, and other reasons.

6.2.1.7 Efficacy Results

Significantly more subjects who received telaprevir had SVR24 compared with subjects in the no-telaprevir group (Figure 11). SVR rates were 72% in the T8/PR group, 79% in the T12/PR group, and 46% in the Pbo/PR48 group. The differences (95% CI) in SVR24 for T8/PR (25.7% [18.8%, 32.6%]) and T12/PR (32.5% [25.9%, 39.2%]) compared with Pbo/PR48 were statistically significant ($P < 0.0001$). The difference in SVR24 for T8/PR group versus T12/PR group was -6.8% (95% CI [-13.1%, -0.5%]).

Figure 11 Study 108 Rates of SVR24 for Telaprevir Plus Peg-IFN/RBV vs Peg-IFN/RBV Alone



* $P < .0001$.

Response-Guided Therapy

Rates of SVR24 for subjects in the T/PR groups who had eRVR and received 24 weeks treatment ranged from 87% to 92% (Table 8). By contrast, SVR24 rates for subjects in the T/PR groups who did not have eRVR and received 48 weeks treatment ranged from 52% to 60%. Thus, eRVR status had a positive predictive value for likelihood of achieving SVR24 when used to guide treatment duration decisions for the individual subject. However, SVR rates among non-eRVR subjects in the T/PR groups were higher than those in the Pbo/PR group, indicating that a proportion of these subjects received benefit from T/PR as well.

Table 8 Study 108 SVR24 Rates by eRVR Status

	T12/PR		T8/PR		Pbo/PR48	
	n	**n (%)**	**n**	**n (%)**	**n**	**n (%)**
Total	**363**	**285 (78.5)**	**364**	**261 (71.7)**	**361**	**166 (46.0)**
eRVR status[a]						
eRVR	212	195 (92.0)	207	179 (86.5)	29	27 (93.1)
non-eRVR	151	90 (59.6)	157	82 (52.2)	332	139 (41.9)

eRVR: extended rapid viral response; SVR: sustained viral response.

[a] For subjects in the T8/PR and T12/PR groups, subjects who had eRVR had a planned treatment duration of 24 weeks and subjects who did not have eRVR had a planned treatment duration of 48 weeks. For subjects in Pbo/PR48 group, efficacy endpoints by eRVR status are presented, but the eRVR status was not used to make any decisions on the treatment duration. All subjects in the Pbo/PR48 group had planned treatment duration of 48 weeks.

SVR by Ribavirin Dose Reductions

Ribavirin dose reductions and interruptions are sometimes required with standard Peg-IFN/RBV treatment and were also reported for telaprevir-based regimens containing Peg-IFN/RBV. In Study 108, 57% of subjects had at least one RBV dose reduction with or without at least 1 dose interruption (Table 9). However, the rates of SVR24 among these subjects were not adversely affected by ribavirin dose reductions.

Table 9 Study 108 SVR24 Rates by RBV Dose Reductions and Interruptions

	T12/PR		T8/PR		Pbo/PR	
	n (%)	SVR, n (%)	n	SVR, n (%)	n	SVR, n (%)
Total	**363**	**285 (78.5)**	**364**	**261 (71.7)**	**361**	**166 (46.0)**
No modifications	143	106 (74.1)	143	100 (69.9)	185	78 (42.2)
At least 1 dose reduction and no interruptions	80	66 (82.5)	73	50 (68.5)	51	27 (52.9)
At least 1 dose interruption and no reduction	0	0	0	0	0	0
At least 1 dose reduction and at least 1 dose interruption	140	113 (80.7)	148	111 (75.0)	124	61 (49.2)

SVR: sustained viral response.
[a] For RBV, 1 subjects is not included due to missing dosing data.

Subgroup Analysis

SVR24 rates were higher in the T/PR groups than in the Pbo/PR48 group in many subgroups, including populations that are difficult to treat with the standard treatment, such as subjects who were black or Hispanic/Latino, had cirrhosis or diabetes, or had high baseline levels of HCV RNA (Table 10, Figure 12). In some subgroups (age > 65 years, HCV genotype unknown) the low number of subjects resulted in wide confidence intervals, and the results should therefore be interpreted with caution.

Table 10 Study 108 SVR Rates By Select Demographics and Baseline Characteristics

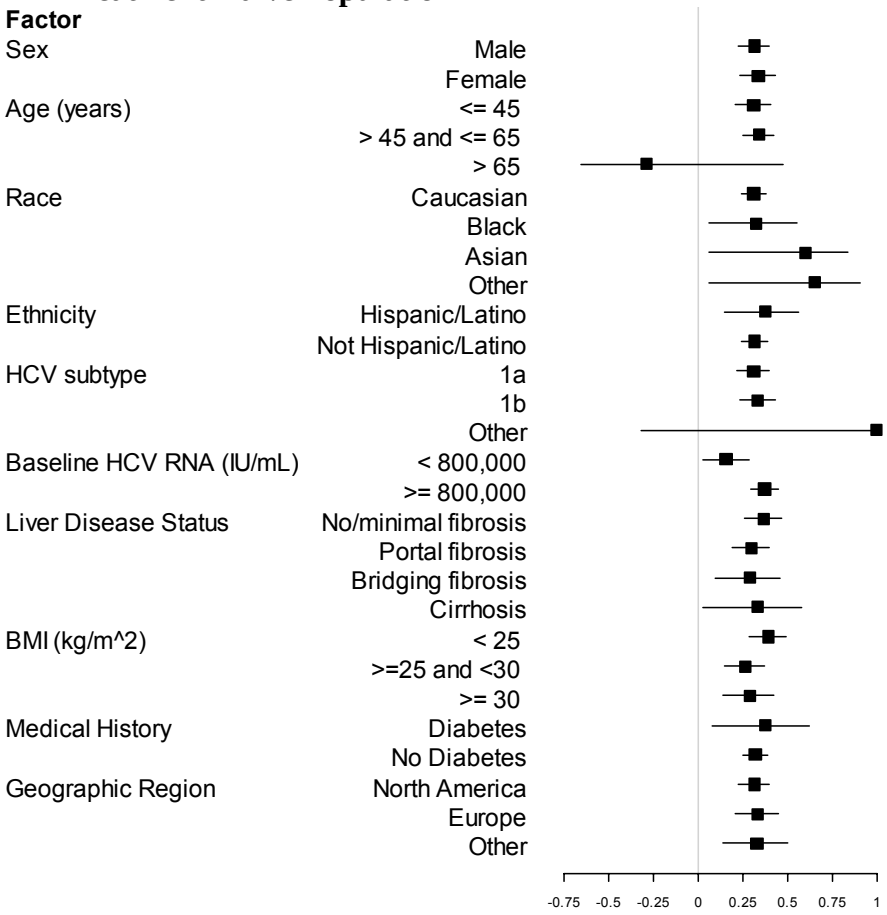
	T8/PR n = 364		T12/PR n = 363		Pbo/PR48 n = 361	
Variable	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**
Total	364	261 (71.7)	363	285 (78.5)	361	166 (46.0)
Sex						
Female	153	105 (68.6)	149	119 (79.9)	150	69 (46.0)
Male	211	156 (73.9)	214	166 (77.6)	211	97 (46.0)
Age, years						
≤45	139	111 (79.9)	142	123 (86.6)	143	79 (55.2)
> 45 and ≤ 65	222	147 (66.2)	214	157 (73.4)	216	85 (39.4)
> 65	3	3 (100)	7	5 (71.4)	2	2 (100)
BMI[a], kg/m^2						
< 25	145	108 (74.5)	155	133 (85.8)	130	60 (46.2)
≥ 25 and < 30	131	95 (72.5)	129	95 (73.6)	144	68 (47.2)
≥ 30	86	57 (66.3)	77	56 (72.7)	87	38 (43.7)
Race						
White	315	229 (72.7)	325	258 (79.4)	318	153 (48.1)
Black	40	24 (60.0)	26	16 (61.5)	28	8 (28.6)
Asian	5	5 (100)	5	5 (100)	10	4 (40.0)
Other	4	3 (75.0)	7	6 (85.7)	5	1 (20.0)
Ethnicity						
Hispanic or Latino	44	30 (68.2)	35	27 (77.1)	38	15 (39.5)
Not Hispanic or Latino	320	231 (72.2)	328	258 (78.7)	323	151 (46.7)
Region						
North America	227	154 (67.8)	214	159 (74.3)	214	91 (42.5)
Europe	100	80 (80.0)	104	87 (83.7)	106	53 (50.0)
Other[b]	37	27 (73.0)	45	39 (86.7)	41	22 (53.7)
Medical History						
Diabetes	23	11 (47.8)	21	15 (71.4)	21	7 (33.3)
No diabetes	341	250 (73.3)	342	270 (78.9)	340	159 (46.8)
HCV Genotype[c]						
1a	210	145 (69.0)	213	157 (73.7)	208	88 (42.3)
1b	151	115 (76.2)	149	127 (85.2)	151	78 (51.7)
1 (unknown)	3	1 (33.3)	1	1 (100)	2	0
Baseline HCV RNA (IU/mL)						
< 800,000	85	70 (82.4)	82	70 (85.4)	82	57 (69.5)
≥ 800,000	279	191 (68.5)	281	215 (76.5)	279	109 (39.1)
Liver Disease Status						
No cirrhosis	338	250 (73.9)	342	270 (78.9)	340	158 (46.5)
No or minimal fibrosis	128	106 (82.8)	134	114 (85.1)	147	71 (48.3)
Portal fibrosis	151	110 (72.8)	156	123 (78.8)	141	69 (48.9)
Bridging fibrosis	59	34 (57.6)	52	33 (63.5)	52	18 (34.6)
Cirrhosis	26	11 (42.3)	21	15 (71.4)	21	8 (38.1)

BMI: body mass index; SVR: sustained viral response.

[a] For BMI, 362 subjects in the T8/PR group and 361 subjects in the T12/PR group were assessed.

[c] 5'NC INNO-LiPA assay.

Figure 12 Study 108 Absolute Differences in SVR Rates between T12/PR and Control Groups and 95% CI for the Difference by Subpopulations in Treatment-Naive Population



On-Treatment Virologic Failure and Relapse

On-treatment virologic failure occurred predominantly in genotype 1a subjects. Sequencing analyses of NS3•4A in subjects who met a virologic stopping rule during the telaprevir treatment showed predominantly higher-level telaprevir-resistant variants. In contrast, subjects who met a virologic stopping rule during the Peg-IFN-alfa-2a and RBV treatment (after Week 12) had either lower-level (approximately 50%) or higher-level (approximately 50%) resistant variants.

Overall, the proportion of subjects with on-treatment virologic failure was higher in the T8/PR group than in the T12/PR group. While virologic failure rates during telaprevir treatment were similar in the T8/PR and T12/PR groups, higher rates of virologic failure were observed during the Peg-IFN-alfa-2a/RBV treatment (after Week 12) in the T8/PR group than in the T12/PR group, and there was more virologic failure with lower-level resistant variants. The increase in the proportion of lower-level telaprevir-resistance variants suggests that 8 weeks may not be a sufficient duration in some of subjects to fully clear lower-level variants and prevent subsequent failure during Peg-IFN-alfa-2a and RBV.

Relapse rates were low in subjects who completed their assigned treatment duration (5% in the T8/PR group and 7% in the T12/PR group). Relapse was generally associated with lower-level telaprevir-resistant variants in both the T8/PR group and T12/PR group.

The majority of subjects (66%) with resistant variants at the post-nadir time point no longer had resistant variants detected by population sequencing within Study 108 (median follow-up time of 46 weeks). Kaplan Meier estimates of the median time to loss of detectable resistant variants varied by NS3 position and ranged from 13 to 44 weeks.

6.2.1.8 Efficacy Conclusions for Study 108

The primary efficacy results observed in this Phase 3 study confirmed the efficacy results reported previously in the Phase 2 telaprevir program with an absolute, significant difference of 26% and 33% in SVR rates for the 8-week and 12-week T/PR regimens compared to standard Peg-IFN/RBV treatment ($P < 0.0001$). This clinical benefit was achieved across a broad range of subjects, including populations who historically have a low SVR rate when treated with standard Peg-IFN/RBV therapy.

Subjects treated with a T/PR regimen that had undetectable HCV RNA at Weeks 4 and 12, and therefore had response guided treatment duration of 24 weeks, had high SVR rates and low relapse rates, suggesting that a 24-week treatment duration was sufficient for subjects with eRVR.

The SVR rate in the T8/PR group (71.7%) was slightly lower than the SVR rate in the T12/PR group (78.9%). This difference may be due, in part, to the higher rate of on-treatment virologic failure during Peg-IFN/RBV treatment in the T8/PR regimen than in the T12/PR regimen, and more on-treatment virologic failure with lower-level resistant variants. This suggests a lower degree of antiviral pressure in the T8/PR group versus the T12/PR group, and that 8-week duration of telaprevir treatment may not have been sufficient in some subjects to fully clear lower-level resistant variants and prevent on-treatment virologic failure during subsequent Peg-IFN/RBV treatment.

Subjects with on-treatment virologic failure during telaprevir treatment had predominantly higher-level telaprevir-resistant variants, suggesting that the T/PR regimen was able to suppress wild-type and lower-level telaprevir-resistant variants. Relapse was generally associated with lower-level resistant variants, and the spectrum of variants was similar between the T8/PR and T12/PR groups.

The majority of subjects (66%) with resistant variants at the post-nadir time point no longer had resistant variants detected by population sequencing within Study 108 (median follow-up time of 46 weeks).

6.2.2 Study C216: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study With Telaprevir in Subjects With Genotype 1 CHC Infection Who Failed Prior Treatment With Pegylated Interferon (Peg-IFN, Peg-IFN-alfa-2a, or Peg-IFN-alfa-2b) Plus Ribavirin (RBV)

6.2.2.1 Study Summary

- The results of this study demonstrated the superior efficacy of telaprevir in combination with Peg-IFN/RBV compared to standard Peg-IFN/RBV treatment in subjects with genotype 1 CHC infection who did not have SVR after prior treatment with Peg-IFN/RBV.
- This clinical benefit was achieved across a broad range of subjects, including populations who historically have a low SVR rate when treated with standard Peg-IFN/RBV therapy (subjects who were black, were Hispanic or Latino, had cirrhosis, had high baseline levels of HCV RNA, or had prior null response to Peg-IFN/RBV therapy).
- The superior efficacy of regimens that included telaprevir was shown consistently and robustly in all categories by response to prior treatment with Peg-IFN/RBV, including subjects with prior relapse, prior null response, and prior partial response, with a 3- to 5-fold increase in SVR rate compared to control across the 3 major categories of treatment failure subjects.

6.2.2.2 Study Design

Study C216 was a randomized, double-blind, placebo-controlled, multicenter study in subjects with genotype 1 CHC who did not have SVR after prior treatment with Peg-IFN/RBV.

Subjects were enrolled at study sites in Argentina, Australia, Austria, Belgium, Brazil, Canada, Switzerland, Germany, Spain, France, the United Kingdom, Israel, Italy, The Netherlands, Poland, Sweden, and the United States.

Subjects were randomized to 1 of 3 treatment groups in a 2:2:1 ratio. Randomization was stratified based on baseline HCV RNA value and on type of prior response (prior nonresponse and prior relapse). Additional stratification was based on type of prior nonresponse (null response and partial response).

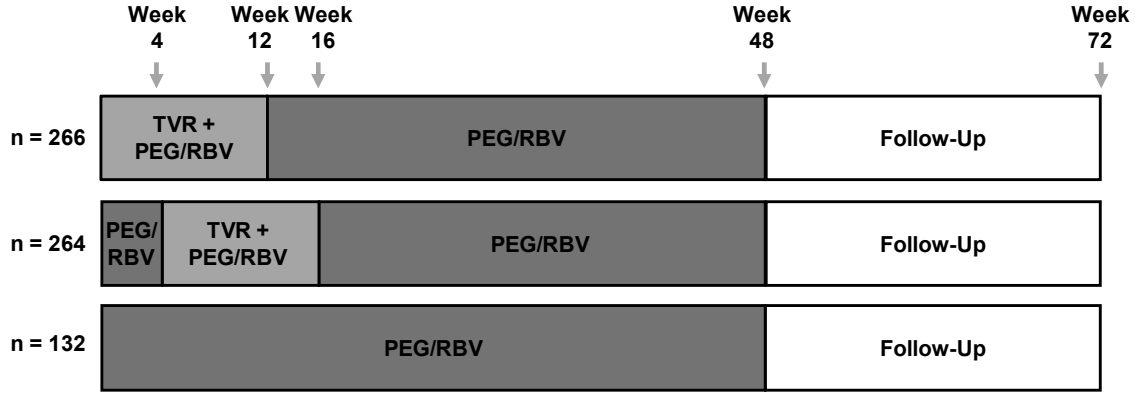
Study C216 assessed (1) the efficacy of telaprevir in combination with Peg-IFN and RBV compared to standard treatment in treatment-failure subjects and (2) the effect of a lead in of telaprevir after a 4-week treatment with Peg-IFN/RBV. The study consisted of a screening period of approximately 4 weeks, a 48-week treatment period, and 24-week follow-up period (Figure 13).

6.2.2.3 Study Population

In addition to the inclusion and exclusion criteria in Section 6.1.1, subjects in Study C216 had either prior nonresponse (never had undetectable HCV RNA during prior treatment) or prior relapse to prior treatment with Peg-IFN/RBV. Prior nonresponse was further categorized as prior null response (< 2 $\log_{10}$ decrease in HCV RNA at Week 12 compared to baseline HCV RNA level) or prior partial response ($\geq$ 2-$\log_{10}$ decrease in HCV RNA at

Week 12 compared to baseline HCV RNA level). Subjects with prior viral breakthrough were excluded. Study design is shown in Figure 13.

Figure 13 Study C216 Design



6.2.2.4 Dose and Duration of Treatment

Two telaprevir regimens, with and without lead in were compared to standard therapy with Peg-IFN/RBV. The 3 treatment groups were randomized in a 2:2:1 ratio, with planned total treatment duration of 48 weeks:

- Treatment group A: telaprevir in combination with Peg-IFN/RBV for 12 weeks; followed by placebo in combination with Peg-IFN/RBV for 4 weeks; followed by Peg-IFN/RBV for 32 weeks
- Treatment group B: placebo in combination with Peg-IFN/RBV for 4 weeks; followed by telaprevir in combination with Peg-IFN/RBV for 12 weeks; followed by Peg-IFN/RBV for 32 weeks
- Treatment group C: placebo in combination with Peg-IFN/RBV for 16 weeks; followed by Peg-IFN/RBV for 32 weeks

After EOT (Week 48 or having discontinued earlier), subjects were followed until 24 weeks after last planned dose in order to assess SVR in subjects with undetectable HCV RNA levels or to collect samples for viral sequencing in the case of detectable HCV RNA or relapse during follow-up.

6.2.2.5 Endpoints and Statistical Considerations

The primary efficacy endpoint was SVR24. The primary analysis for the primary endpoint was a comparison of each of the T12/PR48 and T12(LI)/PR48 groups with the Pbo/PR48 group, using a logistic regression analysis model with SVR as dependent variable and treatment, type of prior response and their interaction, and baseline HCV RNA plasma level as factors. *P* values and 95% CI were calculated to compare SVR rates between the Pbo/PR48 group and each telaprevir treatment group. Analyses were performed separately for the prior relapse population and the prior nonresponse population.

Virologic outcome was updated based on the HCV RNA assessment in a visit window defined as Week 56 to Week 78. In addition, LLOQ of 25 IU/mL was used to determine the virologic response in the follow-up period in the visit window. Treatment

success was defined as subjects who had HCV RNA <25 IU/mL at the last visit in the defined visit window. Relapse was defined as subjects who had HCV RNA <25 IU/mL at the end treatment and ≥25 IU/mL at the last visit in the defined visit window.

6.2.2.6 Demographics and Baseline Disease Characteristics

The majority of subjects in this study were male, white, and between 45 and 65 years old (Table 11). Demographic characteristics were comparable across treatment groups and across subpopulations by prior response. The baseline disease characteristics were comparable across treatment groups and were comparable between the prior relapser and non-responder subpopulations, except for baseline HCV RNA level and severity of liver disease.

Table 11 Study C216 Baseline Demographics and Characteristics

	T12/PR48	T12(LI)/PR48	Pbo/PR48	All subjects
Prior Relapser Population	**(n = 145)**	**(n = 141)**	**(n = 68)**	**(n = 354)**
Male, n (%)	98 (67.6)	99 (70.2)	46 (67.6)	243 (68.6)
White, n (%)	132 (91.0)	136 (96.5)	61 (89.7)	329 (92.9)
Mean age, years (SD)	51.1 (8.54)	50.8 (7.99)	51.0 (9.72)	51.0 (8.55)
Mean BMI, kg/m² (SD)	27.6 (4.86)	27.0 (4.78)	27.6 (4.22)	27.3 (4.71)
Mean Log_{10} HCV RNA, copies (SD)	6.5 (0.62)	6.4 (0.64)	6.5 (0.63)	6.5 (0.63)
Viral load ≥ 800,000, n (%)	124 (85.5)	115 (81.6)	56 (82.4)	295 (83.3)
Cirrhosis, n (%)	28 (19.3)	29 (20.6)	15 (22.1)	72 (20.3)
Prior Non-Responder Population	**(n = 121)**	**(n = 123)**	**(n = 64)**	**(n = 308)**
Male, n (%)	85 (70.2)	90 (73.2)	42 (65.6)	217 (70.5)
White, n (%)	114 (94.2)	116 (94.3)	56 (87.5)	286 (92.9)
Mean age, years (SD)	50.2 (8.49)	51.2 (8.56)	48.6 (9.69)	50.3 (8.80)
Mean BMI, kg/m² (SD)	27.7 (5.24)	27.4 (4.85)	27.2 (5.03)	27.4 (5.03)
Mean Log_{10} HCV RNA, copies (%)	6.7 (0.43)	6.7 (0.42)	6.7 (0.50)	6.7 (0.44)
Viral load ≥ 800,000, n (%)	114 (94.2)	119 (96.7)	58 (90.6)	291 (94.5)
Cirrhosis, n (%)	44 (36.4)	38 (30.9)	15 (23.4)	97 (31.5)

6.2.2.7 Subject Disposition

A total 662 subjects were randomized (Table 12). Of the 662 subjects who were treated, 354 (53.5%) subjects were prior relapsers and 308 (46.5%) subjects were prior non-responders. Among the prior non-responder population, 184 (59.7%) subjects were prior null responders and 124 (40.3%) subjects were partial responders.

Table 12 Study C216 Subject Disposition

	Subjects, n (%)					
	Prior relapsers n = 354			Prior non-responders n = 308		
	T12/PR n = 145	T12(LI)/PR n = 141	Pbo/PR n = 68	T12/PR n = 121	T12(LI)/PR n = 123	Pbo/PR n = 64
Completed	111 (76.6)	121 (85.8)	61 (89.7)	80 (66.1)	91 (74.0)	27 (42.2)
Discontinued	34 (23.4)	20 (14.2)	7 (10.3)	41 (33.9)	32 (26.0)	37 (57.8)
AE	27 (18.6)	15 (10.6)	1 (1.5)	12 (9.9)	14 (11.4)	3 (4.7)
Noncompliance	0	2 (1.4)	0	1 (0.8)	0	2 (3.1)
Virologic failure	2 (1.4)	0	4 (5.9)	24 (19.8)	16 (13.0)	31 (48.4)
Other	5 (3.4)	3 (2.1)	2 (2.9)	4 (3.3)	2 (1.6)	1 (1.6)

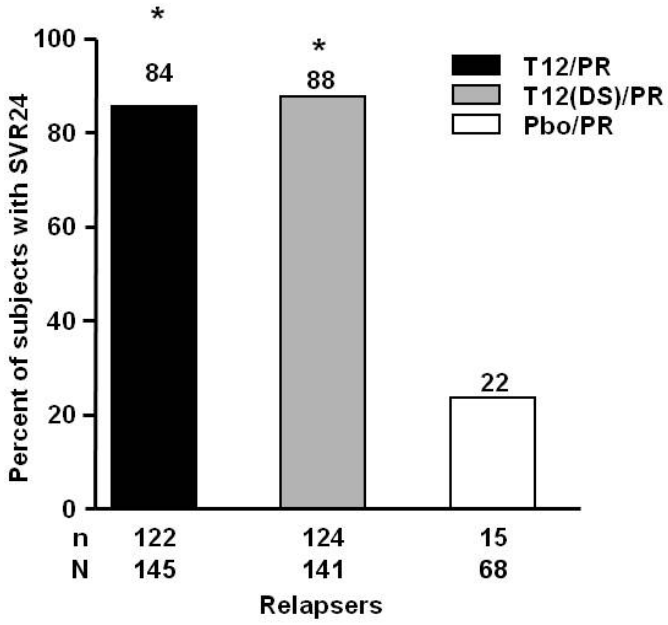
6.2.2.8 Efficacy Results

In prior relapsers and nonresponders, SVR24 rates were statistically significantly higher in the telaprevir treatment groups compared with the placebo group (all *P* values < 0.001).

In prior relapsers, SVR rates were 84% to 88% in the telaprevir treatment groups and 22% in the Pbo/PR48 group. In prior partial responders, SVR rates were 56% to 61% in the telaprevir treatment groups and 15% in the Pbo/PR48 group. In prior null responders, SVR rates were 31% to 33% in the telaprevir treatment groups and 5% in the Pbo/PR48 group.

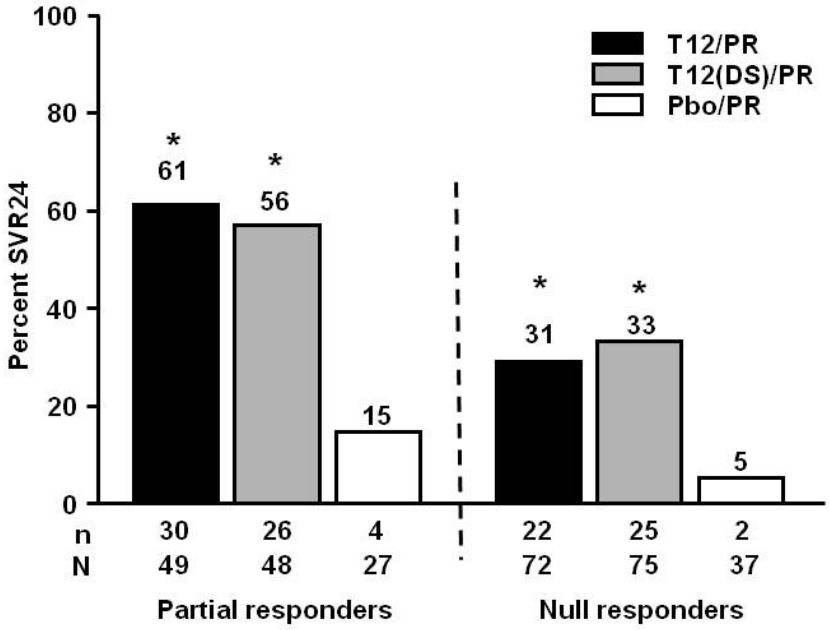
In the prior relapse population, the differences in SVR24 rate for the T12/PR48 and T12(LI)/PR48 groups compared with the Pbo/PR48 group were 62% and 66%, respectively (Figure 14). In the prior partial responder population, the SVR24 rates were 61% and 56% for the T12/PR48 and T12(LI)/PR48 groups compared with 15% for the Pbo/PR48 group, and in the null responder population, the SVR rates were 31% and 33% for the T12/PR48 and T12(LI)/PR48 groups compared with 5% for the Pbo/PR48 group (Figure 15).

Figure 14 Study C216 SVR Rates in Prior Relapsers



* *P* < .001 vs Pbo/PR.
DS: lead-in with telaprevir

Figure 15 Study C216 SVR Rates in Prior Partial Responders and Null Responders



* *P* < .001 vs Pbo/PR.

DS: lead-in with telaprevir

SVR by Ribavirin Dose Reductions

Apart from permanent discontinuation, RBV dose reductions due to AE did not appear to affect the SVR24 rates in the telaprevir groups (Table 13). The number of subjects per subgroup by RBV dose modification in the Pbo/PR48 group was too small to draw meaningful conclusions.

Table 13 Study C216 SVR24 Rates by RBV Dose Reductions

Subgroup Status	Relapser population							
	T12/PR48		T12(LI)/PR48		Pooled T/PR48		Pbo/PR48	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Total	145	121 (83.4)	141	124 (87.9)	286	245 (85.7)	68	16 (23.5)
Action taken towards RBV due to AE								
Permanent discontinuation	16	5 (31.3)	7	1 (14.3)	23	6 (26.1)	4	1 (25.0)
Temporary discontinuation	14	13 (92.9)	14	13 (92.9)	28	26 (92.9)	2	0
Dose reduced	42	39 (92.9)	41	37 (90.2)	83	76 (91.6)	9	3 (33.3)
No interruption/dose reduction	73	64 (87.7)	79	73 (92.4)	152	137 (90.1)	53	12 (22.6)
	Prior Non-responder population							
Total	121	50 (41.3)	123	51 (41.5)	244	101 (41.4)	64	6 (9.4)
Action taken towards RBV due to AE								
Permanent stop	9	0	13	3 (23.1)	22	3 (13.6)	4	0
Temporary stop	4	3 (75.0)	9	2 (22.2)	13	5 (38.5)	1	0
Dose reduced	26	13 (50.0)	24	14 (58.3)	50	27 (54.0)	7	1 (14.3)
No interruption/dose reduction	82	34 (41.5)	77	32 (41.6)	159	66 (41.5)	52	5 (9.6)

N: number of subjects with data; n: number of subjects with SVR

Subgroup Analysis

Among prior relapsers and prior non-responders, SVR24 rates were higher in each telaprevir group than in the Pbo/PR48 group across subgroups by sex, ethnicity, age, and BMI (Table 14). SVR24 rates were higher in each telaprevir group than in the Pbo/PR48 group in white subjects, but number of subjects in the other subgroups by race was too low to allow meaningful comparison across treatment groups. No consistent differences in SVR24 rates across demographic subgroups were observed in the telaprevir groups among prior relapsers or prior non-responders.

The number of subjects in some of the subgroups by baseline disease characteristics was small and results should therefore be interpreted with caution (Table 15). Some 95% CIs were very wide due to a low number of subjects in the subgroup, especially in the populations of prior null-responders and prior partial responders.

Table 14 Study C216 SVR24 Rates by Demographics

Subgroup Status	T12/PR48		T12(LI)/PR48		Pbo/PR48	
	N	n (%)	N	n (%)	N	n (%)
			Prior relapser population			
Total	145	122 (84.1)	141	124 (87.9)	68	15 (22.1)
Sex						
Female	47	41 (87.2)	42	36 (85.7)	22	7 (31.8)
Male	98	81 (82.7)	99	88 (88.9)	46	8 (17.4)
Race						
Black	7	6 (85.7)	4	4 (100)	3	2 (66.7)
White	132	110 (83.3)	136	119 (87.5)	61	13 (21.3)
Asian	3	3 (100)	1	1 (100)	3	0
Age (years)						
≤ 45	32	27 (84.4)	31	27 (87.1)	18	4 (22.2)
45 <age ≤ 65	111	93 (83.8)	107	96 (89.7)	44	11 (25.0)
> 65	2	2 (100)	3	1 (33.3)	6	0
Baseline BMI (kg/m^2)						
< 25	45	37 (82.2)	50	43 (86.0)	19	4 (21.1)
25 ≤ BMI < 30	62	53 (85.5)	59	53 (89.8)	29	6 (20.7)
≥ 30	38	32 (84.2)	32	28 (87.5)	20	5 (25.0)
			Prior partial responder population			
Total	49	30 (61.2)	48	27 (56.3)	27	4 (14.8)
Sex						
Female	20	11 (55.0)	11	5 (45.5)	12	1 (8.3)
Male	29	19 (65.5)	37	22 (59.5)	15	3 (20.0)
Race						
Black	2	1 (50.0)	2	0	6	2 (33.3)
White	46	29 (63.0)	46	27 (58.7)	21	2 (9.5)
Asian	1	1 (100)	0	NA	0	NA
Age (years)						
≤45	11	10 (90.9)	11	6 (54.5)	9	1 (11.1)
45 <age ≤65	36	19 (52.8)	34	20 (58.8)	17	3 (17.6)
>65	2	1 (50.0)	3	1 (33.3)	1	0
Baseline BMI (kg/m^2)						
<25	18	11 (61.1)	12	8 (66.7)	9	2 (22.2)
25 ≤BMI <30	21	15 (71.4)	24	12 (50.0)	11	0
≥30	10	4 (40.0)	11	6 (54.5)	7	2 (28.6)

Table 14 Study C216 SVR24 Rates by Demographics

Subgroup Status	T12/PR48		T12(LI)/PR48		Pbo/PR48	
	N	n (%)	N	n (%)	N	n (%)
			Prior null responder population			
Total	72	22 (30.6)	75	25 (33.3)	37	2 (5.4)
Sex						
Female	16	2 (12.5)	22	8 (36.4)	10	1 (10.0)
Male	56	20 (35.7)	53	17 (32.1)	27	1 (3.7)
Race						
Black	2	1 (50.0)	2	0	2	0
White	68	19 (27.9)	70	24 (34.3)	35	2 (5.7)
Asian	2	0	1	1 (110)	0	NA
Age (years)						
≤45	21	8 (38.1)	13	5 (38.5)	13	1 (7.7)
45 <age ≤65	50	14 (28.0)	60	18 (30.0)	24	1 (4.2)
>65	1	0	2	2 (100)	0	NA
Baseline BMI (kg/m^2)						
<25	22	6 (27.3)	27	9 (33.3)	14	1 (7.1)
25 ≤BMI <30	25	11 (44.0)	29	12 (41.4)	13	0
≥30	25	5 (20.0)	19	4 (21.1)	10	1 (10.0)

Table 15 Study C216 SVR24 Rates by Baseline Disease Characteristics

	T12/PR48		T12(LI)/PR48		Pbo/PR48	
Subgroup Status	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**
			Relapser population			
Total	145	122 (84.1)	141	124 (87.9)	68	15 (22.1)
Genotype (NS3 method)						
1a	65	52 (80.0)	77	67 (87.0)	34	9 (26.5)
1b	77	68 (88.3)	63	56 (88.9)	31	6 (19.4)
Baseline liver disease status						
No or minimal fibrosis	34	30 (88.2)	48	42 (87.5)	20	7 (35.0)
Portal fibrosis	47	38 (80.9)	38	35 (92.1)	18	5 (27.8)
Bridging fibrosis	36	31 (86.1)	26	22 (84.6)	15	2 (13.3)
Cirrhosis	28	23 (82.1)	29	25 (86.2)	15	1 (6.7)
			Prior partial responder population			
Total	49	30 (61.2)	48	27 (56.3)	27	4 (14.8)
Genotype (NS3 method)						
1a	26	14 (53.8)	29	14 (48.3)	16	3 (18.8)
1b	22	15 (68.2)	18	12 (66.7)	10	1 (10.0)
Baseline liver disease status						
No or minimal fibrosis	7	6 (85.7)	11	7 (63.6)	10	0
Portal fibrosis	17	13 (76.5)	12	10 (83.3)	7	3 (42.9)
Bridging fibrosis	7	5 (71.4)	11	5 (45.5)	5	0
Cirrhosis	18	6 (33.3)	14	5 (35.7)	5	1 (20.0)
			Prior null responder population			
Total	72	22 (30.6)	75	25 (33.3)	37	2 (5.4)
Genotype (NS3 method)						
1a	45	12 (26.7)	43	13 (30.2)	17	1 (5.9)
1b	27	10 (37.0)	32	12 (37.5)	20	1 (5.0)
Baseline liver disease status						
No or minimal fibrosis	10	1 (10.0)	9	6 (66.7)	5	0
Portal fibrosis	19	8 (42.1)	21	9 (42.9)	13	1 (7.7)
Bridging fibrosis	17	8 (47.1)	21	8 (38.1)	9	0
Cirrhosis	26	5 (19.2)	24	2 (8.3)	10	1 (10.0)

On-treatment Virologic Failure and Relapse

On-treatment virologic failure was more frequent in prior null-responders with genotype 1a CHC. Higher-level telaprevir-resistant variants were more frequent in subjects with virologic failure during the telaprevir/Pbo treatment phase, suggesting that this regimen was successful at inhibiting wild-type and lower-level telaprevir-resistant variants. Virologic failure during the Peg-IFN-alfa-2a and RBV treatment phase was associated with higher-level and lower-level telaprevir-resistant variants, or wild-type virus.

The relapse rates in subjects in the T/PR groups were 7% to 9% in subjects with prior relapse, 27% to 28% in subjects with prior partial response and 30% to 31% in subjects with prior null response. Relapse was generally associated with lower-level telaprevir-resistant variants or wild-type virus.

A total of 58% of subjects with resistant variants at the post-nadir time point no longer had resistant variants detected by population sequencing at their last visit in Study C216 (median follow-up time of 46 weeks). The median time to loss of detectable telaprevir-resistant variants ranged from 12 to 63 weeks and varied by NS3 position.

6.2.2.9 Efficacy Conclusions for Study C216

The primary efficacy results confirmed the clinical benefit reported previously in the Phase 2 telaprevir program in the treatment-failure population. The results of this study demonstrated the superior efficacy of telaprevir in combination with Peg-IFN/RBV compared to standard Peg-IFN/RBV treatment in subjects with genotype 1 CHC who did not have SVR after prior treatment with Peg-IFN/RBV. The superior efficacy of regimens that included telaprevir was shown consistently and robustly in all categories by response to prior treatment with Peg-IFN/RBV, including subjects with prior relapse, prior null response, and prior partial response.

The proportion of subjects with on-treatment virologic failure was lower among subjects receiving telaprevir than among control subjects. For prior relapsers, on-treatment virologic failure was infrequent in the telaprevir groups and occurred in 1.4% of subjects in the T12/PR48 group, 0.7% in the T12(LI)/PR48 group, and 26.5% in the Pbo/PR48 group. For prior non-responders on-treatment virologic failure occurred in 41.3% of subjects in the T12/PR48 group, 35.8% in the T12(LI)/PR48 group, and 78.1% in the Pbo/PR48 group. On-treatment virologic failure in subjects receiving telaprevir (18.3%, 97/530) was more frequent in prior null-responders and genotype 1a subjects. Subjects who had virologic failure during the telaprevir/placebo treatment phase had predominantly higher-level telaprevir-resistant variants, suggesting that the T/PR regimen was successful at inhibiting wild-type and lower-level telaprevir-resistant variants.

Relapse rates were lower in subjects receiving telaprevir than in control subjects for prior relapsers and prior non-responders. In prior relapsers, the rate of relapse was 9%, 7%, and 69% in the T12/PR48, T12(LI)/PR48, and Pbo/PR48 groups, respectively. In prior partial responders, the rate of relapse was 28%, 27%, and 33% in the T12/PR48, T12(LI)/PR48, and Pbo/PR48 groups, respectively. In prior null responders, the rate of relapse was 31%, 30%, and 71% in the T12/PR48, T12(LI)/PR48, and Pbo/PR48 groups, respectively. Relapse was generally associated with lower-level telaprevir-resistant variants or wild-type virus.

In 58% (60/104) of subjects with telaprevir-resistant variants at the post-nadir time point, resistant variants were no longer detected by population sequence analysis at the end of the study (median follow-up time 46.4 weeks), suggesting that the distribution of viral variants may return to pre-treatment levels over time.

Overall, a lead-in with telaprevir relative to Peg-IFN and RBV did not result in added clinical benefit relative to simultaneous start of telaprevir and Peg-IFN/RBV:

- SVR24 rates were similar between the T12/PR48 and T12(LI)/PR48 groups for prior relapsers, prior partial responders, and prior null responders. The difference in SVR24 rates (T12/PR48 versus T12(LI)/PR48) with 95% CI was -4% (-6.4%, 10.4%) for prior relapsers, 5% (-26.2%, 12.64%) for prior partial responders, and -2% (-12.3%, 17.7%) for prior null responders.

- Subgroup analysis did not identify any particular subgroup that would benefit from a lead-in with telaprevir. Differences were observed, but numbers of subjects were small, and subgroup analysis did not reveal a consistent trend in favor of a lead-in with telaprevir versus simultaneous treatment with telaprevir in combination with Peg-IN/RBV.
- No differences were noted in the on-treatment virologic failure or relapse rate, or type of emerging viral variants between the T12/PR48 and T12(LI)/PR48 arms.

6.3 Supportive Phase 3 Clinical Study

6.3.1 Study 111: A Randomized Study of Stopping Treatment at 24 Weeks or Continuing Treatment to 48 Weeks in Treatment-Naive Subjects with Genotype 1 CHC who Achieve an Extended Rapid Viral Response While Receiving Telaprevir, Peg-interferon alfa 2a (Pegasys®), and Ribavirin (Copegus®)

6.3.1.1 Study Summary

- The overall primary efficacy analysis demonstrates the non-inferiority of the T12/PR24/eRVR+ regimen to the T12/PR48/eRVR+ regimen
- SVR24 rate was high (73.7%) across the entire study population relative to the historical standard of care (38% to 46% SVR), and was similar to the SVR rates observed in the telaprevir treatment arms in Study 108. SVR24 rates in the randomized eRVR+ arms were 92.0% for the T12/PR24 group and 90.0% for the T12/PR48 group.
- This clinical benefit was achieved across a broad range of subjects, including populations that traditionally have a worse outcome with the standard Peg-IFN/RBV treatment (subjects who were black or Hispanic/Latino; or who had cirrhosis, diabetes, or high baseline HCV RNA levels).

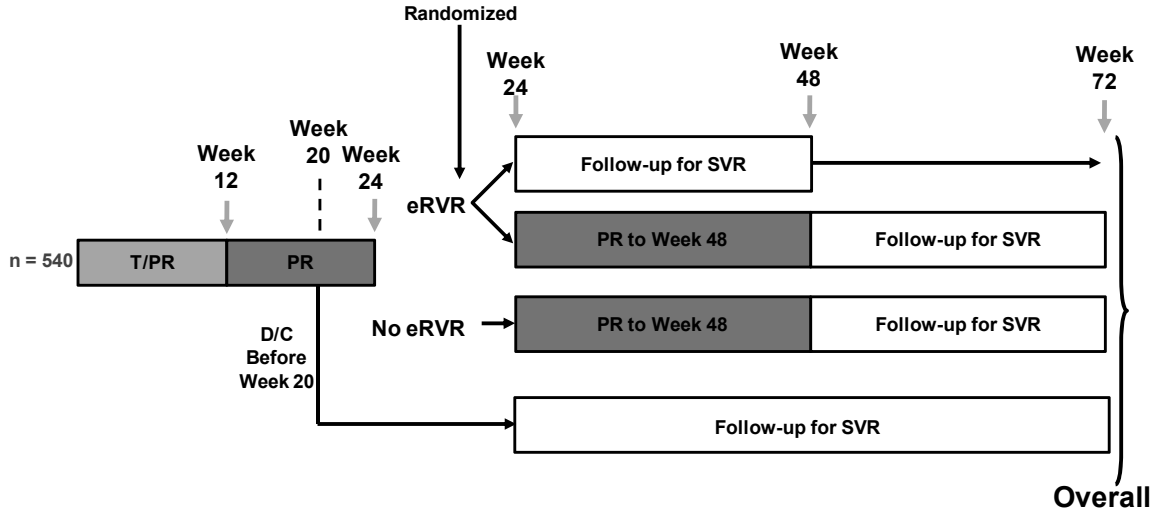
6.3.1.2 Study Design

A randomized, open-label, multicenter study of stopping treatment at 24 weeks or continuing treatment to 48 weeks in treatment-naive subjects with genotype 1 CHC who achieve an extended rapid viral response (eRVR) while receiving telaprevir, Peg-IFN and RBV.

Subjects were enrolled at study sites in Belgium, The Netherlands, and the United States (including Puerto Rico).

Study 111 was designed to determine whether 24 week duration of Peg-IFN/RBV in combination with 12 weeks of telaprevir was non inferior to 48 week duration of Peg-IFN/RBV in combination with 12 weeks of telaprevir with respect to SVR rates in subjects with undetectable HCV RNA at Weeks 4 and 12 (Figure 16).

Figure 16 Study 111 Design



6.3.1.3 Dose and Duration of Treatment

All subjects were assigned to receive a treatment regimen of telaprevir for 12 weeks in combination with Peg-IFN/RBV for at least 24 weeks. Subjects who had undetectable HCV RNA at Weeks 4 and 12 were randomized at Week 20 to either stop study drug treatment at Week 24 (T12/PR24 group) or to continue Peg-IFN/RBV treatment through Week 48 (T12/PR48 group). For subjects who did not have undetectable HCV RNA at Weeks 4 and 12, Peg-IFN/RBV dosing was planned for 48 weeks. Subjects who prematurely discontinued treatment before Week 20 were not randomized or assigned to a treatment regimen.

6.3.1.4 Endpoints and Statistical Considerations

The primary efficacy endpoint was SVR24. The primary comparison was based on CI estimates to rule out the inferiority of the T12/PR24 treatment regimen to the T12/PR48 treatment regimen among subjects with undetectable HCV RNA at Weeks 4 and 12. This was estimated by evaluating the treatment differences in the SVR rates (eRVR+ T12/PR24 minus eRVR+ T12/PR48) and the 95% CI for these groups, such that the entire 2-sided CI is to the right of the pre-defined non-inferiority margin of -10.5%.

SVR rates overall, SVR rates by demographic and baseline characteristics, and relapse rates were updated based on the HCV RNA assessment in a visit window defined below:

- For subjects assigned total treatment duration of 24 weeks, the visit window was Week 32 to Week 78.
- For subjects assigned total treatment duration of 48 weeks, the visit window was Week 56 to Week 78.

In addition, LLOQ of 25 IU/mL was used to update the analysis of the virologic response in the follow-up period in the visit window. Treatment success was defined as subjects who had HCV RNA <25 IU/mL at the last visit in the defined visit window. Relapse was defined as subjects who had HCV RNA <25 IU/mL at the end of treatment and ≥25 IU/mL at the last visit in the defined visit window.

All other analyses were performed as specified in the study statistical analysis plan.

The final analysis of the primary efficacy endpoint was based on CI estimates to rule out the inferiority of the 24-week total treatment regimen (T12/PR24/eRVR+ group) relative to the 48-week treatment regimen (T12/PR48/eRVR+ group). That is, the 24-week treatment regimen would be declared non-inferior to the 48-week treatment regimen if the lower limit of the 2-sided 95% CI on the observed treatment difference between the T12/PR24/eRVR+ group and the T12/PR48/eRVR+ group was greater than the non-inferiority margin, -10.5%.

6.3.1.5 Baseline Demographics and Disease Characteristics

The majority of subjects in the study were male, white, and from North America (Table 16). Subject demography was generally similar across all treatment groups. HCV disease characteristics were similar across all treatment groups.

Table 16 Study 111 Baseline Demographics and Characteristics

	Overall n = 540	**T12PR24 n = 162**	**T12PR48 n = 160**
Male gender, n (%)	325 (60)	104 (64)	97 (61)
Race[a], n(%)			
White	427 (79)	135 (83)	131 (82)
Black	73 (14)	17 (10)	17 (11)
Ethnicity, n (%)			
Hispanic/Latino	54 (10)	18 (11)	11 (7)
Median age, years (range)	51(19 - 70)	51 (22 - 70)	50(19 - 67)
Median BMI, kg/m^2 (range)	27(18 - 54)	28(18 - 53)	27(19 - 49)
HCV RNA ≥ 800,000 IU/mL, n (%)	445 (82)	124 (77)	126 (78)
HCV genotype subtype[c], n (%)			
1a	388 (72)	115 (71)	117 (73)
1b	149 (28)	46 (28)	43 (27)
1, unknown	3 (1)	1 (1)	0
Stage of fibrosis or cirrhosis, n (%)			
Bridging fibrosis	88 (16)	20 (12)	21 (13)
Cirrhosis	61 (11)	18 (11)	12 (8)

[a] Race and ethnicity were self-reported and not mutually exclusive.

6.3.1.6 Subject Disposition

A total of 544 subjects were enrolled, and 4 subjects discontinued the study before receiving their first dose of study drug (Table 17). Of the remaining 540 subjects, 322 subjects were eRVR+ and randomized at week 20 to received either T12/PR24 or T12/PR48; 118 subjects who were eRVR- were assigned to T12/PR481. Subjects who received at least 1 dose of study drug, but who prematurely discontinued treatment before completing the Week 20 visit and were not randomized, were placed in a group designated 'Other'. Subjects in the Other group prematurely discontinued treatment for various reasons (e.g., adverse events, withdrawal of consent, and virologic failure).

Table 17 Study 111 Subject Disposition

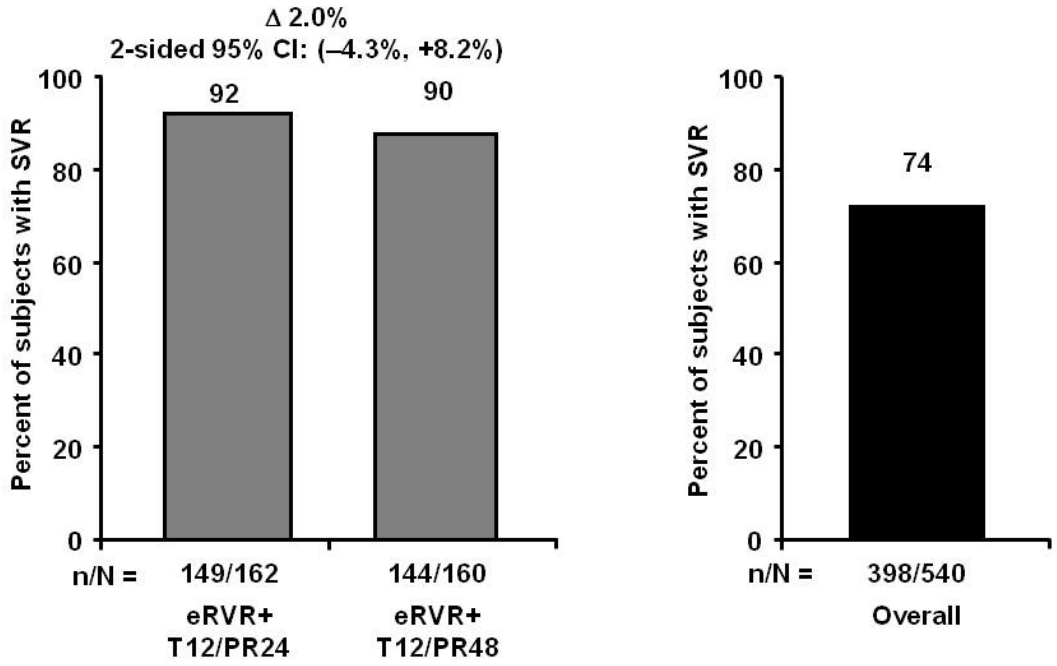
	Subjects, n (%)		
		eRVR+ randomized	
	Overall N = 540	**T12/PR24 n = 162**	**T12/PR48 n = 160**
Completed study	465 (86)	155 (96)	147 (92)
Completed treatment	359 (66)	161 (99)	119 (74)
Discontinued treatment	145 (27)	1 (1)	35 (22)
AEs	95 (18)	1 (1)	20 (13)
Virologic failure	36 (7)	0	6 (4)
Other[a]	50 (0.9)	0	1 (0.6)

[a]Subjects in the "Other" category received at least 1 dose of study drug, but prematurely discontinued treatment for various reasons (e.g., adverse events, withdrawal of consent, and virologic failure) before completing the Week 20 visit and were not randomized.

6.3.1.7 Efficacy Results

The SVR24 rates were at least 90% in the T12/PR24/eRVR+ and T12/PR48/eRVR+ groups (Figure 17). The difference in the SVR24 rates for the 2 groups was non-inferior as the lower limit of the 95% CI.

Figure 17 Study 111 Non-inferiority Analysis of SVR Rates for the 24 vs 48 Week Treatment Regimen



SVR by Ribavirin Dose Reductions

The SVR24 rates in subjects who had no RBV dose modifications, one dose reduction, and one dose interruption were similar across the randomized groups (Table 18). Subjects in the

T12/PR48/eRVR+ group had lower SVR24 rates than for the T12/PR24/eRVR+ group when both dose reductions and dose interruptions occurred.

Table 18 Study 111 SVR24 by RBV Dose Modifications

	Randomized (eRVR+)				Assigned (eRVR-)					
	T12/PR24 n = 162		T12/PR48 n = 160		T12/PR48 n = 118		Other n = 100		Total n = 540	
Variable	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**
No modifications	20	18 (90.0)	16	16 (100)	15	9 (60.0)	8	0	59	43 (72.9)
At least 1 dose reduction and no interruptions	72	65 (90.3)	56	52 (92.9)	45	29 (64.4)	62	18 (29.0)	235	164 (69.8)
At least 1 dose interruption and no reduction	0	0	0	0	0	0	0	0	0	0
At least 1 dose reduction and at least 1 dose interruption	70	66 (94.3)	88	76 (86.4)	58	40 (69.0)	30	9 (30.0)	246	191 (77.6)

Note: Subjects in the Other group who received at least 1 dose of study drug, but prematurely discontinued treatment before Week 20 were not randomized or assigned to a treatment regimen.

Subgroup Analysis

SVR24 rates were higher in subjects with lower baseline HCV RNA levels than in subjects with higher baseline HCV RNA levels (Table 19). This was not the case in the T12/PR48/eRVR+ group, but the number of subjects with baseline levels < 800,000 IU/mL is small. The SVR24 rate for subjects with cirrhosis was 61.1% (11 subjects) in the T12/PR24/eRVR+ group, and 91.7% (11 subjects) in the T12/PR48/eRVR+ group. Any differences should be interpreted with caution due to the small group sizes. For subjects with advanced fibrosis (bridging fibrosis and cirrhosis) the SVR rates were 78.9% and 87.9%, respectively.

The total SVR24 rates were higher for white subjects than for black subjects. However, the SVR24 rates for black subjects was 88.2% in both the randomized T12/PR24/eRVR+ and T12/PR48/eRVR+ groups, which is similar to those in the white subjects. The total SVR24 rates for Hispanic or Latino subjects were lower than those observed for subjects who were not Hispanic or Latino. SVR24 rates in subjects with diabetes appeared lower than in subjects who did not have diabetes.

Table 19 Study 111 SVR Rates by Select Demographics and Baseline Characteristics

	Randomized (eRVR+)				Assigned (eRVR-)					
	T12/PR24 N = 162		T12/PR48 N = 160		T12/PR48 N = 118		Other N = 100		Total N = 540	
Variable	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**
Genotype[a]										
1a	115	104 (90.4)	117	107 (91.5)	84	50 (59.5)	72	20 (27.8)	388	281 (72.4)
1b	46	44 (95.7)	43	37 (86.0)	33	27 (81.8)	27	6 (22.2)	149	114 (76.5)
1, unknown	1	1 (100)	0	NA	1	1 (100)	1	1 (100)	3	3 (100)
Baseline HCV RNA										

Table 19 Study 111 SVR Rates by Select Demographics and Baseline Characteristics

	Randomized (eRVR+)				Assigned (eRVR-)					
	T12/PR24 N = 162		T12/PR48 N = 160		T12/PR48 N = 118		Other N = 100		Total N = 540	
Variable	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**
(IU/mL)										
<800000	38	38 (100)	34	29 (85.3)	10	8 (80.0)	13	8 (61.5)	95	83 (87.4)
≥800000	124	111 (89.5)	126	115 (91.3)	108	70 (64.8)	87	19 (21.8)	445	315 (70.8)
Liver Disease Status										
Cirrhosis	18	11 (61.1)	12	11 (91.7)	12	6 (50.0)	19	3 (15.8)	61	31 (50.8)
No Cirrhosis	144	138 (95.8)	148	133 (89.9)	106	72 (67.9)	81	24 (29.6)	479	367 (76.6)
No or minimal fibrosis	46	45 (97.8)	48	42 (87.5)	27	18 (66.7)	26	6 (23.1)	147	111 (75.5)
Portal fibrosis	78	74 (94.9)	79	73 (92.4)	49	35 (71.4)	38	9 (23.7)	244	191 (78.3)
Bridging fibrosis	20	19 (95.0)	21	18 (85.7)	30	19 (63.3)	17	9 (52.9)	88	65 (73.9)
Race										
Caucasian	135	126 (93.3)	131	118 (90.1)	86	58 (67.4)	75	23 (30.7)	427	325 (76.1)
Black	17	15 (88.2)	17	15 (88.2)	20	13 (65.0)	19	2 (10.5)	73	45 (61.6)
Asian	3	3 (100)	3	3 (100)	2	1 (50.0)	1	1 (100)	9	8 (88.9)
Other	7	5 (71.4)	9	8 (88.9)	10	6 (60.0)	5	1 (20.0)	31	20 (64.5)
Ethnicity										
Hispanic or Latino	18	17 (94.4)	11	10 (90.9)	8	6 (75.0)	17	4 (23.5)	54	37 (68.5)
Not Hispanic or Latino	140	129 (92.1)	146	131 (89.7)	105	69 (65.7)	82	23 (28.0)	473	352 (74.4)
Not allowed to ask per local regulations	4	3 (75.0)	3	3 (100)	5	3 (60.0)	1	0	13	9 (69.2)
Medical History										
Diabetes	8	7 (87.5)	5	4 (80.0)	8	4 (50.0)	14	2 (14.3)	35	17 (48.6)
No diabetes	154	142 (92.2)	155	140 (90.3)	110	74 (67.3)	86	25 (29.1)	505	381 (75.4)

Abbreviations: SVR: sustained viral response; eRVR: extended rapid viral response; NA: not applicable
Note: Subjects in the Other group who received at least 1 dose of study drug, but prematurely discontinued treatment before Week 20 were not randomized or assigned to a treatment regimen.
[a] 5'NC INNO-LiPA assay.

On-treatment Virologic Failure and Relapse

The majority of on-treatment virologic failure and relapse occurred in the assigned T12/PR48/eRVR- and Other groups. Sequencing analyses of NS3•4A in subjects who did not achieve an SVR suggest that the on-treatment virologic failure rate was low (8.1%) and was predominantly observed in genotype 1a subjects. Subjects who had virologic failure during the telaprevir treatment phase had predominantly higher-level telaprevir-resistant variants. Subjects who had virologic failure during the Peg-IFN/RBV treatment phase had higher-level telaprevir-resistant variants, with a minority having lower-level telaprevir-resistant variants.

Relapse rates for subjects who completed their assigned 24- or 48-week treatment duration were low (6.3% in the T12/PR24/eRVR+ group, 0.8% in the T12/PR48/eRVR+ group, and 6.3% in the eRVR- T12/PR48 group). Relapse was generally associated with lower-level resistant variants.

A total of 50% of subjects with resistant variants at the post-nadir time point no longer had resistant variants detected at their last visit. Median time to loss of detectable resistant virus varied by NS3 position and ranged from 12 to 48 weeks.

6.3.1.8 Efficacy Conclusions for Study 111

The rates of SVR24 and SVR72 rates in the randomized T12/PR24/eRVR+ group were non-inferior to those in the T12/PR48/eRVR+ treatment regimen. The SVR24 rate was more than 70% across the entire study population relative to the historical standard of care rates of 46% to 52%. This was achieved even with the inclusion of populations with historically low SVR rates when receiving Peg-IFNRBV treatment alone.

Relapse rates were low in subjects who completed their assigned 24- or 48-week treatment duration in both the randomized eRVR+ and assigned eRVR- groups. The overall relapse rate for the study was 9.2% (45 of 488 subjects). The relapse rate in the randomized T12/PR24/eRVR+ group was 6.3% and 2.5% in the randomized T12/PR48/eRVR+ group.

A total of 55% of subjects with resistant variants at the post-nadir time point no longer had resistant variants detected by population sequencing at their last visit in Study 111 (median follow-up time of 43 weeks).

6.4 Comparison of Efficacy Results of All Studies

Demographic and baseline characteristics were broadly similar among the subjects enrolled in both Phase 3 studies with treatment-naive subjects. Compared to Study 108, the overall study population of Study 111 included more subjects from North America (94.3% in Study 111 versus 60.2% in Study 108), a slightly higher median age (51 versus 49 years), more black subjects (13.5% versus 8.6%), a greater proportion with cirrhosis (11.3% versus 6.3%), more subjects with genotype 1a virus (71.9% versus 58.9%), and a higher proportion (82.4% versus 77.1%) with baseline HCV RNA levels ≥ 800,000 IU/mL.

Efficacy results in treatment-naive and treatment-failure subjects demonstrated a substantial and consistent efficacy benefit from the addition of telaprevir in all populations studied.

Despite slight differences in the demographics of the enrolled populations in the 2 Phase 3 studies in treatment-naive subjects, the SVR rates were consistent: 78.5% in Study 108 and 73.7% in Study 111 for the T12/PR groups.

The SVR rate in the Phase 3 Study C216 in treatment-failure subjects was higher than the SVR rates in the Phase 2 studies in this population, which may have been attributable in part to a lower premature treatment discontinuation rate in the Phase 3 study after improvements in managing rash.

On-treatment responses and efficacy results in treatment-naive and treatment-failure subjects treated with telaprevir demonstrated a substantial and consistent benefit in all populations studied.

The similarity of SVR rates in the Pbo/PR groups of both treatment-naive and prior treatment-failure subjects to those reported with standard Peg-IFN/RBV treatment supports the relevance and generalizability of these findings.

6.5 Clinical Virology

6.5.1 Clinical Resistance to Telaprevir: Sequence Analysis and Phenotypic Characterization

Clinical virology analyses from telaprevir clinical studies were performed to understand the relationship between virologic failure in a telaprevir-containing regimen and the emergence of HCV variants with decreased sensitivity to telaprevir. Sequence analysis of the NS3·4A region was performed in all subjects at baseline and for all subjects who did not achieve an SVR (limit of detection of the sequencing assay ~1,000 IU/mL).

Clinical virology results from clinical studies of telaprevir in combination with Peg-IFN/RBV have shown a clear and consistent resistance profile across all HCV genotypes (1, 2, 3, and 4) and subject populations (treatment-naive and Peg-IFN/RBV treatment-failure) studied. Sequence analyses in subjects not achieving an SVR consistently identified amino acid substitutions at 4 positions in the NS3•4A protease region that were associated with decreased sensitivity to telaprevir, consistent with the mechanism of action for telaprevir. Variants associated with not achieving an SVR were V36A/M, T54A/S, R155K/T, A156S/T/V, and V36M+R155K.

Phenotypic characterization of HCV NS3 variants observed in clinical studies of telaprevir determined that a lower-level resistance to telaprevir (3- to 25-fold decrease in IC50 to telaprevir in a replicon-based phenotypic assay) is conferred by V36A/M, T54A/S, R155K/T, and A156S, and a higher-level resistance to telaprevir (>25-fold decrease in HCV replicon IC50) is conferred by A156T/V and V36M+R155K. All telaprevir-resistant variants remained fully sensitive to IFN-α, RBV and representative HCV nucleoside and non-nucleoside polymerase inhibitors in vitro. Additionally, telaprevir-resistant variants had a decreased replication capacity compared to wild-type.

Two pathways to developing resistance to telaprevir were identified in genotype 1 HCV, depending on subtype. In subjects with genotype 1a, the predominant telaprevir-resistant variants observed were V36M, R155K, or V36M+R155K. In subjects with genotype 1b, the predominant telaprevir-resistant variants observed were V36A, T54A/S, A156S/V/T. These distinct pathways are primarily driven by a higher genetic barrier to developing the V36M and R155K substitutions in genotype 1b (2 nucleotide changes required for each substitution) compared to genotype 1a (single nucleotide change required).

6.5.2 Baseline Resistance

HCV has higher sequence diversity than is found in other chronic viral infections such as HBV or HIV. In addition to the intersubject viral sequence diversity, there is also significant intrasubject viral sequence diversity. New viral variants are constantly being produced due to the high level of HCV replication with a low fidelity RNA polymerase. However drug-resistant variants typically exist at low levels prior to treatment due to their reduced fitness compared to wild-type virus. Baseline (pre-treatment) samples were sequenced for all subjects enrolled in telaprevir clinical studies and analyzed for the presence of known telaprevir-resistant mutations (V36A/M, T54A/S, R155K/T, A156S/T/V). Subjects with naturally occurring telaprevir-resistant variants predominant at baseline are uncommon (detected at 2.7% for T54S and < 1% for V36M, T54A, and R155K, and were not detected for all others). The clinical relevance of the presence of the telaprevir-resistant variants as the

dominant part of quasispecies prior to treatment remains unclear; however, the presence of telaprevir-resistant variants did not necessarily predict treatment failure or preclude treatment success with a telaprevir-based regimen. Other factors, such as response to Peg-IFN and RBV and adherence to the treatment regimen, likely play a larger role in the response and ultimate clinical outcome to the telaprevir treatment regimen.

6.5.3 Resistance Profiles in Subjects who Did Not Achieve SVR with Telaprevir-Based Treatment

The addition of telaprevir to Peg-IFN-alfa-2a and RBV treatment significantly increased SVR rates compared to Peg-IFN/RBV alone. In the subset of subjects who did not achieve an SVR, clinical virology studies were performed to help elucidate the reason for and consequence of treatment failure. Both on-treatment virologic failure and relapse were analyzed, with on-treatment virologic failure further categorized by whether the failure occurred during the telaprevir treatment phase or the Peg-IFN/RBV treatment phase.

In both Phase 2 and 3 studies, on-treatment virologic failure during the telaprevir treatment phase was consistently associated with higher level resistance in both treatment-naive and treatment-failure subjects, suggesting that wild-type and lower-level resistant variants were fully suppressed by the regimen in both subject populations. Of the higher-level resistant variants observed, the V36M+R155K variant has a lower impairment of viral fitness compared to the A156V/T variant. Thus, on-treatment virologic failure during the telaprevir treatment phase was more commonly observed with genotype 1a and associated with the V36M+R155K variant. However, on-treatment virologic failure rates during the telaprevir treatment phase were low in treatment-naive subjects, indicating that the V36M+R155K variant was suppressed by the treatment regimen in the majority of subjects. On-treatment virologic failure rates were also low in prior relapsers, while rates were higher in prior non-responders.

On-treatment virologic failure after telaprevir treatment, during the Peg-IFN/RBV treatment phase, was low in both treatment-naive and treatment-failure populations, and was associated with wild-type virus (predominantly in genotype 1b), and lower- or higher-level resistant variants. These results suggest that the 12-week T/PR regimen was able to suppress wild-type and most of the resistant variants, preventing subsequent on-treatment virologic failure during Peg-IFN-alfa-2a and RBV treatment in the majority of subjects.

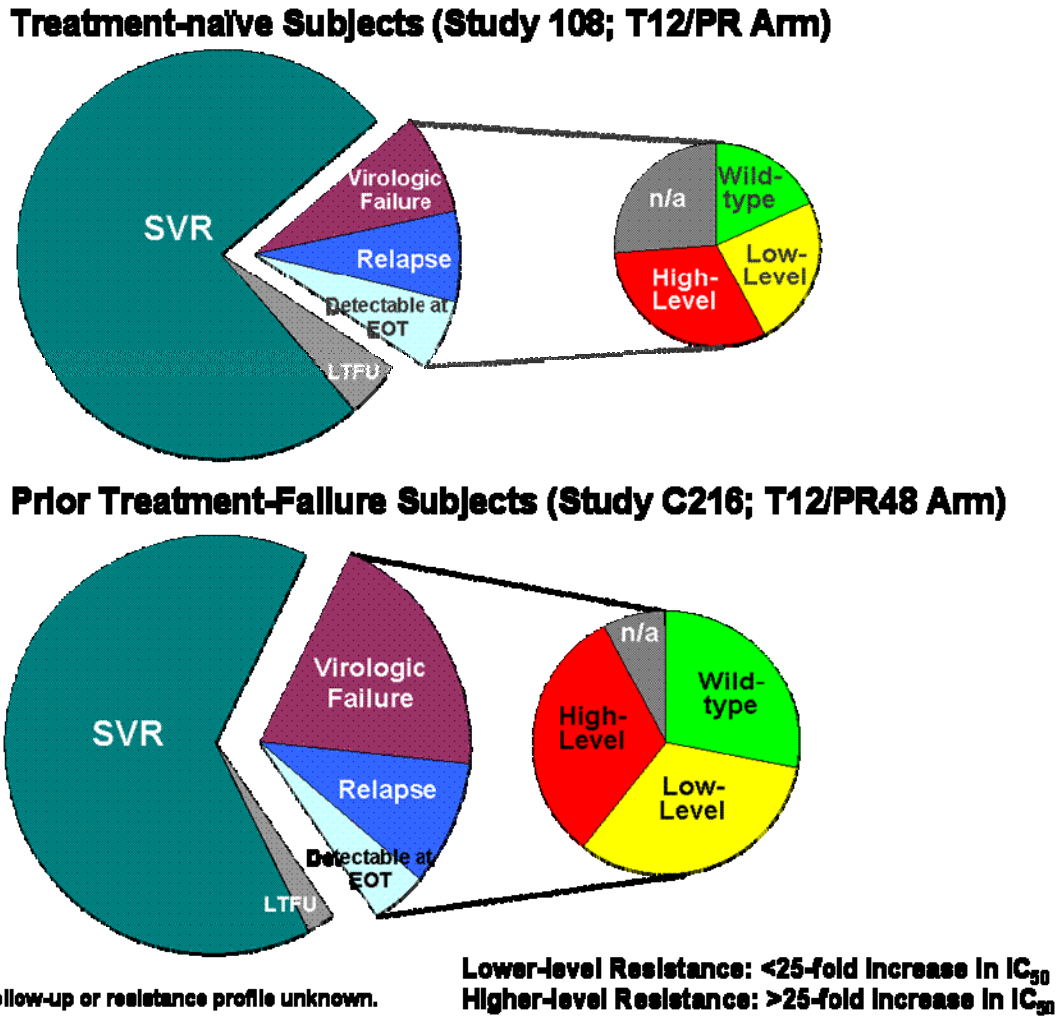
Relapse was defined as having detectable HCV RNA during follow-up after being undetectable at EOT. Relapse is likely due to the growth of a small amount of residual virus that remains below the HCV RNA assay limit of detection at the EOT. Viral sequencing at the time of relapse can provide a window into the viral population present at the time that treatment was stopped. Therefore, results were analyzed separately for subjects who discontinued from treatment early and for subjects who completed the assigned treatment regimen with undetectable HCV RNA, and subsequently relapsed.

In subjects who discontinued treatment early, for reasons other than virologic failure, the viral population observed was dependent on the duration of treatment the subject received. In general, subjects discontinuing from treatment early (< 4 weeks) tended to have predominantly wild-type virus, indicating that a longer duration of telaprevir is required to clear wild-type. In most subjects who received longer durations of treatment (> 8 weeks of

telaprevir), the viral population consisted of telaprevir-resistant variants. In subjects who complete their assigned treatment regimen, relapse was associated with lower-level telaprevir-resistant variants in the majority of T/PR treated subjects for both treatment-naive and treatment-failure populations. The presence of telaprevir-resistant variants in most subjects with relapse suggests that the majority of wild-type virus may be eliminated in the first 12 weeks of T/PR treatment, and that the role of additional Peg-IFN/RBV therapy is to clear any remaining telaprevir-resistant variants. The lower relapse rates in subjects who completed treatment suggest that the additional weeks of Peg-IFN/RBV were able to clear the remaining telaprevir-resistant variants in a majority of subjects.

In summary, clinical virology analyses from clinical studies of telaprevir, Peg-IFN and RBV in treatment-naive and treatment-failure subjects with genotype 1 CHC have provided further insight into the optimal treatment regimen in order to maximize response rates and minimize resistance. These results show that in a T/PR regimen, the primary role of telaprevir is to inhibit wild-type virus and variants with lower-levels of resistance to telaprevir. The primary and complementary role of Peg-IFN/RBV is to clear any remaining telaprevir-resistant variants, especially higher-level telaprevir-resistant variants. Overall, TVR-resistant variants were observed in 12% of treatment-naïve subjects (Study 108; T12/PR arm) and 22% of treatment-experienced subjects after treatment with a telaprevir-containing regimen. Resistant variants were observed in the majority of subjects who did not achieve an SVR (Figure 18).

Figure 18 Resistance Profile in Subjects Who Do Not Achieve SVR



6.5.4 Evolution of Variants After Treatment

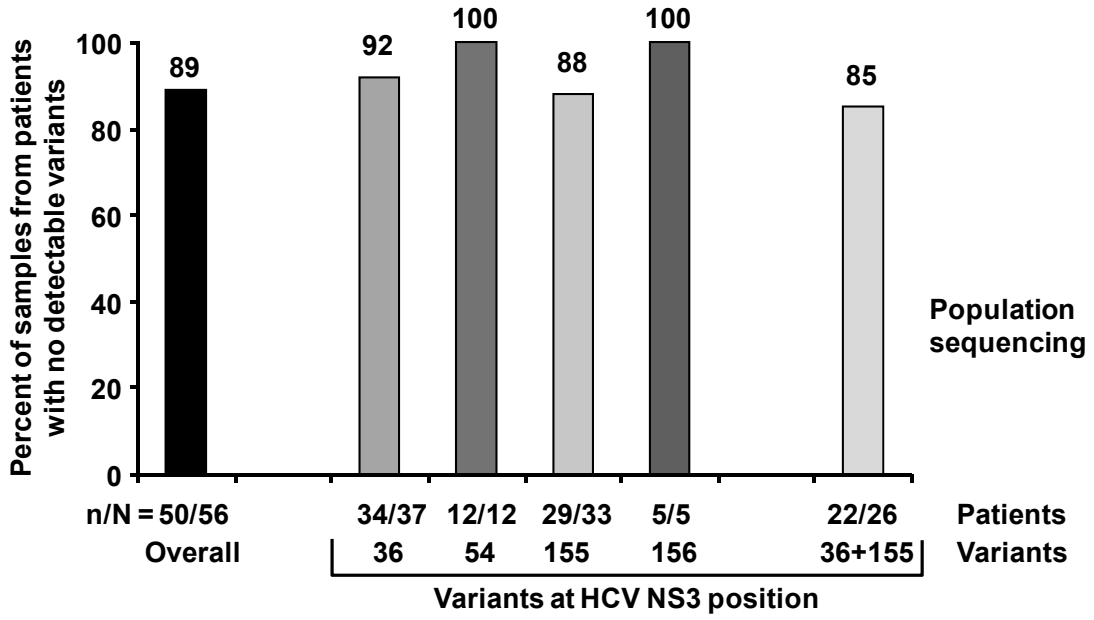
The long-term clinical implications of treatment selected HCV variants with reduced sensitivity to telaprevir have not been established. In subjects that fail treatment with telaprevir, it may be possible that many resistant variants will eventually be replaced by wild-type HCV populations, as wild-type has a fitness advantage in the absence of telaprevir. Unlike HIV or HBV, which both have long-lasting DNA forms that archive resistant mutations, HCV is an RNA virus whose life cycle occurs in the cytoplasm and no long-lived reservoir has been demonstrated for HCV. Thus, clinical implications of resistance for HCV may be different from HIV or HBV. In order to further understand the evolution of resistant variants over time in the absence of drug, viral populations were studied during follow-up in subjects who failed to achieve an SVR.

Of a combined 255 subjects from Phase 3 studies (108, 111 and C216) with a total of 393 resistant variants, 152 (60%) subjects no longer had resistant variants detected by the end of the study (median follow-up of 45 weeks), and results were similar across studies (Study 108, 66% of subjects; Study 111, 55%; Study C216, 58%). Kaplan-Meier estimates of

the median times to loss of detectability of variants at each of these positions were also consistent between studies.

To further understand the evolution of resistant variants after treatment, Study 112 was designed to follow subjects who did not achieve an SVR following a telaprevir-based treatment regimen in Phase 2 and Phase 3 studies for a 3-year period (Section 6.7). An interim analysis was performed on 56 subjects that had failed to achieve SVR with a telaprevir-based regimen and were enrolled from Phase 2 studies that included treatment-naive and prior Peg-IFN/RBV treatment-failure subjects. The population was representative of the eligible population in terms of resistant profiles. The median duration between the end of the previous study and enrolling in Study 112 was 25 months (range 7-36). Of the subjects analyzed for evolution of resistant variants, 89% (50 of 56 subjects) no longer had variants detectable by population sequencing (92% of NS3·36, 100% of NS3·54, 88% of NS3·155, and 100% of NS3·156) during Study 112 (Figure 19).

Figure 19 Study 112 Frequency of Viral Variants At Follow-Up



Median follow-up time from end of prior study of 25 months (range 7-36)

These population sequencing analyses suggest that viral populations in the majority of subjects become ≥ 75% wild-type within the observation period. To determine if subjects that were wild-type by population sequencing had resistant variants present below the limit of detection (~25%), cloned HCV amplicons were sequenced from 20 Study 112 subjects at the pre-treatment time point from the subjects' previous telaprevir study and at the Study 112 time point. All subjects were found to have a similar frequency of resistant populations at baseline and at post-treatment follow-up.

Together these data suggest that changes in the viral population over time favor the replacement of viral variants with wild-type virus for each of the 4 positions predominately associated with telaprevir resistance. These data provide some level of reassurance that viral resistance may resolve over time, and that additional treatment options for subjects who

acquire resistant variants to an antiviral agent may be available, possibly even with the same class of antiviral agents. Currently, however, no re-treatment data are available to validate this hypothesis.

6.5.5 Conclusions

Sequencing analyses of HCV NS3·4A in subjects who did not achieve an SVR suggest the following:

- In a regimen of telaprevir, Peg-IFN, and RBV, the primary role of telaprevir is to inhibit wild-type virus and variants with lower-levels of resistance to telaprevir. The primary and complementary role of Peg-IFN and RBV is to clear any remaining telaprevir-resistant variants
- Telaprevir has a well-characterized and consistent resistance profile with HCV genotype 1 for all subject populations (treatment-naive and treatment-failure) studied (lower-level resistance V36A/M, T54A/S, R155K/T, A156S and higher-level resistance A156T/V, V36M + R155K)
- Telaprevir-resistant variants are less fit than wild-type virus and are sensitive to Peg-IFN, RBV, and polymerase inhibitors in vitro
- Predominant baseline resistance to telaprevir is infrequent (V36M, T54A and R155K, < 1% and T54S, 2.7%) and does not necessarily preclude achieving an SVR with a T/PR regimen
- Analysis in subjects with on-treatment virologic failure suggests
  - On-treatment virologic failure during telaprevir treatment is associated with higher-level telaprevir-resistant variants, and occurs more frequently in genotype 1a compared to 1b
  - On-treatment virologic failure rates on T/PR are low in treatment-naive subjects and prior relapser subjects, but are higher for prior nonresponders subjects
- Analysis in subjects with relapse suggests that relapse is generally associated with lower-level resistant variants
- Resistant variants tend to be replaced by wild-type virus over time in the absence of telaprevir selective pressure

6.6 Durability of SVR

Relapse after achieving SVR after treatment with standard therapy occurs in less than 1% of treated subjects.[30] The durability of SVR achieved with a telaprevir-based regimen was investigated during Phase 2 clinical studies of treatment-naive and treatment-failure subjects, as well as in an interim analysis of a 3-year follow-up study in subjects who had been treated with telaprevir in Phase 2 studies. The subjects in whom durability of SVR was evaluated included subjects who completed treatment as well as subjects who discontinued treatment, and subjects from all telaprevir treatment regimens in the studies, including regimens without RBV and regimens with Peg-IFN/RBV durations of 12, 24, or 48 weeks. Durability of SVR in the Phase 3 studies is not applicable when basing virologic outcome on the HCV RNA

assessment in a visit window through Week 78, as no subjects were followed past this SVR time point.

6.6.1 Phase 2 Studies in Treatment-Naive Subjects

In Phase 2 Studies 104 and 104EU, subjects assigned to telaprevir treatment groups with regimens of less than 48 weeks had HCV assessments for up to 48 weeks beyond SVR to assess the durability of the viral response. Overall, 165 of 167 subjects with SVR in Studies 104 and 104EU had undetectable HCV RNA during follow-up beyond SVR, and 2 subjects had late relapse.

In Study 104, 45 of 54 subjects with SVR in the T12/PR12 and T12/PR24 groups were followed for up to 48 weeks beyond SVR. All 45 subjects continued to have undetectable HCV RNA.

In Study 104EU, 122 of 133 subjects with SVR in the T12/PR12, T12/PR24, and T12/P12 groups were followed for up to 48 weeks beyond SVR. All but 2 of the 122 subjects continued to have undetectable HCV RNA. The 2 subjects with late relapse had prematurely discontinued study drug treatment before Week 10.

In both subjects, the viral sequence at follow-up was similar to the subjects' baseline sequence before treatment, indicating that these subjects had late relapse rather than re-infection. No telaprevir-resistant variants were detected.

6.6.2 Phase 2 Studies in Treatment-Failure Subjects

In Phase 2 Studies 106 and 107, subjects in the telaprevir treatment groups who completed dosing (completed their planned total treatment duration with at least 1 study drug) had an HCV assessment 24 weeks after SVR to assess the durability of the viral response. Overall, 194 subjects in Studies 106 and 107 who completed dosing and had SVR had undetectable HCV RNA during follow-up beyond SVR. No subjects had late relapse.

In Study 106, 131 of 132 subjects in the T12/PR24, T24/PR24, and T24/P24 groups who completed dosing and had SVR were followed for 24 weeks beyond SVR. All 131 subjects continued to have undetectable HCV RNA.

In Study 107, 63 of 64 subjects in the T12/PR24 and T12/PR48 groups who completed dosing and had SVR were followed for 24 weeks beyond SVR. All 63 subjects continued to have undetectable HCV RNA.

In addition, although subjects who prematurely discontinued dosing and had SVR were not required to have a post-SVR follow-up assessment, 9 of 19 subjects in telaprevir treatment groups in Studies 106 and 107 who prematurely discontinued dosing and had SVR also had an assessment 24 weeks after SVR. All 9 of these subjects continued to have undetectable HCV RNA.

6.6.3 Three-Year Follow-Up Study

Study 112 is an ongoing, 3-year follow-up study in subjects who had SVR after treatment with telaprevir in Studies 104, 104EU, 106, 107, 108, 111, and C216. As of 01 March 2010, 123 subjects in Studies 104, 104EU, 106, and 107 were enrolled. Overall, 122 of 123 subjects continued to have undetectable HCV RNA for up to 3 years after EOT. One subject had late

relapse before enrolling in Study 112. This is the same relapse event that occurred during the follow-up period in Study 104EU, as described in Section 6.6.1. Study 112 is further discussed in Section 6.7.

6.6.4 Durability Summary

Of the 361 subjects that (1) received a telaprevir-based regimen, (2) achieved an SVR, and (3) had at least 1 post-SVR follow-up assessment, 2 subjects had late relapse within 6 months after SVR during the study follow-up period. All other subjects with SVR who have been followed for up to 3 years after EOT continued to have undetectable HCV RNA. No subjects had late relapse during the observational period in Study 112, which is ongoing. These data demonstrate that late relapse in subjects treated with a telaprevir-based regimen occurs at a rate similar to what has been reported for standard therapy.[30]

6.7 Study 112: A 3-Year, Virology Follow-up Study in Subjects Previously Treated With Telaprevir in Select Clinical Studies

Study 112 is an ongoing, 3-year follow-up study to evaluate (1) the durability of virologic response in subjects who had an SVR following telaprevir-based treatment in a previous study, and (2) changes in HCV variants over time in subjects who did not have an SVR following telaprevir-based treatment in a previous study.

Eligible subjects must have received at least 1 dose of telaprevir-based treatment in Study 104, 104EU, 106, 107, 108, 111, or C216. Maximum planned enrollment is 150 subjects who had SVR in the previous study and 250 subjects who did not have SVR in the previous study.

6.7.1 Methodology

The primary endpoint for the cohort of subjects with SVR (Cohort A) was the proportion of subjects who maintained undetectable HCV RNA as a function of time since achieving SVR.

The primary endpoint for the cohort of subjects without SVR (Cohort B) was assessment of changes in viral variants with decreased sensitivity to telaprevir as a function of time since EOT in the previous study.

Interim analysis was planned for the purpose of data review by a Scientific Advisory Committee and for regulatory updates. An interim analysis took place with a data cut-off date of 01 March 2010. This interim analysis included 202 subjects: 123 subjects with SVR and 79 subjects without SVR in Phase 2 Study 104, 104EU, 106, or 107. Subjects in the Phase 3 Studies 108, 111, and C216 had not been enrolled at the time of this analysis.

6.7.2 Study 112 Interim Analysis

6.7.2.1 Durability of SVR

Durability of SVR is discussed in more detail in Section 6.6. In study 112, subjects were followed for a median 22 months. A total 122 of 123 subjects (99%) continued to have undetectable HCV RNA and 1 subject had late relapse. The subject with late relapse was in the T12/PR24 group in Study 104EU, had SVR, and was identified with late relapse during that study, prior to enrolling in Cohort A in Study 112.

6.7.2.2 Analysis of Telaprevir-Resistant Variants Over Time

Virology analyses were conducted for subjects in Cohort B that had both detectable telaprevir-resistant variant(s) at the post-nadir time point in the previous study and viral sequencing data available from Study 112. Of the 56 subjects suitable for analysis of telaprevir-resistant viral variants over time, 50 (89.3%) had wild-type virus at follow-up in Study 112 by population sequencing. More details of these analyses are described in Section 6.5.4.

6.7.2.3 Interim Efficacy Conclusions

Data on the durability of SVR in subjects who had SVR, and data on the evolution of telaprevir-resistant viral variants over time after EOT in subjects who did not have SVR, were obtained for a broad range of subjects representative of those treated in Phase 2 studies. The study population comprised treatment-naive and treatment-failure subjects, including prior nonresponders; subjects with different HCV genotype 1 subtypes and stages of liver disease, including cirrhosis; subjects from different geographic regions; and subjects treated with various telaprevir-based regimens, including regimens without RBV.

Durability of SVR with a telaprevir-based regimen was demonstrated in 122 of 123 subjects with SVR who were followed for 5 to 35 months after SVR (median follow-up of 22 months). The remaining subject had been previously identified during Study 104EU. This subject had been treated with telaprevir, Peg-IFN, and RBV for less than 10 weeks, had SVR, and then had late relapse 5 months after SVR. No late relapses occurred during the observational period of Study 112, which is ongoing.

The majority (89%) of subjects had no detectable resistant variants at follow-up in Study 112 by population sequencing. Clonal sequencing data indicate that resistant viral populations in subjects who did not have SVR with a telaprevir-based treatment returned to their pre-treatment state within this observation period.

6.8 SVR by IL28 Genotype

IL28B polymorphisms are linked to differences in SVR rates in HCV treatment naive-subjects treated with Peg-IFN/RBV. The relationship between IL28B genotype and SVR in telaprevir-based therapy was investigated retrospectively in a subset of subjects who enrolled in studies C216 and 108. This analysis was not updated using the criteria described in Section 6.2.1.4.

Enrolment of the Phase 3 studies commenced prior to the discovery of IL28B. In Study 108, IL28B genotype was determined in de-identified left-over specimen available from treatment-naïve genotype 1 HCV patients. In Study C216, patients who consented to genetic testing were included in a sub-analysis which evaluated virologic response by IL28B gentotype.

The racial distribution of subject samples used in these analyses from Study C216 (white [94%], black [4%]) and Study 108 (white [100%]) were different because of sample de-identification requirements in Study 108, which allowed only samples from white subjects to be tested. Subjects had IL28B genotypes of CT (61% and 49%), CC (18% and 33%), and TT (21% and 18%) in studies C216 and 108, respectively. Distribution of IL28B genotypes in

treatment-naïve patients in Study 108 was consistent with previously published results (Ge D, et al. Nat 2009; 461:399-401)

Samples from 42% (454/1088) of Study 108 patients were available in the IL28B dataset; and samples from Study C216 were available for 80% (527/662)

In Study C216, the highest proportion of IL28B TT subjects was among prior null responders (28%) whereas the highest frequency of CC subjects was among prior relapsers (27%). Differences in SVR rates among IL28B CC, CT and CC subjects were only evident when the three subject subpopulations were pooled; however, SVR among CT and TT subjects were still high (Table 20). Thus, in this retrospective analysis, IL28B genotype did not contribute to outcome prediction in prior treatment-failure subjects treated with a telaprevir-based regimen.

In Study 108, SVR rates in the IL28B dataset were comparable to the overall SVR rates in Study 108 Caucasian patients (T12/PR: 78%, T8/PR: 65%, Pbo/PR: 38%) as well as in overall Study 108 patients (T12/PR: 75%, T8/PR: 70%, Pbo/PR: 46%). In Study 108, telaprevir-based therapy more than doubled the rates of SVR in CT/TT subjects, and increased SVR rates in subject with CC genotype, compared with PR therapy alone (Table 21). Non-attainment of eRVR was associated with lower SVR rates across all IL28B genotypes, with the largest decrement in CT/TT subjects.

Table 20 SVR Rates by IL28B Genotype-Analysis of Subjects Enrolled in Study C216

	SVR n (%)							
	Overall population		Prior relapsers		Prior partial responders		Prior null responders	
	Pooled T12/ PR48 Arms n= 422	Pbo/ PR48 Arm n = 105	Pooled T12/ PR48 Arms n = 209	Pbo/ PR48 Arm n = 52	Pooled T12/ PR48 Arms n= 79	Pbo/ PR48 Arm n = 20	Pooled T12/ PR48 Arms n = 134	Pbo/ PR48 Arm n = 33
IL28B CC	76 (79)	17 (29)	58 (88)	12 (33)	8 (63)	5 (20)	10 (0)	0
IL28B CT	266 (60)	58 (16)	117 (86)	30 (20)	57 (58)	10 (20)	92 (29)	18 (6)
IL28B TT	80 (61)	30 (13)	34 (85)	10 (30)	14 (71)	5 (0)	32 (31)	15 (7)

T12/PR48, telaprevir, pegylated interferon-alfa, and ribavirin; Pbo, placebo.
Source: Pol S, et al. Presented at: 46th Annual Meeting of the European Association for the Study of the Liver. March 30-April 3, 2011; Berlin, Germany. Reprinted with permission from the authors.

Table 21 SVR Rates by IL28B Genotype-Analysis of Subjects Enrolled in Study 108

	SVR rates in subjects tested for IL28B allele, % (n/N)				SVR rates in all ADVANCE subjects, % (n/N)
	CC (n = 150)	CT (n = 224)	TT (n = 80)	Total (n=454)	(n = 1088)
T12PR*	90 (45/50)	71 (48/68)	73 (16/22)	78 (109/140)	75 (271/363)
T8PR**	87 (39/45)	58 (44/76)	59 (19/32)	67 (102/153)	69 (250/364)
PR	64 (35/55)	25 (20/80)	23 (6/26)	38 (61/161)	44 (158/361)

*T12PR = T+PR 12 weeks, then PR 12 or 36 weeks depending on eRVR status.
**T8PR = T+PR 8 weeks, then PR 16 or 40 weeks depending on eRVR status.
SVR, Sustained virologic response.
Source: Jacobson IM, et al. Presented at: 46th Annual Meeting of the European Association for the Study of the Liver. March 30- April 3, 2011; Berlin, Germany. Reprinted with permission from the authors.

6.9 Overall Efficacy Conclusions

Telaprevir-containing regimens achieved significantly higher SVR rates in both treatment-naive and treatment-failure populations compared to standard treatment with Peg-IFN/RBV. The rate of SVR was consistently higher in treatment-naive and treatment-failure subjects in both the Phase 2 and Phase 3 programs. This clinical benefit was achieved across a broad range of subjects, including subjects who were black, Hispanic or Latino, had cirrhosis or bridging fibrosis, or had high baseline levels of HCV RNA, or who did not achieve SVR with a prior course of Peg-IFN/RBV, including subjects with prior null response.. The responses in the control groups were comparable to those reported in the literature for Peg-IFN/RBV for the relevant populations, confirming the generalizability of the results, and the strength of the observed differences in SVR rates.

More than half (58.4% in Study 108, 65.2% in Study 111) of treatment-naive subjects on T12/PR achieved eRVR (undetectable HCV RNA at Weeks 4 and 12) and were eligible for 24 weeks of treatment, compared to 48 weeks for standard treatment. The vast majority of these subjects (at least 89.2% in Studies 108 and 111) achieved SVR. In treatment-naive subjects with eRVR, 48 weeks of total treatment did not appear to offer any additional benefit over 24 weeks of treatment (Study 111). These data support the use of response guided therapy for treatment-naive subjects with eRVR.

While response-guided durations were not included in Phase 3 Study C216, the totality of evidence from the telaprevir development program suggests that prior relapsers with eRVR will achieve high SVR rates when treated for a total of 24 weeks. The SVR rate in prior relapsers with eRVR treated with T12/PR48 in Study C216 (95.6%) was comparable or higher than the SVR rate in treatment-naive subjects with eRVR treated with T12/PR24 in Study 108 (89.2%). In Study 106, SVR rates in prior relapsers with eRVR were equally high when they were treated with a 24-week or a 48-week regimen. These data suggest that both treatment-naive and prior relapser subjects with eRVR can shorten treatment duration with Peg-IFN/RBV by 6 months without loss of efficacy, which provides a significant safety and treatment burden benefit. For these reasons, response-guided therapy is recommended for both treatment-naive subjects and prior relapsers.

Comparisons of 8- and 12-week regimens of telaprevir in treatment-naive subjects demonstrated a slight numerical advantage for the longer telaprevir duration, and the timing and resistance pattern of the on-treatment virologic failures supported the conclusion that the 12-week duration was preferable. In addition, in subject subgroups with a traditionally poor response to Peg-IFN/RBV, the 12-week telaprevir regimen was associated with a consistently higher SVR rate compared to the 8 week telaprevir regimen. By contrast, delaying the start of telaprevir in the regimen by 4 weeks in a prior treatment-failure population (Study C216) did not improve SVR rates, and offered no clinical advantage over a simultaneous start.

Although the data supporting the treatment of CHC with a T/PR regimen are primarily based on telaprevir in combination with Pegasys/Copegus, Study C208 showed that there were no relevant differences in SVR rates between treatment with telaprevir and either Pegasys/Copegus or PegIntron/Rebetol, supporting the use of either regimen.

The efficacy of the triple combination therapy is predicated on telaprevir's robust inhibition of wild-type and lower-level telaprevir-resistant virus and the complementary role of Peg-IFN/RBV in inhibiting any remaining telaprevir-resistant variants, primarily those with higher-level telaprevir-resistance. Predominant baseline resistance to telaprevir is infrequent and does not necessarily predict treatment failure; therefore, resistance testing is not required prior to initiating treatment. Although unsuccessful treatment with this regimen may select for resistant virus, stopping rules are being proposed to limit any further evolution. Once telaprevir is discontinued, telaprevir-resistant variants are replaced by wild-type virus over time.

These data support the use of telaprevir in combination with Peg-IFN/RBV as first-line therapy in adult subjects with compensated liver disease (including cirrhosis) who are treatment-naive or have failed prior treatment.

7 DRUG-DRUG INTERACTIONS

In vitro studies using recombinant human cytochrome P450 (CYP) isoforms indicated that CYP3A was the major CYP isoform responsible for telaprevir metabolism. In addition, the observed hydrolytic pathways suggest proteolytic enzymes are likely also involved in the metabolism of telaprevir. Studies using recombinant human CYP supersomes showed that telaprevir was also a CYP3A inhibitor. Time- and concentration-dependent inhibition of CYP3A by telaprevir was observed in human liver microsomes. These results suggested the potential for DDIs between telaprevir and substrates, inducers, and inhibitors of CYP3A. In vitro studies also suggested that telaprevir had low potential to induce CYP2C, CYP3A, or CYP1A and was therefore considered unlikely to demonstrate induction-based DDIs when coadministered with corresponding substrates.

Based on these results, an extensive DDI program was undertaken. The program included interaction studies between telaprevir and a model substrate of P-gp, model substrates, inhibitors, and inducers of CYP3A, as well as drugs commonly used by subjects with CHC, including oral contraceptives, anti-anxiety/insomnia , anti-depressants, lipid-lowering, anti-ulcer, HIV medications, methadone, and immunosuppressants used in organ transplant.

Clinical drug-drug interaction studies were performed to determine the PK parameters for telaprevir and co-administered drugs (Table 22 and Table 23). Results from these studies show that telaprevir can affect the PK of co-administered drugs that are CYP3A substrates and/or transported by P-gp. Telaprevir PK may also be affected by inducers of CYP3A. Due to the potent CYP3A inhibitory effect of telaprevir itself, the effect of co-administration of another CYP3A inhibitor (e.g., ritonavir, ketoconazole, or ritonavir-boosted HIV protease inhibitors) on the exposure to telaprevir is unlikely after repeated administration of telaprevir when non-CYP mediated metabolic pathways may play the major role in the metabolism of telaprevir. This is shown by the lack of an increase in telaprevir exposure on coadministration with ritonavir, both at steady state, in Table 22. Additionally, in Study 008, telaprevir exposure (C_{max} and AUC_{8h}) obtained after 3 doses of 1250 mg telaprevir q8h followed by a single 400-mg dose of ketoconazole coadministered with a fourth and final 1250-mg dose of telaprevir, was only approximately 20% higher than that obtained by a single 1250-mg dose of telaprevir followed by 3 doses of 750 mg q8h.

Table 22 Drug Interactions: Summary of Pharmacokinetic Parameters for Telaprevir in the Presence of Coadministered Drugs

Coadministered Drug	Dose and Schedule		n	Effect on TVR PK[a]	LS Mean Ratio (90% CI) of Telaprevir PK With/Without Coadministered Drug		
	Coadministered Drug	Telaprevir			C_{max}	AUC or $C_{avg,ss}$[b]	C_{min}
Escitalopram	10 mg qd for 7 days	750 mg q8h for 14 days	13	↔	1.00 (0.95; 1.05)	0.93 (0.89; 0.97)	0.91 (0.86; 0.97)
Esomeprazole	40 mg qd for 6 days	750 mg single dose	24	↔	0.95 (0.86; 1.06)	0.98 (0.91; 1.05)	NA
Ketoconazole	Ketoconazole 400 mg single dose	750 mg single dose	17	↑	1.24 (1.10; 1.41)	1.62 (1.45; 1.81)	NA

Table 22 Drug Interactions: Summary of Pharmacokinetic Parameters for Telaprevir in the Presence of Coadministered Drugs

Coadministered Drug	Dose and Schedule			Effect on TVR PK[a]	LS Mean Ratio (90% CI) of Telaprevir PK With/Without Coadministered Drug		
	Coadministered Drug	Telaprevir	n		C_{max}	AUC or $C_{avg,ss}$[b]	C_{min}
Oral Contraceptive	Norethindrone/ ethinyl estradiol 0.5 mg/0.035 mg qd for 21 days	750 mg q8h for 21 days	23	↔	1.00 (0.93; 1.07)	0.99 (0.93; 1.05)	1.00 (0.93; 1.08)
Rifampin	600 mg qd for 8 days	750 mg single dose	16	↓	0.14 (0.11; 0.18)	0.08 (0.07; 0.11)	NA
Anti-HIV Drugs							
Atazanavir (ATV)/ritonavir (rtv)	300 mg ATV/ 100 mg rtv qd for 20 days	750 mg q8h for 10 days	14	↓	0.79 (0.74; 0.84)	0.80 (0.76; 0.85)	0.85 (0.75; 0.98)
Darunavir (DRV)/ritonavir (rtv)	600 mg DRV/ 100 mg rtv bid for 20 days	750 mg q8h for 10 days	11 (N=14 for C_{max})	↓	0.64 (0.61; 0.67)	0.65 (0.61; 0.69)	0.68 (0.63; 0.74)
Efavirenz	600 mg qd for 20 days	750 mg q8h for 10 days	21	↓	0.91 (0.82; 1.02)	0.74 (0.65; 0.84)	0.53 (0.44; 0.65)
Fosamprenavir (fAPV)/ ritonavir (rtv)	700 mg fAPV/ 100 mg rtv bid for 20 days	750 mg q8h for 10 days	18	↓	0.67 (0.63; 0.71)	0.68 (0.63; 0.72)	0.70 (0.64; 0.77)
Lopinavir (LPV)/ritonavir (rtv)	400 mg LPV/ 100 mg rtv bid for 20 days	750 mg q8h for 10 days	12	↓	0.47 (0.41; 0.52)	0.46 (0.41; 0.52)	0.48 (0.40; 0.56)
Ritonavir	100 mg single dose	750 mg single dose	14	↑	1.30 (1.15; 1.47)	2.00 (1.72; 2.33)	NA
Ritonavir	100 mg q12h for 14 days	750 mg q12h for 14 days	5	↓	0.85 (0.63; 1.13)	0.76[b,c] (0.60; 0.97)	0.68 (0.57; 0.82)
Tenofovir disoproxil fumarate (TDF)	300 mg qd TDF for 7days	750 mg q8h for 7 days	16	↔	1.01 (0.96; 1.05)	1.00 (0.94; 1.07)	1.03 (0.93; 1.14)
Tenofovir disoproxil fumarate (TDF) and efavirenz (EFV)	600 mg EFV /300 mg TDF qd for 7 days	1125 mg q8h for 7 days	15	↓	0.86[c] (0.76; 0.97)	0.82[c] (0.73; 0.92)	0.75[c] (0.66; 0.86)
	600 mg EFV /300 mg TDF qd for 7 days	1500mg q12h for 7 days	16	↓	0.97[c] (0.88; 1.06)	0.80[b,c] (0.73; 0.88)	0.52[c] (0.42; 0.64)

NA = not available/ not applicable; N = Number of subjects with data; qd = once daily; bid = twice daily; q8h = every 8 hours; q12h = every 12 hours

[a] The direction of the arrow (↑ = *increase,* ↓ = *decrease,* ↔ = *no change*) indicates the direction of the change in PK

[b] $C_{avg,ss}$ = Average concentrations at steady state (AUC_τ/τ).

[c] Value with co-administered drug and telaprevir / value with telaprevir 750 mg q8h alone

Table 23 Drug Interactions: Summary of Pharmacokinetic Parameters for Coadministered Drugs in the Presence of Telaprevir

Coadministered Drug	Dose and Schedule		n	Effect on Drug PK[a]	LS Mean Ratio (90% CI) of Coadministered Drug PK With/Without Telaprevir[b]		
	Coadministered Drug	Telaprevir			C_{max}	AUC	C_{min}
Alprazolam	0.5 mg single dose	750 mg q8h for 10 days	17	↑	0.97 (0.92; 1.03)	1.35 (1.23; 1.49)	NA
Amlodipine	5 mg single dose	750 mg q8h for 7 days	19	↑	1.27 (1.21; 1.33)	2.79 (2.58; 3.01)	NA
Atorvastatin	20 mg single dose	750 mg q8h for 7 days	19	↑	10.60 (8.74;12.85)	7.88 (6.84; 9.07)	NA
Cyclosporine A (CsA)	100 mg single dose when administered alone; 10 mg single dose when coadministered with telaprevir (D8)	750 mg q8h for 11 days	9	↑	0.13 (0.11;0.16) **Dose norm.:** 1.32 (1.08;1.60)	0.46 (0.39; 0.55) **Dose norm.:** 4.64 (3.90;5.51)	NA
Digoxin	2 mg single dose	750 mg q8h for 11 days	20	↑	1.50 (1.36; 1.65)	1.85 (1.70; 2.00)	NA
Escitalopram	10 mg qd, for 7 days	750 mg q8h for 14 days	13	↓	0.70 (0.65; 0.76)	0.65 (0.60; 0.70)	0.58 (0.52; 0.64)
Ethinyl estradiol (EE), coadministered with norethindrone (NE)	0.035 mg qd EE/ 0.5 mg qd NE for 21 days	750 mg q8h for 21 days	24	↓	0.74 (0.68; 0.80)	0.72 (0.69; 0.75)	0.67 (0.63; 0.71)
Ketoconazole	400 mg single dose	1250 mg q8h for 4 doses	81	↑	1.23 (1.14; 1.33)	1.46 (1.35; 1.58)	NA
	200 mg single dose	1250 mg q8h for 4 doses	28	↑	1.75 (1.51; 2.03)	2.25 (1.93; 2.61)	NA
R-Methadone	Methadone maintenance therapy (40 to 120 mg/daily)	750 mg q8h for 7 days	15	↓	0.71 (0.66; 0.76)	0.71 (0.66; 0.76)	0.69 (0.64; 0.75)
S-Methadone	Methadone maintenance therapy (40 to 120 mg/daily)	750 mg q8h for 7 days	15	↓	0.65 (0.60; 0.71)	0.64 (0.58; 0.70)	0.60 (0.54; 0.67)
Midazolam (iv)	0.5 mg iv single dose	750 mg q8h for 9 days	22	↑	1.02 (0.8; 1.31)	3.40 (3.04; 3.79)	NA
Midazolam (oral)	2 mg oral single dose	750 mg q8h for 11 days	21	↑	2.86 (2.52; 3.25)	8.96 (7.75; 10.35)	NA
Norethindrone (NE), coadministered with EE	0.035 mg qd EE/ 0.5 mg qd NE for 21 days	750 mg q8h for 7 days	24	↔	0.85 (0.81; 0.89)	0.89 (0.86; 0.93)	0.94 (0.87; 1.0)
Tacrolimus	2 mg single dose when	750 mg q8h for 13 days	9	↑	2.34 (1.68;3.25)	17.6 (13.2; 23.3)	NA

Table 23 Drug Interactions: Summary of Pharmacokinetic Parameters for Coadministered Drugs in the Presence of Telaprevir

Coadministered Drug	Dose and Schedule		n	Effect on Drug PK[a]	LS Mean Ratio (90% CI) of Coadministered Drug PK With/Without Telaprevir [b]		
	Coadministered Drug	Telaprevir			C_{max}	AUC	C_{min}
	administered alone; 0.5 mg single dose when coadministered with telaprevir (D8)				**Dose norm.:** 9.35 (6.73;13.0)	**Dose norm.:** 70.3 (52.9;93.4)	
Zolpidem	5 mg single dose	750 mg q8h for 10 days	19	↓	0.58 (0.52;0.66)	0.53 (0.45; 0.64)	NA
Anti-HIV Drugs							
Atazanavir (ATV), boosted with ritonavir (rtv)	300 mg ATV/ 100 mg rtv qd for 20 days	750 mg q8h for 10 days	7	↔	0.85 (0.73; 0.98)	1.17 (0.97; 1.43)	1.85 (1.40; 2.44)
Darunavir (DRV), boosted with ritonavir (rtv)	600 mg DRV/ 100 mg rtv bid for 20 days	750 mg q8h for 10 days	11[b]	↓	0.60 (0.56; 0.64)	0.60 (0.57; 0.63)	0.58 (0.52; 0.64)
	600 mg DRV/ 100 mg rtv bid for 24 days	1125 mg q12h for 4 days	15	↓	0.53 (0.47; 0.59)	0.49 (0.43; 0.55)	0.42 (0.35; 0.51)
Efavirenz	600 mg qd for 20 days	750 mg q8h for 10 days	21	↔	0.84 (0.76; 0.93)	0.93 (0.87; 0.98)	0.98 (0.94; 1.02)
Efavirenz (EFV), coadministered with tenofovir disoproxil fumarate (TDF)	600 mg EFV /300 mg TDF qd for 7 days	1125 mg q8h for 7 days	15	↓	0.76 (0.68; 0.85)	0.82 (0.74; 0.90)	0.90 (0.81; 1.01)
	600 mg EFV /300 mg TDF qd for 7days	1500 mg q12h for 7days	16	↓	0.80 (0.74; 0.86)	0.85 (0.79; 0.91)	0.89 (0.82; 0.96)
Fosamprenavir (fAPV), boosted with ritonavir (rtv)	700 mg fAPV/ 100 mg bid rtv for 20 days	750 mg q8h for 10 days	18	↓	0.65 (0.59; 0.70)	0.53 (0.49; 0.58)	0.44 (0.40; 0.50)
	700 mg fAPV/ 100 mg bid rtv for 24 days	1125 mg q12h for 4 days	17[c]	↓	0.60 (0.55; 0.67)	0.51 (0.47; 0.55)	0.42 (0.37; 0.47)
Lopinavir (LPV), boosted with ritonavir (rtv)	400 mg LPV/ 100 mg rtv b.i.d. for 20 days	750 mg q8h for 10 days	12	↔	0.96 (0.87; 1.05)	1.06 (0.96; 1.17)	1.14 (0.96; 1.36)
Tenofovir disoproxil fumarate	300 mg qd for 7 days	750 mg q8h for 7 days	16	↑	1.30 (1.16; 1.45)	1.30 (1.22; 1.39)	1.41 (1.29;1.54)

Table 23 Drug Interactions: Summary of Pharmacokinetic Parameters for Coadministered Drugs in the Presence of Telaprevir

Coadministered Drug	Dose and Schedule		n	Effect on Drug PK[a]	LS Mean Ratio (90% CI) of Coadministered Drug PK With/Without Telaprevir [b]		
	Coadministered Drug	Telaprevir			C_{max}	AUC	C_{min}
Tenofovir, on coadministration of tenofovir disoproxil fumarate (TDF) and efavirenz (EFV)	600 mg EFV /300 mg TDF qd for 7 days	1125 mg q8h for 7 days	15	↑	1.22 (1.12; 1.33)	1.10 (1.03; 1.18)	1.17 (1.06; 1.28)
	600 mg EFV /300 mg TDF qd for 7 days	1500 mg q12h for 7 days	16	↑	1.24 (1.13; 1.37)	1.10 (1.03; 1.17)	1.06 (0.98; 1.15)

[a] The direction of the arrow (↑ = *increase*, ↓ = *decrease*, ↔ = *no change*) indicates the direction of the change in PK.
[b] n = 14 for $C_{max.}$
[c] n = 18 for $C_{min.}$

In interpreting these results, in addition to metabolic DDIs, protein displacement has been shown to occur both in vitro and in vivo during combination with telaprevir and may explain some of the observed lowered concentrations of telaprevir or the concomitant medication. In an in vitro study, it was shown that ritonavir and warfarin increased the free fraction of telaprevir by about 30%. Although telaprevir did not change protein binding of ritonavir or warfarin in this in vitro study, an increase in the free fraction of R-methadone by about 33% was observed in an in vivo DDI study. Because of this increase in free fraction, the unbound (i.e. effective) R-methadone concentration was not affected during co-administration of telaprevir, despite a reduction in the total R-methadone concentrations by about 30%. Since the HIV protease inhibitors included in the DDI studies are highly bound to plasma proteins (85% to 99%), with varying contribution of albumin and alpha-acid glycoprotein, competition for binding sites could contribute to the observed changes in total concentrations for these agents. In this case, the unbound concentrations would likely remain unchanged and the interaction may not be clinically significant.[31]

8 CLINICAL SAFETY

The telaprevir safety population included 3,819 subjects exposed to telaprevir in pooled and non-pooled analyses of 43 Phase 1-3 studies (Table 24). From these 43 studies, there were 5 completed Phase 2 studies and 3 completed Phase 3 studies that were conducted in patients with genotype 1 chronic hepatitis C in which 2830 subjects were exposed to telaprevir.

Telaprevir safety data were pooled across studies as appropriate, given the design and population of the individual studies, to provide a comprehensive safety summary and analysis, to improve the precision of incidence estimates, and to account for the total safety experience available.

Table 24 Overall Safety Populations

Study Type (Population)	Number of Subjects Exposed to Telaprevir[a]
Pooled Phase 1 single-dose studies (healthy subjects)	315
Pooled Phase 1 multiple-dose studies (healthy subjects)[b]	362
Non-pooled Phase 1 studies (healthy subjects)[c]	209
Non-pooled Phase 1b/2a studies (subjects with CHC)	103
Pooled Phase 2-3 studies (regardless of type of control or prior treatment status, subjects with CHC)	2,830
Total Exposure	**3,819**

[a] All subjects who received at least one dose of telaprevir
[b] Including subjects of Part A (healthy subjects) of the Phase 1b Study 101
[c] Referring to non-HCV-infected subjects, regardless of comorbidities such as renal or hepatic impairment
Note: this table does not include the 3 ongoing studies, 2 taste-profiling studies, 8 studies conducted by Mitsubishi Tanabe Pharma Company, and 1 investigator-initiated study.

Safety data from Phase 2 studies demonstrated that the safety profile of telaprevir in treatment-naive subjects was similar to that in prior treatment-failure subjects. As a result, safety data from placebo-controlled studies in both treatment-naive and treatment-failure subjects from Phase 2 and 3 were pooled as this represents the most clinically relevant comparison between telaprevir and placebo. Since the T12/PR arms from these placebo-controlled studies are consistent with the proposed label indication and make up the majority of subjects who received telaprevir in these studies, the primary comparisons are made between the T12/PR and Pbo/PR groups. Subjects who were randomized to receive 8 weeks of telaprevir in Phase 3 or 24 weeks of telaprevir in Phase 2 are not included in this T12/PR group, but their safety data are described in the Any T/PR group that is included in several general safety tables. Additionally, it is important to note that this placebo-controlled pooling was the treatment population from which all sub-group analyses and the adverse drug reaction (ADR) evaluation was conducted. Safety data from the placebo-controlled pooling of Phase 2-3 studies are shown in Sections 8.1 to 8.7.

Safety data from each of the individual Phase 3 studies was also analyzed since the treatment populations or study designs in each of these studies varied. Safety data from individual Phase 3 studies are shown in Section 8.1.10.

After NDA submission and during the FDA review, an additional pooling was conducted using just the Phase 3 studies (Studies 108, 111, and C216); two were placebo-controlled

(108, C216) and one was not (111). This pooling included all treatment arms in these studies, and therefore included 1797 subjects exposed to telaprevir, Peg-IFN-alfa-2a, and RBV and 493 subjects exposed to placebo, Peg-IFN-alfa-2a, and RBV. Safety analyses were conducted with the subject data in this pooling to support the safety data included in the draft package insert. It may be concluded that there are no relevant qualitative differences in the safety data from this Phase 3 study pooling as compared with the data from the placebo-controlled Phase 2-3 pooling, but small quantitative differences exist. The results of these pooled analyses of the three Phase 3 studies are shown in Section 8.7 of this briefing document.

8.1 Safety Data from Phase 2-3 Studies in Subjects With Genotype 1 CHC

As noted above, the analysis of safety results from the pooled placebo-controlled Phase 2-3 studies is focused on the T12/PR group because this group is most relevant to the proposed telaprevir treatment regimen, and is most directly comparable with the Pbo/PR group. Data for all subjects who received telaprevir in combination with Peg-IFN/ RBV (Any T/PR group) are shown in some tables, but results are not further discussed because of the overall similarities with the T12/PR group.

8.1.1 Extent of Exposure

In the pooled placebo-controlled Phase 2-3 studies, 2012 subjects received at least 1 dose of telaprevir with Peg-IFN/RBV or with Peg-IFN alone. In the primary analyses for the Phase 2-3 placebo-controlled pooling, 1346 subjects from the T12/PR group are compared with 764 subjects from the Pbo/PR group (Table 25).

In all, 73.0% of subjects in the T12/PR group and 49.1% of subjects in the Pbo/PR group completed treatment with at least 1 study drug in their treatment regimen. In the T12/PR group, there were 326.32 subject-years of treatment exposure and in the Pbo/PR group, there were 190.38 subject-years of treatment exposure across the five placebo-controlled Phase 2-3 studies.

Adverse events led to premature discontinuation more frequently in the T12/PR group compared with the Pbo/PR group, whereas reaching a virologic endpoint was the most commonly reported reason for premature discontinuation in the Pbo/PR group.

Table 25 Placebo-Controlled Phase 2-3 Studies: Subject Disposition and Reasons for Discontinuation

Study Drug Discontinuation Type, n (%)	T12/PR (750 mg q8h) n = 1,346	Any T/PR n = 1,823	Pbo/PR n = 764
Completed	982 (73.0)	1297 (71.1)	375 (49.1)
Discontinued – reason[a]	364 (27.0)	526 (28.9)	389 (50.9)
Adverse Event	145 (10.8)	211 (11.6)	53 (6.9)
Death	0	0	1 (0.1)
Lost to Follow-up	6 (0.4)	9 (0.5)	10 (1.3)
Physician Decision	9 (0.7)	9 (0.5)	3 (0.4)
Subject Ineligible to Continue the Study	1 (0.1)	1 (0.1)	0
Subject Non-Compliant	31 (2.3)	50 (2.7)	10 (1.3)
Subject Reached A Virologic Endpoint[b]	131 (9.7)	197 (10.8)	289 (37.8)
Subject Withdrew Consent	8 (0.6)	10 (0.5)	7 (0.9)
Other	33 (2.5)	39 (2.1)	16 (2.1)

[a] Subjects were counted as discontinuing their treatment regimen if they discontinued all study drugs in their regimen (telaprevir/placebo, Peg-IFN, and RBV, as applicable). Discontinuation of study drugs may not have occurred at the same time. Reasons for discontinuation of the last drug(s) in the treatment regimen as reported by the investigator are listed in this table.

[b] Subjects discontinued based on their virologic response status and predefined virologic stopping rules.

N: number of subjects with data; n: number of subjects with that observation.

8.1.2 Baseline Demographics and Disease Characteristics of the Safety Population

Baseline demographics were balanced between treatment groups (Table 26). The majority of subjects were male, white, and residents of North America or Europe. Most subjects were between the ages of 45 and 65 years.

Mean baseline HCV RNA levels and mean time since HCV diagnosis were similar in the T12/PR and Pbo/PR groups (Table 27). More subjects in the T12/PR group had cirrhosis compared with the Pbo/PR group; this was most likely because of the 2:2:1 (treatment:treatment:placebo) randomization scheme in study C216, which contained the highest proportion of subjects with cirrhosis. In the other 2 studies, in which subjects with cirrhosis were enrolled (Studies 106 and 108), the randomization ratio was equal.

Similar proportions of treatment-naive subjects and subjects who had failed prior treatment with Peg-IFN/RBV were randomized to both groups. In contrast, the Pbo/PR group had a substantially higher proportion of treatment-naive subjects than subjects with prior treatment failure. Again, this difference was most likely related to the 2:2:1 (treatment:treatment:placebo) randomization ratio used in study C216, which enrolled the most treatment-failure subjects.

Table 26 Placebo-Controlled Phase 2-3 Studies: Demographic Data

Variable	T12/PR (750 mg q8h) n = 1,346	Any T/PR n = 1,823	Pbo/PR n = 764
Sex, n (%)			
Female	465 (34.5)	651 (35.7)	300 (39.3)
Male	881 (65.5)	1172 (64.3)	464 (60.7)
Race, n (%)			
Asian	24 (1.8)	29 (1.6)	19 (2.5)
Black	75 (5.6)	126 (6.9)	60 (7.9)
Other	37 (2.7)	44 (2.4)	15 (2.0)
White	1210 (89.9)	1624 (89.1)	670 (87.7)
Ethnicity, n (%)			
Hispanic or Latino	117 (8.7)	170 (9.3)	75 (9.8)
Not Hispanic or Latino	1229 (91.3)	1653 (90.7)	689 (90.2)
Age category, n (%)			
≤ 45 years	414 (30.8)	567 (31.1)	278 (36.4)
> 45 to ≤ 65 years	912 (67.8)	1232 (67.6)	477 (62.4)
> 65 years	20 (1.5)	24 (1.3)	9 (1.2)
BMI category, n (%)			
< 25 kg/m²	521 (38.7)	686 (37.6)	269 (35.2)
≥ 25 to < 30 kg/m²	528 (39.2)	714 (39.2)	303 (39.7)
≥ 30 kg/m²	290 (21.5)	414 (22.7)	190 (24.9)
Region, n (%)			
Europe	547 (40.6)	657 (36.0)	274 (35.9)
North America	645 (47.9)	975 (53.5)	426 (55.8)
Other	154 (11.4)	191 (10.5)	64 (8.4)

N: number of subjects with data; n: number of subjects with observations. The number of subjects with data can vary per variable, but the % reflects the true percentage of observations.

There were no relevant differences in the distribution of demographic and baseline disease characteristics between subgroups, except for a greater number of subjects with cirrhosis and bridging fibrosis in the treatment-failure population compared with the treatment-naive population, and a higher number of subjects with cirrhosis and bridging fibrosis in subjects aged 45 to 65 years compared with subjects 45 years or younger.

Table 27 Placebo-Controlled Phase 2-3 Studies: Baseline Disease Characteristics

Subjects, N (%)	T12/PR (750 mg q8h) n = 1,346	Any T/PR n = 1,823	Pbo/PR n = 764
Baseline log_{10} HCV RNA (log_{10} IU/mL)			
Mean (SD)	6.49 (0.637)	6.47 (0.653)	6.44 (0.661)
Median (Range)	6.60 (2.0; 7.8)	6.58 (2.0; 7.8)	6.57 (2.9; 7.9)
Time since HCV diagnosis (years)			
Mean (SD)	7.53 (7.258)	7.21 (7.094)	6.24 (6.328)
Median (Range)	5.80 (0.1; 94.4)	5.30 (0.1; 94.4)	4.45 (0.2; 40.1)
Assessment of liver fibrosis[a], n (%)			
No or minimal fibrosis	406 (30.2)	554 (30.4)	262 (34.3)
Portal fibrosis	518 (38.5)	709 (38.9)	299 (39.1)
Bridging fibrosis	243 (18.1)	335 (18.4)	139 (18.2)
Cirrhosis	179 (13.3)	225 (12.3)	64 (8.4)
Prior Response, n (%)			
Treatment-naive	701 (52.1)	1065 (58.4)	518 (67.8)
Treatment-failure	645 (47.9)	758 (41.6)	246 (32.2)

[a] Result of most recent liver biopsy. The allowed time window in which subjects must have had a liver biopsy depended on the study. Liver biopsies were performed maximally 3 years before the first day of study drug dosing.
AFP: alpha-fetoprotein.
N: number of subjects with data; n: number of subjects with observations. The number of subjects with data can vary per variable, but the % reflects the true percentage of observations.

8.1.3 Concomitant Therapies

During the telaprevir/placebo treatment phase, concomitant use of acetaminophen (48.8% vs 49.2%) and ibuprofen (19.5% vs 22.0%) was similar in the T12/PR and Pbo/PR groups, whereas diphenhydramine hydrochloride (13.9% vs 8.4%) and hydroxyzine (10.4% vs 2.7%) were used more frequently in the T12/PR group compared with the Pbo/PR group. This pattern of concomitant therapies use is consistent with the higher incidence of pruritus and rash in the T12/PR group and may represent treatment for those conditions. No other concomitant therapies were used by more than 10% of subjects in the T12/PR group during the telaprevir/placebo treatment phase.

During the overall treatment phase, the most common concomitant therapies used were acetaminophen (51.2% vs 51.4%), ibuprofen (21.6% vs 24.5%), diphenhydramine hydrochloride (15.5% vs 10.7%), and hydroxyzine (13.0% vs 5.1%) in the T12/PR and Pbo/PR groups, respectively. In addition, hydrocortisone was used by 10.8% of subjects in the T12/PR group during the overall treatment phase compared with 6.4% of subjects in the Pbo/PR group.

8.1.4 Summary of Adverse Events by Preferred Term

The majority of subjects in both the T12/PR and Pbo/PR groups experienced AEs during the telaprevir/placebo treatment phase (Table 28). In the T12/PR group, no AE-related deaths occurred during the telaprevir/placebo treatment phase, whereas 1 AE-related death occurred in the placebo group. Serious AEs, AEs of at least grade 3, and AEs leading to permanent treatment discontinuation were all higher in the T12/PR group than in the Pbo/PR group.

These results are consistent with analyses of AEs that occurred during the telaprevir/placebo treatment phase in each individual Phase 3 study (Section 8.1.10).

Table 28 Placebo-Controlled Phase 2-3 Studies: Summary of Adverse Events – *Telaprevir/Placebo Treatment Phase*

Adverse Events, n (%)	T12/PR (750 mg q8h) n = 1,346	Any T/PR n = 1,823[a]	Pbo/PR n = 764
AEs	1,323 (98.3)	1,797 (98.6)	740 (96.9)
Deaths	0[b]	0[b]	1 (0.13)[b,c]
SAEs	93 (6.9)	121 (6.6)	22 (2.9)
AEs of at least grade 3	321 (23.8)	417 (22.9)	94 (12.3)
AEs leading to permanent discontinuation of			
T/Pbo	191 (14.2)	273 (15.0)	31 (4.1)
all study drugs at 1 time	109 (8.1)	157 (8.6)	28 (3.7)
AEs at least possibly related to T/Pbo	1,275 (94.7)	1,746 (95.8)	707 (92.5)

[a] Includes T8 arms from Study 108 and T24 arm from Study 106.
[b] Refers to the number (%) of subjects who died as a result of an AE with onset during the telaprevir/placebo treatment phase.
[c] 1 subject with a life-threatening AE that was not resolved at last study visit subsequently died due to this AE.
N: number of subjects with data.

In the overall treatment phase, there was a small increase in the incidence of AEs, as compared with the telaprevir/placebo treatment phase (Table 29).

In addition to the 1 subject in the Pbo/PR group who had an AE leading to death during the telaprevir/placebo treatment phase, 1 subject each in the T12/PR and Pbo/PR groups died as a result of an AE with onset during Peg-IFN/RBV treatment.

The incidence of SAEs, AEs of grade 3 or higher, AEs leading to permanent discontinuation of Peg-IFN, and AEs leading to permanent or temporary discontinuation of RBV or RBV dose reduction were all higher in the T12/PR group than in the Pbo/PR group. The majority of temporary discontinuations of RBV were due to anemia-related events, gastrointestinal disorders, and skin and subcutaneous tissue disorders and the majority of RBV dose reductions were due to anemia-related events (Section 8.2.2).

Table 29 Placebo-Controlled Phase 2-3 Studies: Summary of Adverse Events – *Overall Treatment Phase*

Adverse Events, n (%)	T12/PR (750 mg q8h) n = 1,346	Any T/PR n = 1,823	Pbo/PR N = 764
AEs	1330 (98.8)	1805 (99.0)	746 (97.6)
Deaths	1 (< 0.1)[a]	1 (< 0.1)[a]	3 (0.4)[a,b]
SAEs	154 (11.4)	201 (11.0)	52 (6.8)
AEs of at least grade 3	402 (29.9)	522 (28.6)	142 (18.6)
AEs leading to permanent discontinuation of			
T/Pbo	191 (14.2)	273 (15.0)	31 (4.1)
Peg-IFN	147 (10.9)	212 (11.6)	53 (6.9)
RBV	157 (11.7)	228 (12.5)	53 (6.9)
AEs leading to temporary discontinuation of RBV	124 (9.2)	175 (9.6)	38 (5.0)
AEs leading to RBV dose reduction	326 (24.2)	439 (24.1)	123 (16.1)

[a] Refers to the number (%) of subjects who died as a result of an AE with onset during the overall treatment phase.
[b] Includes 1 subject with a life-threatening AE that was not resolved at last study visit. The subject subsequently died due to this AE.
N: number of subjects with data

8.1.5 Common Adverse Events

During the telaprevir/placebo treatment phase, the most commonly reported AEs (more than 20% of subjects in the T12/PR group) were fatigue, pruritus, nausea, headache, influenza-like illness, rash, anemia, insomnia, diarrhea, and pyrexia (Table 30). The AEs that were reported more frequently in the T12/PR group than in the Pbo/PR group (at least 5.0% higher) were pruritus, nausea, rash, anemia, and diarrhea.

Table 30 Placebo-Controlled Phase 2-3 Studies: Incidence of Adverse Events in More Than 20% of Subjects – *Telaprevir/Placebo Treatment Phase*

Adverse Events, n (%)	T12/PR (750 mg q8h) n = 1,346	Pbo/PR n = 764
Fatigue	700 (52.0)	392 (51.3)
Pruritus	632 (47.0)	189 (24.7)
Nausea	531 (39.5)	223 (29.2)
Headache	521 (38.7)	289 (37.8)
Influenza-like illness	444 (33.0)	235 (30.8)
Rash	443 (32.9)	132 (17.3)
Anemia	392 (29.1)	95 (12.4)
Insomnia	365 (27.1)	182 (23.8)
Diarrhea	353 (26.2)	144 (18.8)
Pyrexia	277 (20.6)	161 (21.1)

Note: If a subject has multiple events within a SOC or preferred term, the subject is counted once.
The incidence of adverse events highlighted in orange was ≥ 5% higher in the T12/PR group compared with the Pbo/PR group.

For AEs that were reported less frequently (in 5.0-20.0% range), the AEs that were reported more frequently (at least 5.0% higher) in the T12/PR group than in the Pbo/PR group were hemorrhoids, anorectal discomfort, anal pruritus, and dysgeusia (Table 31).

Table 31 Placebo-Controlled Phase 2-3 Studies: Incidence of Adverse Events in 5.0% to 20% of Subjects More Common in the Telaprevir Group – *Telaprevir/Placebo Treatment Phase*

Adverse Events, n (%)	T12/PR (750 mg q8h) n = 1,346	Any T/PR n = 1,823	Pbo/PR n = 764
Asthenia	242 (18.0)	302 (16.6)	125 (16.4)
Eye disorders	227 (16.9)	308 (16.9)	98 (12.8)
Investigations	207 (15.4)	272 (14.9)	93 (12.2)
Cough	201 (14.9)	272 (14.9)	135 (17.7)
Myalgia	193 (14.3)	274 (15.0)	143 (18.7)
Dry skin	194 (14.4)	244 (13.4)	112 (14.7)
Irritability	183 (13.6)	265 (14.5)	127 (16.6)
Dyspnea	180 (13.4)	238 (13.1)	80 (10.5)
Depression	177 (13.2)	239 (13.1)	109 (14.3)
Vomiting	167 (12.4)	230 (12.6)	69 (9.0)
Chills	166 (12.3)	249 (13.7)	109 (14.3)
Hemorrhoids	164 (12.2)	224 (12.3)	20 (2.6)
Dizziness	150 (11.1)	214 (11.7)	82 (10.7)
Arthralgia	146 (10.8)	207 (11.4)	123 (16.1)
Injection site erythema	140 (10.4)	194 (10.6)	62 (8.1)
Anorexia	129 (9.6)	183 (10.0)	66 (8.6)
Dysgeusia	128 (9.5)	170 (9.3)	32 (4.2)
Dry mouth	110 (8.2)	149 (8.2)	37 (4.8)
Decreased appetite	109 (8.1)	145 (8.0)	63 (8.2)
Anorectal discomfort	106 (7.9)	143 (7.8)	16 (2.1)
Abdominal pain	103 (7.7)	123 (6.7)	55 (7.2)
Neutropenia	102 (7.6)	155 (8.5)	95 (12.4)
Alopecia	98 (7.3)	130 (7.1)	67 (8.8)
Anxiety	89 (6.6)	128 (7.0)	66 (8.6)
Ear and labyrinth disorders	86 (6.4)	108 (5.9)	54 (7.1)
Anal pruritus	83 (6.2)	106 (5.8)	7 (0.9)
Back pain	78 (5.8)	99 (5.4)	77 (10.1)
Dyspnea exertional	74 (5.5)	105 (5.8)	41 (5.4)
Dyspepsia	74 (5.5)	93 (5.1)	43 (5.6)
Pharyngolaryngeal pain	72 (5.3)	94 (5.2)	37 (4.8)
Pruritus generalized	72 (5.3)	99 (5.4)	16 (2.1)
Vision blurred	69 (5.1)	99 (5.4)	29 (3.8)
Disturbance in attention	67 (5.0)	98 (5.4)	42 (5.5)
Vascular disorders	60 (4.5)	86 (4.7)	43 (5.6)
Pain	59 (4.4)	85 (4.7)	51 (6.7)
Injury, poisoning and procedural complications	48 (3.6)	68 (3.7)	43 (5.6)
Abdominal pain upper	44 (3.3)	59 (3.2)	39 (5.1)

N: number of subjects with data; n: number of subjects with observation
Note: If a subject has multiple events within a SOC or preferred term, the subject is counted once.

8.1.6 Adverse Events Grade 3 or Higher

During the telaprevir/placebo treatment phase, anemia was the most frequently reported AE of Grade 3 or higher occurring in more than 0.5% of subjects in the T12/PR group (Table 32). Additional grade 3 or higher AEs reported in more than 0.5% of subjects included neutropenia, leukopenia, rash, pruritus, fatigue, thrombocytopenia, and nausea.

Table 32 Placebo-Controlled Phase 2-3 Studies: Incidence of Adverse Events of at Least Grade 3 That Occurred in More Than 0.5% of Subjects – *Telaprevir/Placebo Treatment Phase*

Adverse Events, n (%)	T12/PR (750 mg q8h) n = 1,346	Any T/PR n = 1,823	Pbo/PR n = 764
Any AE of at least grade 3	321 (23.8)	417 (22.9)	94 (12.3)
Blood and lymphatic system disorders			
Anemia	64 (4.8)	92 (5.0)	6 (0.8)
Neutropenia	49 (3.6)	62 (3.4)	31 (4.1)
Leukopenia	29 (2.2)	32 (1.8)	10 (1.3)
Thrombocytopenia	16 (1.2)	18 (1.0)	1 (0.1)
Lymphopenia	8 (0.6)	8 (0.4)	1 (0.1)
Skin and subcutaneous tissue disorders			
Rash	29 (2.2)	41 (2.2)	1 (0.1)
Pruritus	17 (1.3)	21 (1.2)	1 (0.1)
Rash generalized	7 (0.5)	9 (0.5)	0
Rash maculopapular	7 (0.5)	7 (0.4)	0
General disorders and administration site conditions			
Fatigue	16 (1.2)	25 (1.4)	3 (0.4)
Asthenia	11 (0.8)	11 (0.6)	3 (0.4)
Influenza like illness	6 (0.4)	7 (0.4)	4 (0.5)
Investigations			
Neutrophil count decreased	11 (0.8)	12 (0.7)	3 (0.4)
White blood cell count decreased	8 (0.6)	8 (0.4)	1 (0.1)
Blood uric acid increased	7 (0.5)	7 (0.4)	0
Gastrointestinal disorders			
Nausea	13 (1.0)	18 (1.0)	1 (0.1)
Nervous system disorders			
Headache	10 (0.7)	12 (0.7)	7 (0.9)
Psychiatric disorders			
Insomnia	7 (0.5)	8 (0.4)	2 (0.3)

N: number of subjects with data; n: number of subjects with observations
Note: If a subject has multiple events within a SOC or preferred term, the subject is counted once.

8.1.7 Adverse Events by Prior Treatment Status

In both the T12/PR and Pbo/PR groups, the frequency of SAEs, AEs of grade 3 or higher and AE-related discontinuations were comparable between treatment-naive subjects and prior treatment-failure subjects (Table 33).

Table 33 Placebo-Controlled Phase 2-3 Studies: Summary of Adverse Events by Prior Treatment Status – *Telaprevir/Placebo Treatment Phase*

	T12/PR (750 mg q8h)		Pbo/PR	
Adverse events, n (%)	Treatment-naive n = 701	Treatment-failure n = 645	Treatment-naive n = 518	Treatment-failure n = 246
SAEs	54 (7.7)	39 (6.0)	12 (2.3)	10 (4.1)
AEs of at least grade 3	153 (21.8)	168 (26.0)	62 (12.0)	32 (13.0)
AEs leading to permanent discontinuation of T/Pbo	111 (15.8)	80 (12.4)	22 (4.2)	9 (3.7)

In the T12/PR group, treatment-naive subjects reported greater frequency of nausea (45.8% vs 32.6%), dizziness (14.1% vs 7.9%), depression (16.0% vs 10.1%), insomnia (29.7% vs 24.3%), and abdominal pain upper (6.1% vs 0.2%) compared with prior treatment-failure subjects during the telaprevir/placebo phase. Conversely, abdominal pain (10.4% vs 5.1%) and leukopenia (5.9% vs 2.1%) were more frequently reported by prior treatment failure subjects compared with treatment-naive subjects during the telaprevir/placebo phase.

8.1.8 Adverse Drug Reactions

Adverse drug reactions (ADRs) are either AEs or laboratory abnormalities that are considered at least possibly related to the use of a drug. Using a structured and systematic review of all AEs from both the Phase 2-3 program and from the Phase 1 program, a list of all potential ADR preferred terms for the telaprevir development program was created. This list was carefully analyzed by a cross-functional group of physicians and statisticians and a final ADR list was generated.

The incidence of adverse drug reactions (ADRs) of at least grade 2 was higher in the T12/PR group than in the Pbo/PR group (see Appendix). During the telaprevir/placebo treatment phase, the most frequently reported ADRs of at least Grade 2 in the T12/PR group with an incidence of at least 3.0% were anemia, rash, pruritus, nausea, diarrhea, vomiting, hemorrhoids, and proctalgia. Likewise, the most frequently reported ADRs of at least Grade 3 in the T12/PR group with an incidence of at least 1.0% were anemia, rash, thrombocytopenia, lymphopenia, pruritus, nausea.

Laboratory abnormality-related ADRs observed in more than 20.0% of subjects in the T12/PR group included hemoglobin, absolute lymphocyte count, platelet count, and hyperuricemia (see Appendix).

8.1.9 Deaths, Serious Adverse Events, and Discontinuations from Treatment

8.1.9.1 Deaths

In the pooled placebo-controlled Phase 2-3 studies, 5 of the 2,012 subjects in the telaprevir groups and 4 of the 764 subjects in the placebo group died (Table 34). None of the 9 deaths occurred during the telaprevir/placebo treatment phase. One death that occurred in the telaprevir groups was considered possibly related to telaprevir by the investigator. This death was caused by malignant lung neoplasm that developed 96 days after discontinuing telaprevir. The subject died 138 days after receiving the last dose of telaprevir.

Table 34 Placebo-Controlled Phase 2-3 Studies: Deaths

Study	Age/ Gender	Event	Time to event (days)	Study drug action	Additional factors
T/PR Arm					
C216	59/M	End stage pulmonary carcinoma	138[a]	Peg-IFN/RBV discontinued	38 years smoking 12-20 cigarettes/day
108	37/F	Death	295[a]	n/a	Decompensated liver cirrhosis, viral infection, and pneumonia
108	47/M	Death	403[a]	n/a	Suspected upper respiratory viral infection
108	49/F	Suicide	396[a]	n/a	Self-inflicted gunshot
104	51/F	Car accident	323[a]	n/a	n/a
Pbo/PR Arm					
106	52/M	NSCLC	32[c]	n/a	Tobacco use, asbestosis
C216	48/F	ARDS and cholecystitis	324[c]	n/a	n/a
C216	56/F	Coma unknown origin	-44[c]	All drugs discontinued	Blood culture positive for staph aureus
108	56/M	Suicide	96[c]	n/a	Self inflicted gunshot; history of hypothyroidism (TSH 45.0 IU/mL)

[a] After last dose of telaprevir.
[b] After last dose of telaprevir, Peg-IFN, and RBV.
[c] After last dose of placebo.

8.1.9.2 Serious Adverse Events

During the telaprevir/placebo treatment phase, anemia and rash were the only SAEs reported in more than 0.5% of subjects in the T12/PR group (Table 35). To further assess the potential association between telaprevir administration and SAEs, a conservative analysis was conducted that included all SAEs that occurred during the telaprevir/placebo phase or within 30 days after this phase. This analysis did not identify any additional SAEs occurring in more than 0.5% of the subjects in the T12/PR group.

Table 35 Placebo-Controlled Phase 2-3 Studies: Incidence of Serious Adverse Events That Occurred in More Than 0.5% of Subjects −*Telaprevir/Placebo Treatment Phase*

Adverse events, n (%)[a]	T12/PR (750 mg q8h) N = 1346	Any T/PR N = 1823	Pbo/PR N = 764
Any SAE	93 (6.9)	121 (6.6)	22 (2.9)
Blood and lymphatic system disorders			
Anemia	21 (1.6)	34 (1.9)	3 (0.4)
Skin and subcutaneous tissue disorders			
Rash	10 (0.7)	12 (0.7)	0

[a] Adverse events by system organ class and preferred term.
N: number of subjects with data; n: number of subjects with observations
Note: If a subject has multiple events within a SOC or preferred term, the subject is counted once.

8.1.9.3 Discontinuations Due to Adverse Events

Adverse events more frequently led to permanent discontinuation of all study drugs in the T12/PR group than in the Pbo/PR group (Table 36). Rash and anemia were the AEs that were most frequently associated with treatment discontinuation in the T12/PR arm.

Table 36 Placebo-Controlled Phase 2-3 Studies: Incidence of Adverse Events that Occurred in More Than 0.5% of Subjects Leading to Permanent Discontinuation of All Study Drugs – *Telaprevir/Placebo Treatment Phase*

Adverse event, n (%)	T12/PR (n = 1,346)	Pbo/PR (n = 764)
Rash	13 (1.0)	0 (0)
Anemia	11 (0.8)	3 (0.4)
Fatigue	10 (0.7)	6 (0.8)
Pruritus	8 (0.6)	1 (0.1)
Nausea	5 (0.4)	8 (1.0)
Myalgia	2 (0.1)	4 (0.5)

8.1.10 Adverse Events from the Individual Phase 3 Studies

The three Phase 3 studies for telaprevir enrolled either treatment-naive or prior treatment-failure populations, utilized different randomization ratios, and assessed different treatment durations. Therefore, safety data for each Phase 3 study were analyzed without pooling to identify any additional potential safety signals. Overall, safety data from individual studies were consistent with that reported in the pooled analysis.

8.1.10.1 Study 108 Adverse Events

In study 108, 1,061 subjects (97.5%) experienced 1 or more AEs classified as related to study drug during the telaprevir/placebo treatment phase (Table 37), compared with 1070 subjects (98.3%) during the overall treatment phase. Four deaths occurred during the study, including 1 death that occurred during the overall treatment phase and 3 deaths that occurred after the safety follow-up but prior to the Week 72 assessment; no deaths were classified as related to telaprevir or placebo by the investigator.

Table 37 Study 108: Summary of Adverse Event Incidence −*Telaprevir/Placebo Treatment Phase*

Adverse Events, n (%)	T8/PR n = 364	T12/PR n = 363	T/PR n = 727	Pbo/PR n = 361
≥ 1 AE	362 (99.5)	361 (99.4)	723 (99.4)	347 (96.1)
≥ 1 AE classified as related to any study drug[a]	359 (98.6)	359 (98.9)	718 (98.8)	343 (95.0)
≥ 1 serious AE (SAE)	18 (4.9)	19 (5.2)	37 (5.1)	7 (1.9)
≥ 1 related SAE[a]	15 (4.1)	15 (4.1)	30 (4.1)	4 (1.1)
AEs leading to death	0	0	0	0
AEs that led to reduction of dose of any study drug[b]	143 (39.3)	126 (34.7)	269 (37.0)	82 (22.7)
AEs that led to interruption of dosing of any study drug[b]	44 (12.1)	50 (13.8)	94 (12.9)	20 (5.5)
AEs that led to permanent discontinuation of telaprevir/placebo only	27 (7.4)	41 (11.3)	68 (9.4)	3 (0.8)
AEs that led to permanent discontinuation of treatment regimen[c]	28 (7.7)	25 (6.9)	53 (7.3)	13 (3.6)
AEs that led to permanent discontinuation of all study drugs at 1 time	26 (7.1)	19 (5.2)	45 (6.2)	13 (3.6)

[a] At least possibly related to any study drug per investigator.
[b] Dose reduction and interruption was for 1 or more study drugs.
[c] Discontinuation of study drugs may have not occurred at the same time; the adverse event(s) that led to permanent discontinuation of treatment regimen occurred when the last study drug(s) (1, 2, or 3 study drugs) was discontinued.

8.1.10.2 Study C216 Adverse Events

In study C216, the majority of subjects in each treatment group experienced 1 or more AEs during the telaprevir/placebo phase (Table 38). Most AEs were Grade 1 or 2 in severity; however, Grade 3 AEs were more frequent in the pooled T/PR48 group than in the Pbo/PR48 group. The majority of subjects experienced at least 1 AE that was considered at least possibly related to telaprevir/placebo by the investigator during the telaprevir/placebo treatment phase.

Three deaths occurred during the study. One subject in the Pbo/PR group died during the telaprevir/placebo treatment phase and 1 subject in both the T12(LI)/PR48 and Pbo/PR48 groups died during the follow-up phase. The subject in the T12(LI)/PR48 group died during follow-up due to an SAE reported during treatment with Peg-IFN/RBV alone (lung neoplasm malignant considered possibly related to telaprevir/placebo by the investigator; reported onset 96 days after last intake of telaprevir/placebo). Both deaths in the Pbo/PR48 group resulted from SAEs considered not related to telaprevir/placebo by the investigator.

Table 38 Study C216: Summary of Adverse Event Incidence –*Telaprevir/Placebo Treatment Phase*

Adverse Events, n (%)	T12/PR48	T12(LI)/PR48	Pooled T/PR48	Pbo/PR48
Relapser population	**n = 145**	**n = 141**	**n = 286**	**n = 68**
Any AE	140 (96.6)	134 (95.0)	274 (95.8)	67 (98.5)
Deaths	0	0	0	0
Any SAE	12 (8.3)	5 (3.5)	17 (5.9)	0
Any grade 3 AE	43 (29.7)	40 (28.4)	83 (29.0)	9 (13.2)
Any AE leading to permanent discontinuation of telaprevir/placebo	27 (18.6)	15 (10.6)	42 (14.7)	1 (1.5)
Any AE related to telaprevir	130 (89.7)	125 (88.7)	255 (89.2)	55 (80.9)
Any AE related to Peg-IFN	137 (94.5)	133 (94.3)	270 (94.4)	65 (95.6)
Any AE related to RBV	131 (90.3)	128 (90.8)	259 (90.6)	58 (85.3)
Non-responder population	**n = 121**	**n = 123**	**n = 244**	**n = 64**
Any AE	118 (97.5)	121 (98.4)	239 (98.0)	59 (92.2)
Deaths	0	0	0	1 (1.6)
Any SAE	6 (5.0)	12 (9.8)	18 (7.4)	4 (6.3)
Any grade 3 AE	34 (28.1)	35 (28.5)	69 (28.3)	12 (18.8)
Any AE leading to permanent discontinuation of telaprevir/placebo	12 (9.9)	14 (11.4)	26 (10.7)	3 (4.7)
Any AE related to telaprevir/placebo	107 (88.4)	108 (87.8)	215 (88.1)	46 (71.9)
Any AE related to Peg-IFN	114 (94.2)	117 (95.1)	231 (94.7)	58 (90.6)
Any AE related to RBV	107 (88.4)	113 (91.9)	220 (90.2)	57 (89.1)
Null-responder population	**n = 72**	**n = 75**	**n = 147**	**n = 37**
Any AE	70 (97.2)	74 (98.7)	144 (98.0)	33 (89.2)
Deaths	0	0	0	1 (2.7)
Any SAE	3 (4.2)	5 (6.7)	8 (5.4)	2 (5.4)
Any grade 3 AE	14 (19.4)	24 (32.0)	38 (25.9)	9 (24.3)
Any AE leading to permanent discontinuation of telaprevir/placebo	3 (4.2)	10 (13.3)	13 (8.8)	2 (5.4)
Any AE at related to telaprevir/placebo	64 (88.9)	66 (88.0)	130 (88.4)	22 (59.5)
Any AE related to Peg-IFN	68 (94.4)	70 (93.3)	138 (93.9)	33 (89.2)

8.1.10.3 Study 111 Adverse Events

In Study 111, 6.9% of subjects experienced 1 or more AEs during the telaprevir/placebo phase that led to permanent discontinuation of treatment (Table 39). The most common AEs during the telaprevir/placebo phase that led subjects to permanently discontinue the treatment regimen were fatigue, anemia, nausea, and vomiting. There were no deaths during either treatment phase of the study; however, 1 death occurred during the extended follow-up period.

Table 39 Study 111: Summary of Adverse Event Incidence −*Telaprevir/Placebo Treatment Phase*

	Randomized (eRVR+)		Assigned (eRVR-)		Subtotal T12/PR48	
Adverse Events, n (%)	**T12/PR24 n = 162**	**T12/PR48 n = 160**	**T12/PR48 n = 118**	**Other[d] n = 100**	**(eRVR+/-) n = 278**	**Total n = 540**
≥ 1 AE	161 (99.4)	160 (100)	117 (99.2)	99 (99.0)	277 (99.6)	537 (99.4)
≥ 1 AE classified as related to any study drug[a]	161 (99.4)	159 (99.4)	117 (99.2)	98 (98.0)	276 (99.3)	535 (99.1)
≥ 1 serious AE (SAE)	3 (1.9)	6 (3.8)	2 (1.7)	16 (16.0)	8 (2.9)	27 (5.0)
≥ 1 related SAE[a]	2 (1.2)	5 (3.1)	0	13 (13.0)	5 (1.8)	20 (3.7)
AEs leading to death	0	0	0	0	0	0
AEs that led to reduction of dose of any study drug[b]	69 (42.6)	68 (42.5)	49 (41.5)	44 (44.0)	117 (42.1)	230 (42.6)
AEs that led to interruption of dosing of any study drug[b]	25 (15.4)	26 (16.3)	23 (19.5)	13 (13.0)	49 (17.6)	87 (16.1)
AEs that led to permanent discontinuation of telaprevir only	21 (13.0)	20 (12.5)	13 (11.0)	11 (11.0)	33 (11.9)	65 (12.0)
≥ 1 AE that led to permanent discontinuation of all study drug[c]	0	0	0	37 (37.0)	0	37 (6.9)

[a] At least possibly related to any study drug, per investigator.
[b] Dose reduction and interruption was for Peg-IFN/RBV only.
[c] Discontinuation of study drugs may have not occurred at the same time; the adverse event(s) that led to permanent discontinuation of the treatment regimen occurred when as the last study drug(s) (1, 2, or 3 study drugs) was discontinued.
[d] Subjects in the Other group received at least 1 dose of study drug, but prematurely discontinued treatment before Week 20 and were not randomized or assigned to a treatment regimen.

8.2 Additional Analyses of Specific Adverse Events

To comprehensively assess AEs that occurred more frequently in the telaprevir treatment arms that may be considered most relevant to individual subjects, additional analyses were conducted on rash, pruritus, anemia, and anorectal signs and symptoms.

To evaluate these safety events, special search categories (SSCs) were created that included all possible investigator-defined preferred AE terms that might represent rash, pruritus, anemia, or anorectal signs and symptoms. All preferred AE terms that might represent similar medical concepts (even from different system organ classes) were included into the SSCs established for each of these four commonly occurring AEs. In this SSC analysis, any individual subject who reported a preferred AE term that was included in one of these pre-defined SSCs was included in the frequency for that SSC, but each individual subject could be counted only once for an individual SSC.

The 5 pooled placebo-controlled Phase 2-3 studies formed the basis for this analysis; the SSC data from these pooled studies was comparable to the data from a larger pooling that also included uncontrolled Phase 2-3 studies.

8.2.1 Rash

Rash is a well-described AE in subjects receiving Peg-IFN/RBV, but the frequency and severity of rash were higher in subjects receiving telaprevir plus Peg-IFN/RBV compared with subjects receiving Peg-IFN/RBV alone.

To improve the management of rash and thereby minimize its impact on subjects, and to potentially understand the mechanism underlying the rash, a rash assessment and management plan was initiated during the placebo-controlled Phase 2 studies (104 and 104EU), and was later modified for Phase 3 as new data became available. The rash assessment and management plan specifically defined criteria for evaluating rash severity, and provided general rash management recommendations. The plan also included mandatory permanent study regimen discontinuation for Grade 3 rashes in the ongoing Phase 2 studies and additional modifications that were implemented based on Phase 2 experience.

Overall, the rash assessment and management plan had no effect on the rate of rash occurrence; however, it did have an effect on the rate of rash-related discontinuations of all treatment drugs during the Phase 3 program. In Phase 3, 1.1% of T12/PR subjects had rash-related discontinuations of all study drugs compared with 6.2% in Phase 2 (Table 40). Therefore, modifications made to the rash management plan appear to have been effective in allowing subjects to remain on treatment.

Table 40 Placebo-Controlled Phase 2-3 Studies: Permanent Discontinuation of All Study Drugs due to Rash SSC Events in Phase 2 Studies Versus Phase 3 Studies – *Overall Treatment Phase*

Permanent Discontinuation of All Study Drugs	T12/PR (750 mg q8h)		Any T/PR		Pbo/PR	
	N	n (%)	N	n (%)	N	n (%)
Phase 2 studies	450	28 (6.2)	566	35 (6.2)	271	1 (0.4)
Phase 3 studies	893	10 (1.1)	1257	13 (1.0)	493	0

N: number of subjects with data, n: number of subjects with observation
Note that results in this table are based on Peg-IFN discontinuation since per protocol subjects had to discontinue all other drugs if Peg-IFN was discontinued.

In the pooled placebo-controlled Phase 2-3 studies, rash SSC events were more frequently reported in the T12/PR group than in the Pbo/PR group during the telaprevir/placebo treatment phase (Table 41). In both groups, the majority of subjects with rash SSC events had events of Grade 1 or 2. Rash SSC events of at least grade 3 were observed at a higher rate in the T12/PR group than in the Pbo/PR group, and these events led to permanent discontinuation of telaprevir/placebo more frequently in the T12/PR group than in the Pbo/PR group.

Pooling of rash data in the 5 placebo-controlled studies allowed several characteristics about rash SSC events occurring in the T12/PR group to be described:

- The majority events began during the first 4 weeks of treatment, and many resolved during the first 24 weeks of treatment

- The median time to onset was 25.0 days in the T12/PR group compared with 40.5 days in the Pbo/PR group. First onset of rash occurred within 4 weeks after the initiation of telaprevir treatment in about one-third of all cases
- 92.1% of events did not progress to a higher severity grade
- Of the 807 subjects in the T12/PR group who experienced an event during the overall treatment phase, 621 (77.0%) received concomitant medication for the treatment of rash. This included 433 subjects (53.7%) who received topical corticosteroids, 319 subjects (39.5%) who received systemic antihistamines, and 50 subjects (6.2%) who received systemic corticosteroids
- Multivariate logistic regression analysis indicated that age, BMI, region, race, and prior treatment status had an effect on the probability to develop rash during the telaprevir/placebo treatment phase; however, the observed differences between subgroups were < 10% for all variables except race
- Logistic regression analysis suggested that there was no statistically significant relationship between occurrence and severity of events and exposure to telaprevir and Peg-IFN/RBV concentrations at Week 4

Table 41 Placebo-Controlled Phase 2-3 Studies: Summary of Rash SSC Events – *Telaprevir/Placebo Treatment Phase*

Number (%) of subjects with:	**T12/PR (750 mg q8h) N = 1,346**	**Any T/PR N = 1,823**	**Pbo/PR N = 764**
AEs	746 (55.4)	1007 (55.2)	250 (32.7)
Deaths	0	0	0
SAEs	23 (1.7)	26 (1.4)	0
AEs of at least grade 3	65 (4.8)	81 (4.4)	3 (0.4)
AEs of grade 2	186 (13.8)	242 (13.3)	44 (5.8)
AEs of grade 1	495 (36.8)	684 (37.5)	203 (26.6)
AEs leading to permanent discontinuation of T/Pbo	78 (5.8)	107 (5.9)	2 (0.3)
AEs leading to permanent discontinuation of all study drugs at the same time	35 (2.6)	43 (2.4)	0
AEs at least possibly related to T/Pbo	701 (52.1)	949 (52.1)	225 (29.5)
AEs of at least grade 3, AEs leading to permanent discontinuation of any study drug, or SAEs	92 (6.8)	125 (6.9)	3 (0.4)

N = Number of subjects with data.

8.2.1.1 Dermatology Expert Panel (DEP) Summary Report

A DEP was convened to evaluate rash events potentially associated with telaprevir and to characterize rash cases based on their review. The panel reviewed 221 rash cases from the telaprevir development program, primarily from Phases 2-3.

Based on a thorough review of photographs and biopsies, the DEP concluded that the visual appearance and histopathology of rash associated with telaprevir is comparable to the rash associated with Peg-IFN/RBV, though telaprevir-associated rashes were of increased severity and extent.

Relative to common drug rashes (e.g. due to antibiotics), the DEP also concluded that the telaprevir-related rash is different clinically and histologically. In particular, telaprevir-associated rashes are of greater severity, may occur at any time during treatment, and resolve over weeks after discontinuation of telaprevir.

Case presentations suggestive of urticaria were very infrequent; none that the DEP assessed appeared to be life-threatening type 1 hypersensitivity reactions or anaphylactic reactions. No cases were fatal.

The DEP determined that almost all rashes involved < 30% body surface area (BSA); this differed from the assessment of investigators who judged most rashes to have > 50% BSA involvement. The DEP also concluded that rashes were primarily pruritic and eczematous; though some had an additional maculopapular component; these rashes are not consistent with a typical hypersensitivity reaction. A DEP consultant dermatopathologist reviewed blinded biopsy samples from these 221 cases and was able to group the rash histopathology patterns into a limited number of subtypes. Histologic examination showed that most rashes had a spongiotic pattern with lymphocytic perivascular infiltration, which correlates with the eczematous appearance. None of the biopsies was suggestive of vasculitis.

Actual diagnoses made by clinical investigators sometimes diverged from the diagnosis made by members of the DEP.

There is no worldwide consensus on the definition of severe cutaneous adverse reaction (SCAR); however, per consensus by the DEP, dermatological conditions that are life-threatening and frequently attributed to drug therapy were reported as SCAR, including Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP). In order to consistently assess cases for SCAR, the DEP adapted scoring sheets used by RegiSCAR (European Registry of Severe Cutaneous Adverse Reactions (SCAR) to Drugs and Collection of Biological Samples; http://regiscar.uni-freiburg.de/). Similar to RegiSCAR, suspected SCAR cases were to be scored for likelihood of diagnosis (i.e., definite, probable and possible).

Clinical investigators in the telaprevir development program reported 6 individual subjects with a SCAR.

- One confirmed case of SJS that occurred 11 weeks after telaprevir discontinuation and was attributed to another medication
  - DEP considered this as definitive SJS
- One case in Japan that occurred 43 days after the 1st dose of T/PR, where the subject had a fever and lymphadenopathy but also had significant eosinophilia and was considered to have features probably suggestive of SJS
  - DEP considered this as probable SJS and possible DRESS
- One case in Japan that occurred 64 days after the start of treatment, where the subject had extensive target lesions and eosinophilia
  - DEP considered this as definite DRESS

- One case that occurred 53 days after the start of treatment, where the subject had a grade 3 rash and eosinophilia
  - DEP considered this as possible DRESS
- One case described as DRESS by the investigator
  - DEP considered this as unlikely to be DRESS
- One case in Japan that was described as SJS by the investigator
  - DEP considered this unlikely to be SJS

In summary, of these 6 SCAR cases reported by investigators, the DEP assessed 4 as suspected SCAR cases (1 definite SJS, 1 definite DRESS and 2 possible DRESS cases). The one definite SJS case (study 108) occurred eleven weeks after the last dose of telaprevir while the subject was on peginterferon, ribavarin and bupropion. This case was assessed as not drug related.

In addition to a review of investigator reported SCAR cases, the DEP identified 2 cases suggestive of SJS (1 probable and 1 possible) and 9 cases suggestive of DRESS (1 probable, 8 possible). Hence the DEP identified a total of 3 cases suggestive of SJS and 11 cases suggestive of DRESS. Of note, 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.

8.2.1.2 Human Leukocyte Antigen (HLA) Genotypes and MDR1 Genotypes in Subjects With Rash

An analysis of multiple HLA alleles was performed to determine if the genetic background of any individual subject may increase or decrease the risk of developing a rash with T/PR treatment.

HLA typing of subjects with and without rash did not reveal a strong association of any HLA allele with rash in subjects receiving T/PR. No association was discerned for the presence of a C3435T or C1236T MDR1 genotype and rash severity.

8.2.1.3 Treatment and Management of Rash

The rashes reported in the majority of subjects were of mild to moderate severity and did not progress. While no specific treatment recommendations can be made, many subjects with rash were given treatment for it, and the most common of these were oral or topical antihistamines and/or topical corticosteroids.

Telaprevir treatment discontinuation was not required for the majority of subjects who reported rash. Rash-related discontinuation of telaprevir/placebo occurred in 5.8% of subjects in the T12/PR group and in 0.3% of subjects in the Pbo/PR group. Rash-related discontinuation of all study drugs occurred in 2.6% of subjects in the T12/PR group and in 0 subjects in the Pbo/PR group. In subjects who discontinued treatment, improvement of rash occurred after discontinuation, however some rashes may take weeks for complete resolution.

During the telaprevir clinical program, if a severe rash (involving more than 50% BSA) occurred, telaprevir was to be discontinued immediately; Peg-IFN/RBV could have been continued. If improvement was not observed within 7 days of telaprevir discontinuation, sequential or simultaneous interruption or discontinuation of RBV and/or Peg-IFN could be considered. If medically indicated, earlier interruption or discontinuation of Peg-IFN/RBV could be considered. Subjects were to be monitored until the rash resolved.

Any rash associated with significant systemic symptoms, mucous membrane ulceration, target lesions, epidermal detachment, vesicles, or bullae required immediate and permanent discontinuation of telaprevir, Peg-IFN, and RBV treatment.

8.2.2 Anemia and Hemoglobin Analyses

Anemia is a well-recognized AE in subjects receiving Peg-IFN/RBV, and telaprevir has been shown to have an additive but reversible effect on the incidence and severity of anemia.

Both Peg-IFN and RBV treatment are associated with decreased hemoglobin levels and anemia. Ribavirin monotherapy results in a dose-dependent, extravascular, hemolytic anemia in most subjects, whereas Peg-IFN suppresses bone marrow red blood cell production. No specific mechanism has been identified yet for the effect of telaprevir on hemoglobin; however, a multivariate logistic regression analysis demonstrated a statistically significant relationship between occurrence and severity of hemoglobin abnormalities during the telaprevir/placebo phase, exposure (AUC) to telaprevir, and Peg-IFN and RBV concentrations at Week 4. In vitro mechanistic evaluations revealed no direct effects of telaprevir on typical human erythrocyte cell health parameters.

In a pooled analysis of the placebo-controlled Phase 2-3 telaprevir studies, subjects receiving T/PR had higher rates of anemia SSC events, Grade 3 anemia, and anemia-related discontinuations (Table 42). The incidence of anemia in the T12/PR group was highest during the second month of treatment, with a median time to onset of 44 days and median duration of 85 days (Figure 20). By comparison, the median duration of anemia in the Pbo/PR group was 115 days.

In Phase 2-3 studies, anemia was managed with RBV dose reductions in accordance with approved RBV labeling. If RBV was permanently discontinued for anemia, telaprevir/placebo had to be permanently discontinued as well. Erythropoiesis-stimulating agents (ESAs) were prohibited from most studies, and their use was reported in only 1.0% and 0.8% of T12/PR and Pbo/PR subjects, respectively. A single study that allowed use of ESAs (Study C208) was not placebo-controlled and is therefore not included in this safety analysis.

Table 42 Placebo-Controlled Phase 2-3 Studies: Summary of Anemia SSC Events – *Telaprevir/Placebo Treatment Phase*

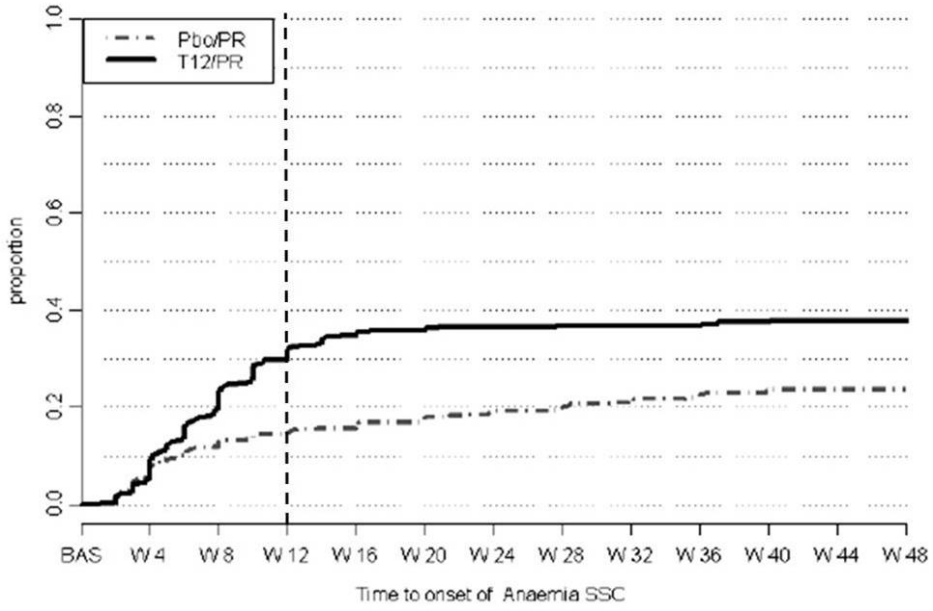
	Subjects, n (%)	
Anemia SSC Events	**T12/PR (750 mg q8h) N = 1,346**	**Pbo/PR N = 764**
AEs	432 (32.1)	113 (14.8)
Deaths	0	0
SAEs	22 (1.6)	3 (0.4)
AEs ≥ grade 3	66 (4.9)	6 (0.8)
AEs leading to permanent discontinuation of		
T/Pbo	37 (2.7)	4 (0.5)
RBV	17 (1.3)	3 (0.4)
all study drugs at the same time	12 (0.9)	4 (0.5)
AEs leading to RBV dose reduction	291 (21.6)	72 (9.4)
Other Management		
Blood transfusions, %	1.6	0.1
ESAs, %	1.0	0.8

During the telaprevir treatment phase, anemia was reported more than twice as frequently for subjects in the T12/PR group than in the Pbo/PR group. Discontinuation of telaprevir/placebo due to anemia SSC events showed no clear association with time on treatment. Anemia that was serious, at least grade 3 in severity, or led to permanent discontinuation of telaprevir/placebo was infrequent, though more frequently observed in the T12/PR group than in the Pbo/PR group. In addition, AEs leading to permanent or temporary discontinuation of RBV or to RBV dose reductions were also more frequently observed in the T12/PR group than in the Pbo/PR.

During the overall treatment phase, anemia infrequently led to permanent discontinuation of Peg-IFN (1.0% with T12/PR and 0.5% with Pbo/PR) or RBV (1.6% with T12/PR and 0.5% with Pbo/PR). In contrast, RBV dose reductions occurred in 23.9% of T12/PR subjects and 13.9% of Pbo/PR subjects in the overall treatment phase. Temporary discontinuations of RBV occurred in 4.8% and 1.6% of subjects in the T12/PR and Pbo/PR groups, respectively. Although premature discontinuation of RBV was associated with a decrease in SVR, RBV dose reductions and interruptions did not appear to adversely affect SVR rates.

A multivariate regression analysis identified sex, age, BMI, and region as potential risk factors for anemia; however, the observed differences between subgroups were 10.0% or less for sex, age, and BMI.

Figure 20 Placebo-Controlled Phase 2-3 Studies: Time to Onset of First Anemia SSC Event - *Overall Treatment Phase*



8.2.2.1 Hemoglobin Laboratory Results

A mean decline of hemoglobin of 2-3 g/dL has been consistently reported in studies of Peg-IFN/RBV therapy, requiring RBV dose reductions or discontinuations in some subjects.[32] Decreases in hemoglobin requiring modifications in the treatment regimen, including RBV does reductions and discontinuations, were also experienced in the telaprevir clinical development program.

In a pooled analysis of hemoglobin abnormalities in the placebo-controlled Phase 2-3 telaprevir studies, grade 1 to 4 hemoglobin abnormalities were observed in 93.3% and 79.2% of subjects in the T12/PR and Pbo/PR groups, respectively. Likewise, grade 3 decreases in hemoglobin were observed in 51.1% and 24.0% of subjects in the T12/PR and Pbo/PR groups, respectively.

During the first 4 weeks of treatment, mean baseline hemoglobin levels were reduced by 3.0 g/L in the T12/PR group and 2.6 g/dL in the Pbo/PR group (Figure 21). At week 12, mean baseline hemoglobin levels were reduced by 4.0 g/dL in the T12/PR group and 3.1 g/dL in the Pbo/PR group. In both groups, the hemoglobin level nadir was reached between weeks 12 to 14 of treatment. Hemoglobin nadir values below 10.0 g/dL were observed in a total of 33.7% and 13.6% of subjects in the T12/PR and Pbo/PR groups, respectively, whereas hemoglobin nadir values below 8.5 g/dL were observed in 8.3% and 2.3% of subjects in the T12/PR and Pbo/PR groups, respectively.

After completion of telaprevir treatment in the T12/PR group, hemoglobin levels increased to levels observed in the Pbo/PR group over a 12-week period. There were also sharp increases in hemoglobin levels 4 weeks after completion of treatment in subjects who completed either 24 weeks of T/PR treatment or 48 weeks of T/PR or Pbo/PR treatment (Figure 22).

Figure 21 Placebo-Controlled Phase 2-3 Studies: Mean (SE) Values of Hemoglobin (g/dL) Over Time – *Overall Treatment Phase*

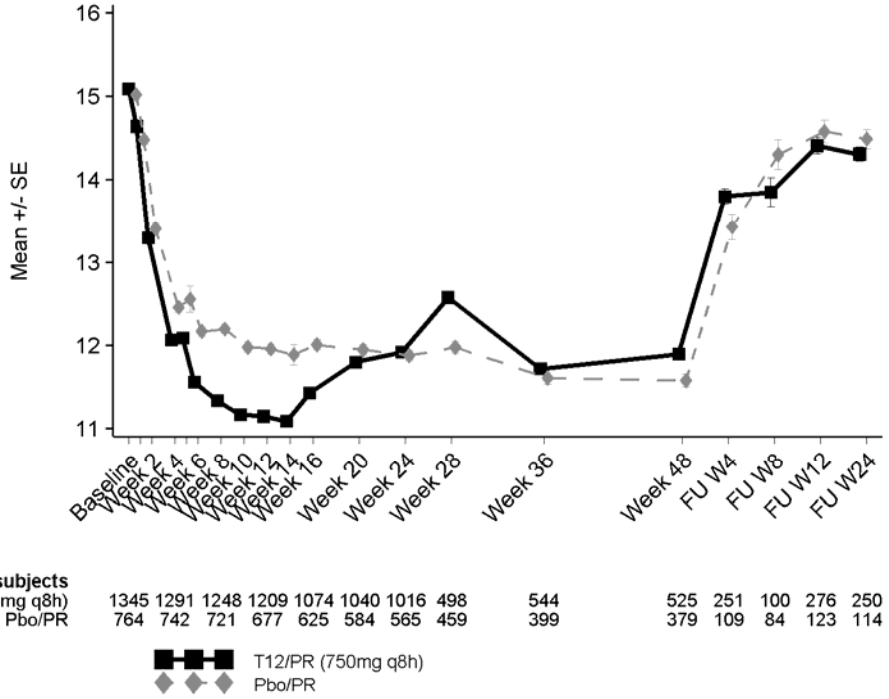
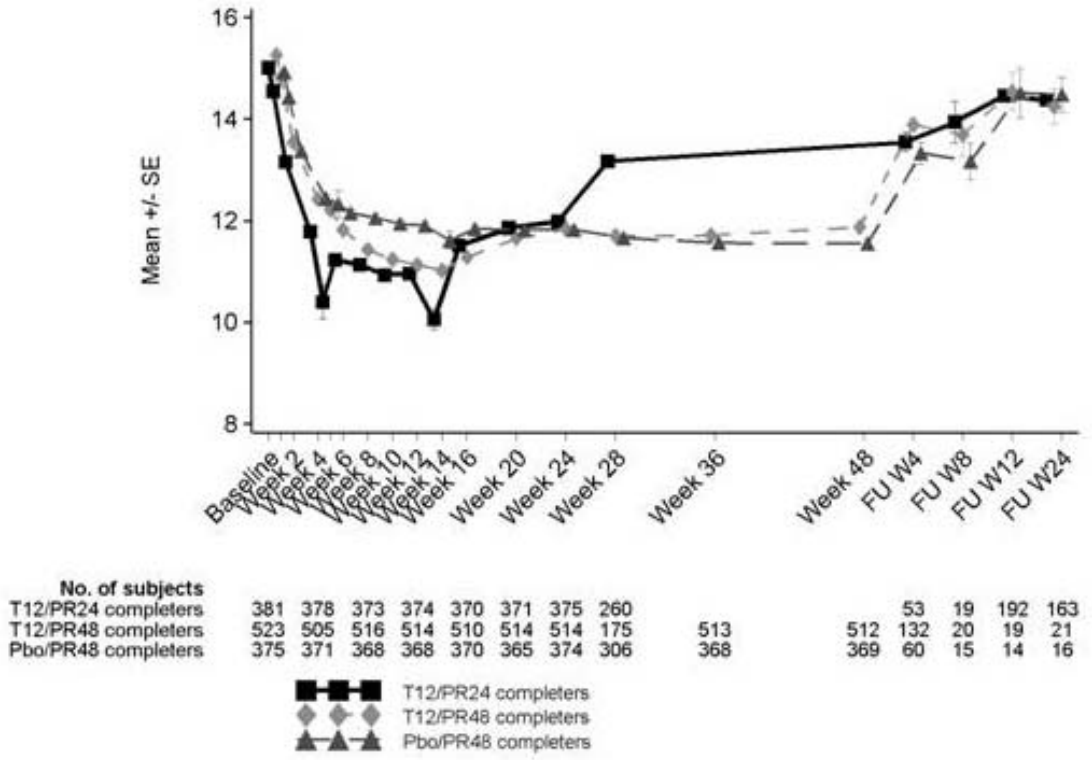


Figure 22 Placebo-Controlled Phase 2-3 Studies: Hemoglobin Levels Over Time in Subjects Who Completed 24 Weeks or 48 Weeks of Therapy



Relationship Between Hemoglobin Abnormalities and Pharmacokinetic Parameters

A possible relationship between the occurrence and severity of hemoglobin abnormalities during the telaprevir/placebo phase and PK parameters was evaluated by means of logistic regression analysis, based on data from the pooled controlled and uncontrolled Phase 2-3 studies.

This analysis indicated that there was a statistically significant relationship between the occurrence and severity of hemoglobin abnormalities during the telaprevir/placebo phase and 3 PK parameters: exposure (AUC) to telaprevir ($P < 0.001$), Peg-IFN concentration at Week 4 ($P < 0.001$), and RBV concentration at Week 4 ($P < 0.001$).

Reticulocytes Percentage and Reticulocyte Production Index

Decreases in mean hemoglobin values were more pronounced in the T12/PR group than in the Pbo/PR group. However, the corresponding increase in mean reticulocyte percentage was blunted relative to the hemoglobin changes seen for the T12/PR group as compared with the Pbo/PR group.

Mean reticulocyte production index (RPI) values suggest that peripheral destruction of red blood cells is likely to be the main mechanism of treatment-induced anemia up to Week 8. Thereafter, the RPI is inadequate in the T12/PR group (< 2) in the presence of anemia,

suggesting an additional mechanism is likely to be related to production of red blood cells in those subjects.

Telaprevir use may be associated with a mild bone marrow suppressive effect that could explain the larger shift in hemoglobin values compared with baseline levels. This is supported by the blunted reticulocytosis, and slightly higher lymphopenia and thrombocytopenia observed during the same period. After the end of telaprevir/placebo treatment, hemoglobin and reticulocyte differences between the T12/PR and Pbo/PR groups resolved rapidly.

Subgroup Analyses for Hemoglobin Abnormalities

Differences between subgroups of 10.0% or more for hemoglobin decreases of Grade 2 or higher in the T12/PR group included a higher incidence in subjects older than 45 years than in subjects aged 45 years or under, and a higher incidence in white subjects than in black subjects (of uncertain relevance due to the low number of black subjects).

In the Pbo/PR group, comparable differences were observed between these subgroups.

No differences were observed for hemoglobin decreases of Grade 2 or higher in the T12/PR group between female and male subjects (78.7% and 79.5%, respectively) and between subjects of different BMI categories (< 25 kg/m^2: 78.5%, 25-30 kg/m^2: 81.9%, and ≥ 30 kg/m^2: 75.1%).

8.2.2.2 Treatment and Management of Anemia

During the telaprevir clinical program, hemoglobin was monitored and RBV reduced in accordance with PEG-IFN/RBV prescribing information. If ribavirin was permanently discontinued for the management of anemia, telaprevir was also to be permanently discontinued. If telaprevir was discontinued for anemia, patients may have continued treatment with peginterferon alfa and ribavirin. Ribavirin could be restarted per the dosing modification guidelines for ribavirin. The dose of telaprevir could not be reduced and telaprevir could not be restarted if discontinued. In the telaprevir clinical program, erythropoietin stimulating agent (ESA) use was generally prohibited.

8.2.3 Anorectal Signs and Symptoms

In the pooled placebo-controlled Phase 2-3 studies, anorectal SSC events were more frequently reported in the T12/PR group than in the Pbo/PR group during the telaprevir/placebo treatment phase (Table 43). Serious anorectal SSC events, events of at least grade 3, and events leading to permanent discontinuation of telaprevir/placebo occurred in < 1.0% of the subjects in the T12/PR group and did not occur in the Pbo/PR group.

During the telaprevir/placebo treatment phase, hemorrhoids (12.2% vs 2.6%), anorectal discomfort (7.9% vs 2.1%), and anal pruritus (6.2% vs 0.9%) were the most frequently reported preferred terms within the anorectal SSC in the T12/PR group versus the Pbo/PR group. Other anorectal SSC event preferred terms were reported in less than 5.0% of subjects in the T12/PR group.

The median time to onset of the first anorectal SSC event during the overall treatment phase was 9.0 days (range: 1 to 350 days) in the T12/PR group and 37.0 days (range: 1 to 351 days) in the Pbo/PR group.

Table 43 Placebo-Controlled Phase 2-3 Studies: Summary of Anorectal SSC Events – *Telaprevir/Placebo Treatment Phase*

Number (%) of subjects with:	**T12/PR (750 mg q8h) N = 1346**	**Any T/PR N = 1823**	**Pbo/PR N = 764**
AEs	352 (26.2)	475 (26.1)	41 (5.4)
Deaths	0	0	0
SAEs	1 (< 0.1)	1 (< 0.1)	0
AEs of at least grade 3	9 (0.7)	12 (0.7)	0
AEs leading to permanent discontinuation of T/Pbo	7 (0.5)	8 (0.4)	0
AEs at least possibly related to T/Pbo	278 (20.7)	374 (20.5)	33 (4.3)

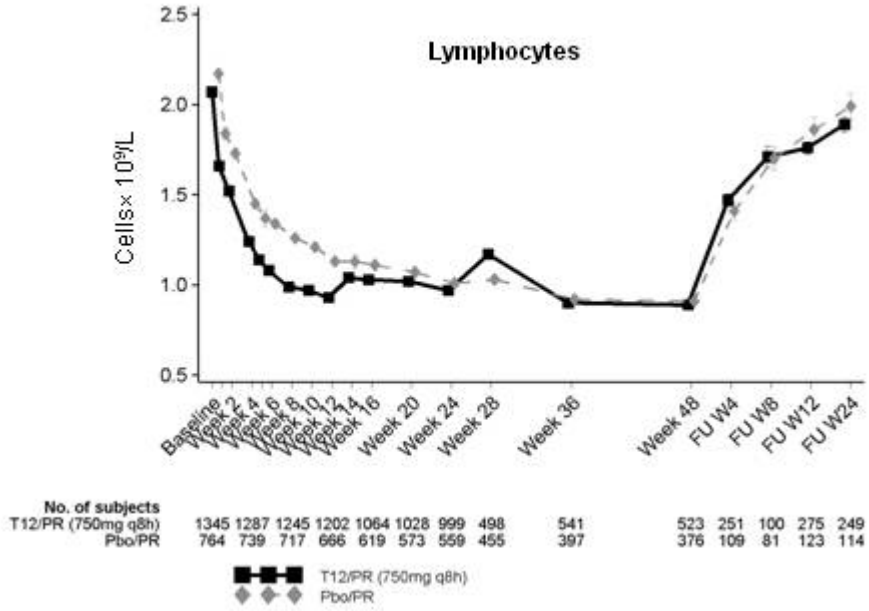
The median duration of anorectal SSC events starting during the overall treatment phase was 57.0 days (range: 1 to 519 days) in the T12/PR group and 53.0 days (range: 2 to 471 days) in the Pbo/PR group. These data should be interpreted with caution as they can be influenced by the time between protocol-planned assessments and the variability of end date reporting across sites.

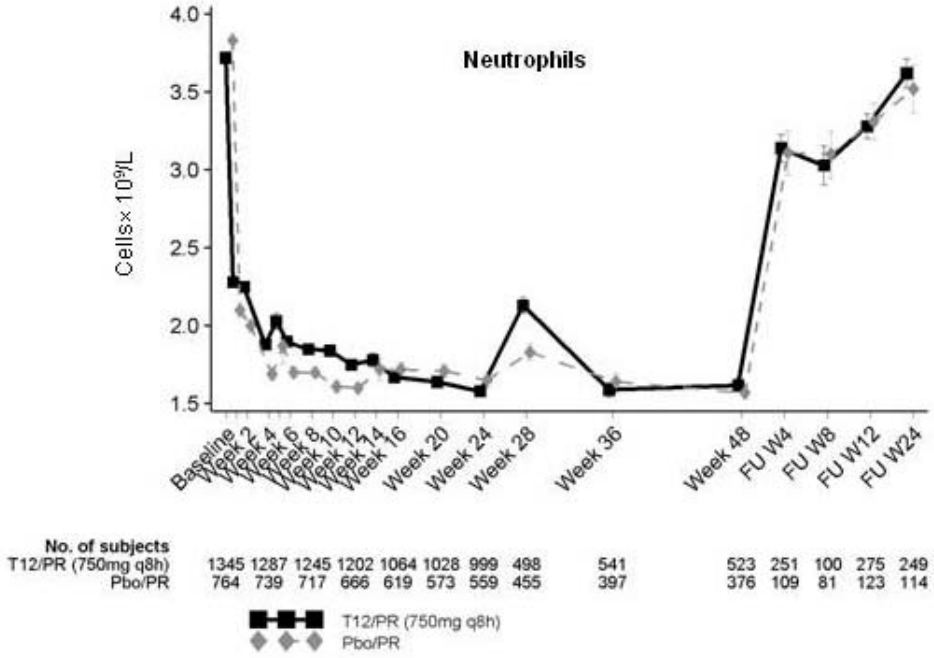
In the T12/PR group, no relevant differences in incidence of anorectal SSC events were observed between subgroups during the telaprevir/placebo phase.

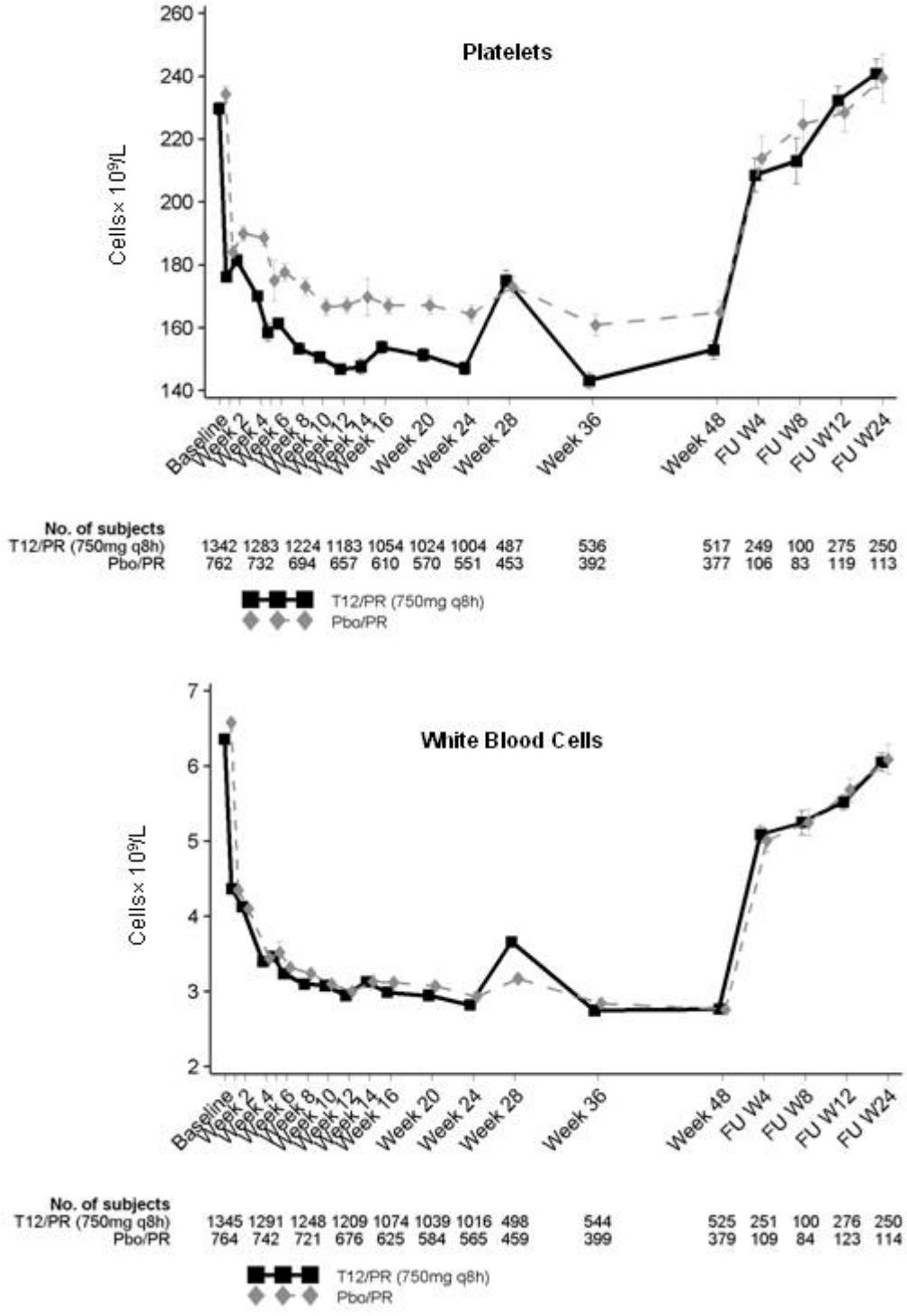
8.3 Clinical Laboratory Evaluations

Laboratory abnormalities were more commonly observed in the T12/PR group than in the Pbo/PR group during the telaprevir/placebo treatment phase. Most treatment-emergent graded laboratory abnormalities were Grade 1 or 2. The most frequently observed laboratory abnormalities of Grade 2 or higher (> 10.0%) in the T12/PR group were decreases in hemoglobin, lymphocyte count, neutrophil count, platelet count, and white blood cell (WBC) count, as well as hyperuricemia, increases in total cholesterol, and hyperbilirubinemia. The incidence of these abnormalities was higher in the T12/PR group than in the Pbo/PR group, with the exception of decreases in neutrophil count, which was similar in both groups (Figure 23).

Figure 23 Placebo-Controlled Phase 2-3 Studies: Changes in Hematology-Related Parameters







The most frequent treatment-emergent Grade 3 or 4 abnormalities were decreases in lymphocyte count, neutrophil count, and WBC count, as well as hyperuricemia. Except for decreased neutrophils, incidences were higher in the T12/PR group than in the Pbo/PR group.

For all other parameters, the incidence of Grade 3 or 4 abnormalities was < 5% in the T12/PR group.

The greatest changes in laboratory parameters from baseline were observed during the first month of treatment. Differences between the T12/PR and Pbo/PR groups generally disappeared after discontinuation of telaprevir.

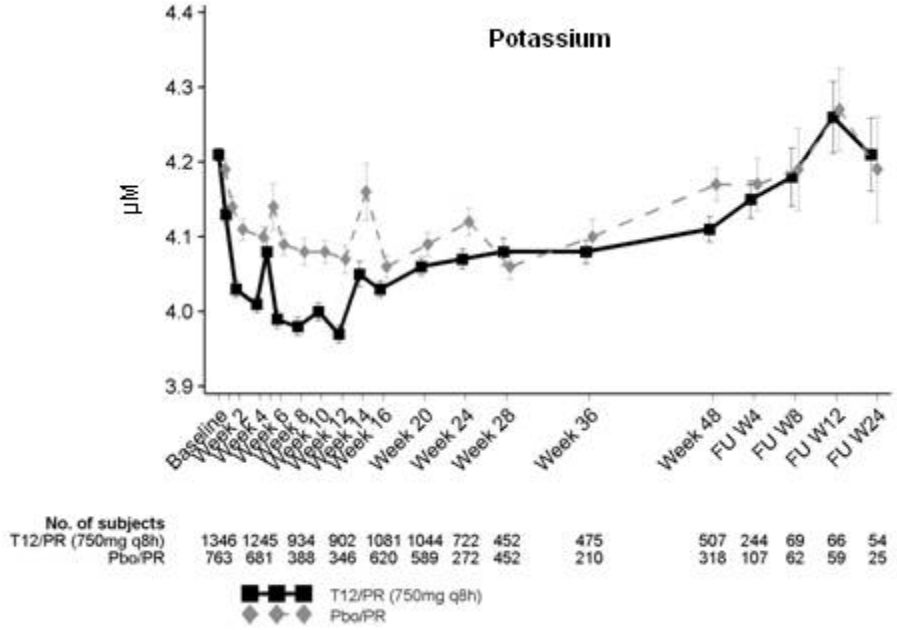
Consistent with the underlying liver disease, mean baseline alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values were high in the T12/PR and Pbo/PR groups.

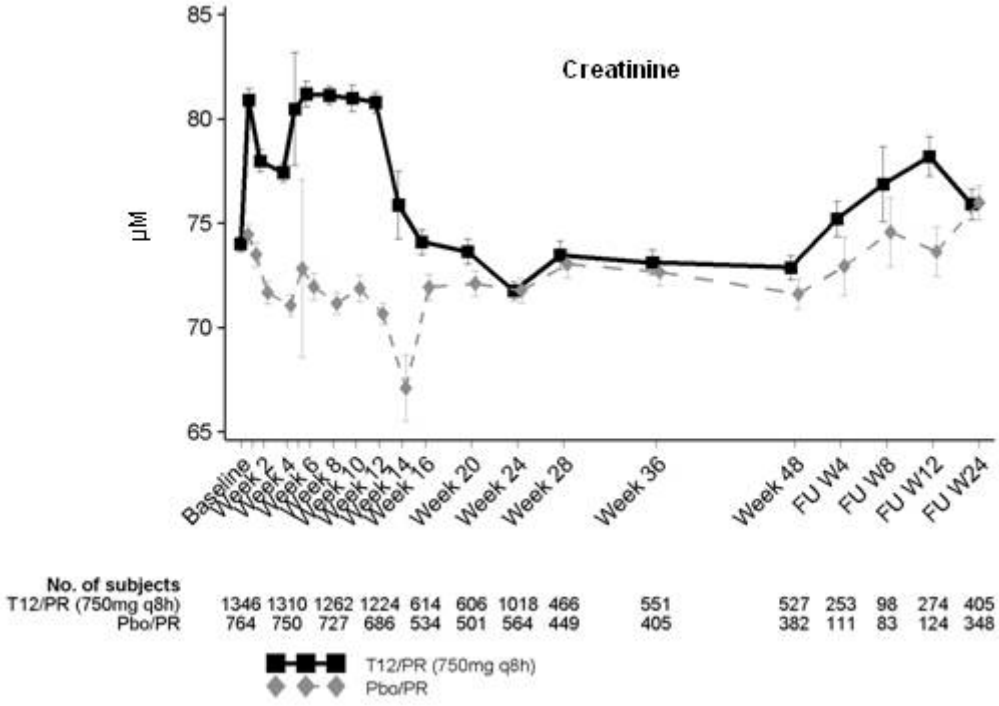
After start of treatment, decreases in mean ALT and AST were observed in both groups, but showed a greater and more rapid improvement (decrease) in the T12/PR group than in the Pbo/PR group until Week 20, consistent with the greater decrease in HCV RNA observed in the T12/PR group. From Week 20 onwards, mean decreases in ALT and AST were similar in both groups, after which ALT and AST levels remained stable.

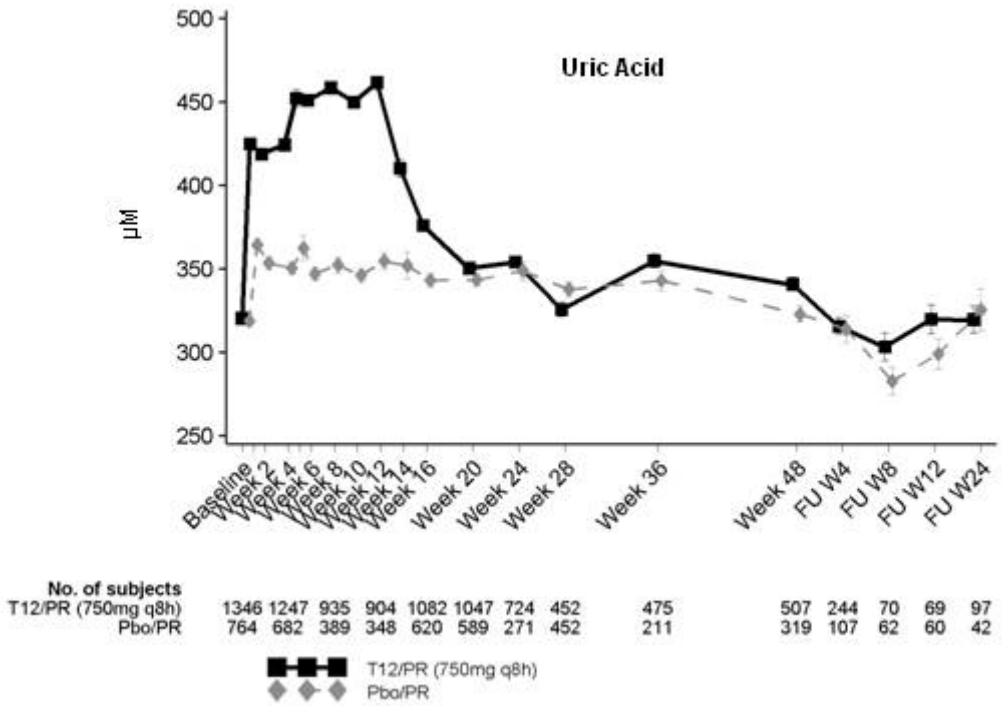
Mean creatinine increased slightly during telaprevir treatment in the T12/PR group followed by a decrease toward the mean baseline value by Week 16, after which mean values remained stable throughout the rest of the study (Figure 24). For potassium, mean decreases over time were observed in both the T12/PR and Pbo/PR groups. These decreases were minimal, but the magnitude of decrease was larger for the T12/PR group. For uric acid, a mean increase was observed during the first week of treatment in the T12/PR group; a smaller mean increase was observed in the Pbo/PR group. After Week 12, uric acid levels in the T12/PR group dropped to the levels observed in the Pbo/PR group. Clinical complications from increased uric acid were observed infrequently in the T12/PR and Pbo/PR groups and differences in mean uric acid levels between these groups disappeared at the end of telaprevir dosing.

During telaprevir/placebo treatment, mean low density lipoprotein (LDL) increased slightly in the T12/PR group and decreased slightly in the Pbo/PR group. The increases observed in the T12/PR group resolved upon completion of telaprevir dosing.

Figure 24 Placebo-Controlled Phase 2-3 Studies: Changes in General Chemistry Parameters







8.4 Subgroup Analysis

In general, both AEs and laboratory abnormalities were reported at comparable rates between subgroups of gender, age, BMI, region, race, prior treatment status, hepatic fibrosis, and baseline HCV RNA.

Nonetheless, for the T12/PR group, some noteworthy differences were observed in these subgroups:

- Women had higher rates of SAEs, Grade 3 AEs, AE-related discontinuations, and certain AE preferred terms compared with men in the T12/PR group; the same trend was observed in subjects with lower BMI compared with subjects with higher BMI. Sex and BMI had a modest influence on telaprevir plasma concentrations; however, these differences were found to be within the variability of telaprevir exposure in the population studied. Furthermore, the observation of similar differences by sex and BMI in the Pbo/PR group suggests that factors other than telaprevir exposure may play a role
- Subjects in the higher age groups reported slightly higher rates of certain AE preferred terms and laboratory abnormalities, but these may be reflective of differences in overall health
- The regional differences observed for AEs are more likely reflective of different reporting practices. Other than differences in triglyceride levels (that may reflect dietary intake differences), most laboratory abnormality rates were comparable across regions
- Since the large majority of subjects in both the T12/PR and Pbo/PR groups were white, observed racial differences should be interpreted cautiously

- Prior treatment status was not associated with relevant differences in either AEs or laboratory abnormalities
- For baseline fibrosis status, SAEs and AEs of at least Grade 3 were reported at higher rates in cirrhotics than in subjects with milder fibrosis levels; most AEs occurred at similar rates between these fibrosis subgroups. Thrombocytopenia and decreases in platelet count were more frequently reported in subjects with cirrhosis than in subjects with milder fibrosis levels; this may be due to hypersplenism in cirrhotic subjects

8.5 Safety in Special Populations

8.5.1 Hepatic and Renal Failure

One Phase I study (C132) assessed the PK, safety, and tolerability of a single dose of telaprevir in subjects with severe renal impairment (calculated CrCl < 30 mL/min). Pharmacokinetic results showed limited impact on telaprevir exposure (10% increased C_{max} and 21% increased AUC_{∞} for total telaprevir as compared with healthy subjects. The safety data from this study were consistent with those of Phase 1 studies in healthy volunteers who did not have such comorbidities; there were no otherwise clinically relevant findings that have not already been described.

Two multiple-dose Phase I studies (006 and 012) were conducted to assess the PK, safety, and tolerability of telaprevir in subjects with either mild hepatic impairment (Child-Pugh Class A) or moderate hepatic impairment (Child-Pugh Class B). Pharmacokinetic results showed that hepatic impairment was associated with reduced telaprevir exposure at steady state (AUC_{8h}): approximately 15% lower exposure with mild hepatic impairment and approximately 46% lower exposure with moderate hepatic impairment. The safety data from these studies were generally consistent with those of other Phase 1 studies in healthy volunteers who did not have such comorbidities; there were no AEs of unusual frequency or severity, apart from a higher incidence of pollakiuria (60%) and diarrhea (50%) reported in subjects with mild hepatic impairment compared with healthy volunteers (10% and 0%, respectively).

Telaprevir has not been studied in subjects with severe hepatic impairment, defined as Child-Pugh Class C (score ≥ 10) or decompensated liver disease.

8.5.2 HIV Coinfection

Several Phase 1 studies were conducted to examine the potential DDIs between telaprevir and commonly used anti-retroviral therapy (ART).

Results of these studies informed the design of Study 110 in HCV-1/HIV-1 coinfected subjects, in which telaprevir in combination with Peg-IFN/ RBV was administered to subjects who were treatment-naive for HCV and not receiving ART (Part A) or treatment-naive for HCV and receiving ART (Part B). In Part B, subjects must be on stable regimens of efavirenz or ritonavir-boosted atazanavir in addition to tenofovir/FTC or 3TC.

An interim analysis was performed on 59 of 60 subjects (one subject data unavailable) who had begun telaprevir-based or control treatment (Part A, n = 13; Part B, n = 46). Subjects were predominantly male (88%), white (69%), infected with genotype 1a virus (68%), and

had baseline HCV RNA > 800,000 IU/mL (83%). Mean age was 46 years, and 10% of subjects had advanced liver fibrosis based on liver biopsy.

The proportion of subjects with undetectable HCV RNA at 4 weeks (RVR) and 12 weeks (cEVR) were substantially higher in subjects receiving telaprevir-based therapy compared with control treatment (Table 44).

Two subjects receiving ART experienced HCV viral breakthrough. Discontinuations due to AEs occurred in 2 subjects (3%) and no subjects in the T/PR and placebo groups, respectively. Pruritus, nausea, vomiting, fever, anorexia, and dizziness were more frequent in subjects who received T/PR compared with controls. No cases of severe rash were reported and no unexpected changes in CD4 or in HIV RNA levels were observed in subjects receiving an ART regimen compared with control therapy.

Table 44 Interim Analysis of HCV Virologic Responses in HIV/HCV Co-Infected Subjects Receiving T/PR or PR Alone With or Without Concomitant ART

	Part A		Part B				Total	
	No ART		EFV/TDF/FTC		ATV/r + TDF + FTC/3TC			
Subjects, n (%)	T/PR n = 7	Control n = 6	T/PR n = 16	Control n = 8	T/PR n = 14	Control n = 8	T/PR n = 37	Control n = 22
RVR[a]	5 (71)	0 (0)	12 (75)	1 (12)	9 (64)	0 (0)	26 (70)	1 (5)
cEVR[a]	5 (71)	1 (17)	12 (75)	1 (12)	8 (57)	1 (12)	25 (68)	3 (14)

[a] Determined by Roche TaqMan v2, lower limit of quantitation (LLOQ) = 25 IU/mL.
Abbreviations: 3TC, lamivudine (2', 3'-didexoy-3'-thiacytidine); ART, anti-retroviral therapy; EFV, efavirenz; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate.
Source: Sulkowski MS et al. Submitted abstract to Conference on Retroviruses and Opportunistic Infections. Feb 27-Mar2, 2011, Boston MA. Abstract 146LB.

8.5.3 Pregnancy and Lactation

While telaprevir has shown no teratogenic potential in rats and mice and is not considered a developmental toxicant in these species, this treatment must always be coadministered with RBV, a drug with significant teratogenic and/or embryocidal potential in all animal species. As a result of the need for combination treatment with RBV and Peg-IFN, the labelled contraindications and warnings applicable to RBV and Peg-IFN are applicable to this combination regimen as well.

Estrogen-based hormonal contraceptives may not be reliable during telaprevir dosing [see *DDI interactions, Section 7]*]. Therefore, during our clinical studies, female subjects of childbearing potential were to use 2 additional methods of effective birth control during telaprevir dosing and for 2 months after the last intake of telaprevir.

No adequate and well-controlled studies of telaprevir in pregnant or lactating women have been conducted. Since telaprevir must be co-administered with PEG-IFN/RBV and RBV has known teratogenic potential, telaprevir should not be used during pregnancy.

Nonclinical studies have demonstrated lacteal transfer of telaprevir in rats. It is not known whether telaprevir is excreted in human milk. No data on lactation and effects to a newborn child are available from the clinical studies.

8.6 Safety Data from Studies Conducted by Other Sponsors or Organizations

Telaprevir has been tested in clinical studies in Japan by Mitsubishi Tanabe Pharma Company. Mitsubishi sponsored and conducted 8 clinical studies exclusively in Japan . Of these studies, 5 were completed and CSRs were translated and reviewed. Data of 2 Phase 3 studies were incomplete and one Phase 3 study was ongoing at the time of the cut-off date of 16 July 2010; of these studies, the only data available for review were SAE data.

All serious adverse event data from the 8 Mitsubishi-sponsored studies have been reviewed by cross-functional representatives from Tibotec BVBA and Vertex Pharmaceuticals Incorporated.

Although the incidence of SAEs in these Mitsubishi-sponsored studies were higher than those in the studies conducted by Tibotec and Vertex, likely reflective of different reporting practices, there was no specific pattern apparent from these SAEs. The data did not reveal any new relevant safety findings related to telaprevir (see Section 8.2.1).

8.7 Pooling of Phase 3 Studies

After NDA submission and during the FDA review period, an additional pooling was performed with Phase 3 study data (Studies 108, 111, and C216), and key adverse event analyses were conducted on this pooled dataset (See Appendix).

Importantly, there are no relevant qualitative differences in the safety data from this Phase 3 study pooling as compared with the safety data from the pooling of the five placebo-controlled Phase 2-3 studies; there are only small quantitative differences.

The incidence of ADRs is provided in Table 49 in the Appendix. A comparison of the adverse drug reaction (ADR) analyses for the Phase 3 pooling versus the Phase 2 and 3 pooling showed quantitative differences in the incidence of some ADRs but no relevant qualitative differences.

Laboratory abnormality ADRs were also analyzed for the Phase 3 pooling, and these again had no qualitative differences, only small quantitative differences from the placebo-controlled Phase 2-3 pooling.

8.8 Overall Safety Conclusions

The safety profile of telaprevir in subjects with genotype 1 CHC has been well characterized during the development program in both treatment-naive subjects and prior treatment-failure subjects. A consistent pattern and frequency of AEs was reported in both populations.

The placebo-controlled pooling contains safety data from 1346 subjects from the T12/PR group and 764 subjects from the Pbo/PR group. These data provide a robust safety evaluation and are the most relevant to the benefit risk assessment of the proposed telaprevir treatment regimen (12 weeks of telaprevir treatment, in combination with Peg-IFN/RBV for 24 or 48 weeks). Data from the Pbo/PR group are representative of the established safety profile of the Peg-IFN/RBV regimen.

Most subjects in the T12/PR group completed 12 weeks of treatment with telaprevir/placebo. A total of 73.0% of subjects in the T12/PR group and 49.1% of subjects in the Pbo/PR group

completed the intended treatment. Total treatment exposure was 326.32 subject years in the T12/PR group and 190.38 subject-years in the Pbo/PR group.

While additional poolings have been performed with qualitatively comparable safety data, the adverse event profile from the telaprevir/placebo treatment phase and from the T12/PR group are the most relevant and have been the primary focus of this summary; only small increases in AE frequency occurred in the overall treatment phase as compared with the telaprevir/placebo treatment phase.

Safety data from the Phase 3 studies were generally consistent with that from the Phase 2 studies, though there were fewer full treatment regimen discontinuations due to rash in Phase 3 (1.1% in Phase 3 versus 6.2% in Phase 2, in the T12/PR group), largely influenced by the adjustments made to the rash assessment and management plan in the Phase 3 studies.

While nearly all subjects in the T12/PR group, as in the Pbo/PR group, reported at least 1 AE, most were Grade 1 or Grade 2 in severity, non-serious, and not associated with either telaprevir or full treatment regimen discontinuation. The addition of telaprevir to a Peg-IFN/ RBV regimen resulted in higher rates of SAEs, AEs of at least Grade 3, and AE-related telaprevir/placebo discontinuations, mostly due to rash and anemia. Although rash and anemia are well-described AEs in subjects receiving Peg-IFN/RBV, the frequency and severity of both were higher in subjects in the T12/PR group than in the Pbo/PR group.

Adverse Events

The most frequently occurring AEs (> 20.0%) in the T12/PR group for which the rates were higher than in the Pbo/PR group were pruritus, anemia, diarrhea, rash, and nausea. Adverse events known to be associated with Peg-IFN/RBV treatment were also frequently reported but with comparable incidence between the T12/PR and Pbo/PR groups (fatigue, headache, influenza-like illness, insomnia, and pyrexia). Among AEs reported in 5.0% to 20.0% of subjects, hemorrhoids, anorectal discomfort, anal pruritus, dysgeusia, and generalized pruritus occurred more frequently in the T12/PR than in the Pbo/PR group.

Adverse events of at least Grade 3 or AEs leading to permanent discontinuation of telaprevir/placebo that occurred more frequently in the T12/PR group than in the Pbo/PR group included anemia, rash, and pruritus. Serious AEs that occurred more frequently in the T12/PR group than in the Pbo/PR group were anemia and rash.

Most AEs began in the first 4 weeks of treatment in both the T12/PR and Pbo/PR groups. Many AEs resolved within the first 24 weeks of treatment as evidenced by the lower prevalence of these AEs thereafter. AEs that are classically associated with Peg-IFN/ RBV therapy persisted in subjects remaining on treatment after Week 24 as their prevalence remained stable. These data suggest that a shorter Peg-IFN/RBV treatment duration (24 weeks instead of 48 weeks) could be associated with fewer safety events and represent a clinically relevant tolerability benefit for individual subjects.

Across the pooled placebo controlled Phase 2 and 3 studies, there were 5 deaths among subjects receiving telaprevir and 4 deaths in the control group. No deaths occurred during telaprevir treatment. One death was considered to be possibly related to telaprevir by the investigator.

Rash

Although rash SSC events were observed in 55.4% of subjects in the T12/PR group, they were infrequently serious (1.7%) or treatment-limiting; rash resulted in discontinuation of telaprevir/placebo in 5.8% of subjects in the T12/PR group.

Based on a review of 221 rash cases, the DEP concluded that with the exception of greater severity and extent of BSA involvement, the visual appearance of rash with a telaprevir-based regimen was comparable to the rash reported with Peg-IFN/RBV use. Telaprevir-associated rash was typically eczematous in appearance and commonly had predominant spongiosis on biopsy. While the likelihood of SCARs is low, careful monitoring for these important events and immediate discontinuation of treatment is required if they occur.

The DEP concluded that rash observed with the telaprevir-based regimens differed clinically and histopathologically from typical allergic drug reactions in that time to onset and time to resolution after treatment discontinuation were longer, and they did not commonly have an eosinophilic component. Cases had no features suggestive of type 1 hypersensitivity reactions and uncommonly had urticarial components.

First onset of rash can occur at any time after start of telaprevir but the majority of rash SSC events began during the first 4 weeks of treatment. Progression of rash severity was reported for less than 10% of the cases, and many rash SSC events resolved during the first 24 weeks of treatment, as demonstrated by the decrease in prevalence after Week 24.

Topical corticosteroids, systemic antihistamines, and systemic corticosteroids administered for the treatment of rash were used more frequently among subjects who experienced rash in the T12/PR group than in the Pbo/PR group. Relative to Phase 2, there were fewer rash-related discontinuations of all study drugs during Phase 3.

Pruritus

Pruritus SSC events were reported more frequently in the T12/PR group than in the Pbo/PR group (51.5% vs 26.4%). Most were Grade 1 or 2 in severity, not serious, and not treatment-limiting.

Anemia and Hemoglobin analyses

Hemoglobin decreases of grade 2 to 4 were observed in 79.2% of subjects in the T12/PR group and in 51.0% of subjects in the Pbo/PR group. Mean hemoglobin levels decreased rapidly during the first 4 weeks in both groups and continued to decrease thereafter, but with a larger decrease in the T12/PR group. The hemoglobin nadir was observed at the end of telaprevir dosing (Weeks 12-14): 33.7% of subjects in the T12/PR group reached a hemoglobin level < 10.0 g/dL and 8.3% reached a hemoglobin level < 8.5 g/dL. The corresponding increase in mean reticulocyte percentage was blunted relative to the magnitude of the hemoglobin changes in the T12/PR group compared with the Pbo/PR group. The additional effect of telaprevir on hemoglobin and reticulocyte levels resolved after end of telaprevir dosing.

These hemoglobin and reticulocyte results suggest that peripheral destruction of red blood cells, as has been described for RBV, is likely to be the main mechanism of treatment-induced anemia up to Week 8. The lower magnitude reticulocytosis, and slightly higher magnitude lymphopenia and thrombocytopenia compared with control, suggest that

telaprevir use may also be associated with a mild bone marrow suppressive effect that resolves after the end of telaprevir treatment.

Subgroup analyses indicated that subjects older than 45 years were at greater risk of anemia SSC events and hemoglobin decreases of Grade 2 or higher. The incidence of anemia SSC events was also higher in female than in male subjects, but this difference was not observed for hemoglobin decreases of Grade 2 or higher.

In the placebo-controlled studies, anemia was primarily managed by RBV dose reduction and infrequently resulted in full regimen discontinuation. Anemia led to discontinuation of telaprevir/placebo in 2.7% of subjects in the T12/PR group. Blood transfusions and ESA use were infrequent.

Anorectal signs and symptoms

Anorectal SSC events (mainly hemorrhoids, anorectal discomfort, and anal pruritus) were reported more frequently in the T12/PR group than in the Pbo/PR group (26.2% versus 5.4%). Most were grade 1 or 2 in severity, not serious, and not treatment-limiting.

Laboratory Safety

The majority of treatment-emergent laboratory abnormalities were of Grade 1 or 2 in both the T12/PR and Pbo/PR groups. Differences in pattern for mean changes over time in the T12/PR group compared with the Pbo/PR group were observed for hemoglobin, lymphocytes, platelets, uric acid, potassium, creatinine, TSH, total bilirubin, total cholesterol, and LDL. These differences resolved after the end of telaprevir dosing for all parameters except platelet count.

Laboratory abnormalities of Grade 2 or higher and Grade 3 or higher were observed more frequently in the T12/PR group than in the Pbo/PR group for:

- Decreases in hemoglobin, lymphocytes and platelets
- Increases in uric acid, total bilirubin, total cholesterol, and LDL

Except for anemia, the incidence of ADRs for AE-terms associated with laboratory abnormalities was below 4.0%. The most frequently observed were hyperuricemia and thrombocytopenia. Other ADRs for AE-terms associated with laboratory abnormalities were hypothyroidism (1.9%), hypokalemia (1.8%), and blood creatinine increased (0.2%). The incidence of these events was higher in the T12/PR group than in the Pbo/PR group

Adverse Drug Reactions

A thorough and systematic review of the datasets allowed for the identification of ADRs associated with telaprevir.

ADR grouped terms reported in at least 10.0% of subjects in the T12/PR group were pruritus, rash, nausea, anemia, diarrhea, vomiting, hemorrhoids, and proctalgia. The same terms were also the most frequently reported (incidence of ≥ 3.0%) ADRs of at least Grade 2. Among these ADRs, the largest differences between the T12/PR and Pbo/PR groups were observed for rash, anemia, pruritus, hemorrhoids, and proctalgia.

The most frequently reported ADRs of at least Grade 3 in the T12/PR group (incidence of ≥ 1.0%) were anemia, rash, thrombocytopenia, lymphopenia, pruritus, and nausea.

Laboratory abnormality-related ADRs observed in >20.0% of subjects in the T12/PR group were decreases in hemoglobin, absolute lymphocyte count, and platelet count, and hyperuricemia.

Safety in Special Populations

The evaluation of AEs and laboratory abnormalities by age, race, and sex showed no relevant differences in the safety profile of telaprevir with the exception of age > 45 years, which was associated with a higher rate of anemia SSC events and hemoglobin laboratory abnormalities, and female sex, which was associated with a higher rate of anemia SSC events.

A Phase 1 DDI study demonstrated that coadministration of telaprevir with ethinyl estradiol (EE)- and norethindrone-based oral contraceptives reduced EE exposure; as a result, the effectiveness of hormonal contraceptives or of estrogens used in hormone replacement therapy may be reduced. No adequate and well-controlled studies of telaprevir in pregnant or lactating women have been conducted.

Limited impact on the telaprevir PK was observed when administering a single dose of telaprevir 750 mg to subjects with severe renal impairment and there were no new or otherwise relevant safety findings that had not been previously described in studies conducted in healthy volunteers without comorbidities. Multiple-dose administration of telaprevir has not been investigated in subjects with renal impairment.

Safety data from 2 multiple-dose Phase I studies in subjects with mild hepatic impairment or moderate hepatic impairment were consistent with those from studies in healthy volunteers without comorbidities. There were no AEs of unusual frequency or severity other than pollakiuria and diarrhea in subjects with mild hepatic impairment. Pollakiuria was infrequently reported in other studies with telaprevir. Telaprevir has not been studied in subjects with severe hepatic impairment.

Only limited safety data are available for subjects > 65 years of age and there are no data for subjects > 75 years of age. There are no safety data in the pediatric and adolescent population.

Data from an interim analysis of a Phase 2a study in subjects with HCV-1 and HIV-1 coinfection (Study 110) revealed no safety concerns; to date, the safety and tolerability of telaprevir in subjects with HCV/HIV coinfection receiving HAART medication or not receiving HAART medication has been consistent with that observed in monoinfected CHC subjects receiving a telaprevir-based regimen.

Overall Conclusions

The safety profile of telaprevir has been well characterized during the development program, with a consistent pattern and frequency of AEs reported in treatment-naive subjects and in prior treatment-failure subjects. The most frequent ADRs that had a higher incidence under combined treatment with telaprevir, Peg-IFN and RBV compared with Peg-IFN/RBV alone were rash, anemia, pruritus, hemorrhoids, and proctalgia; most of these were Grade 1 or 2 in severity.

Laboratory abnormalities that occurred more frequently under combined treatment with telaprevir, Peg-IFN and RBV were decreases in hemoglobin, platelets, and lymphocytes, and increases in uric acid, total bilirubin, total cholesterol and LDL.

Despite the higher incidence and severity of some specific AEs and some laboratory abnormalities, and a higher discontinuation rate of telaprevir/placebo, the majority of subjects completed the treatment regimen. Adverse events and changes in laboratory parameters generally emerged in the first 4 weeks of treatment. Most AEs resolved after end of the 12-week telaprevir treatment period.

Some AEs that have been classically associated with Peg-IFN and RBV therapy persisted in subjects remaining on treatment after Week 24, suggesting that shorter Peg-IFN/RBV durations (24 weeks compared to 48 weeks) could be associated with a clinically relevant tolerability benefit for individual subjects.

9 90-DAY SAFETY UPDATE

The 90-Day safety update includes data from 4 ongoing studies of telaprevir for the reporting period 17 July, 2010 through 31 October, 2010, and was submitted on February 14, 2011 (Table 45). During the reporting period, a total of 6 subjects had 11 SAEs and 1 subject experienced an AE that led to discontinuation of telaprevir/placebo (Table 46). One SAE led to death and, at last follow up, 1 event was reported as ongoing and all other events resolved.

Table 45 Clinical Studies Included in the Safety Update

Study Number	Purpose of study
VX10-950-023	Characterize the sensory attributes of the 250-mg telaprevir pediatric chewable tablet formulation using the Flavor Profile method of descriptive sensory analysis
0810010040 (Investigator Initiated)	Determine the intrahepatic and plasma HCV viral kinetics and quasispecies in subjects treated with telaprevir and Peg-IFN/RBV.
VX-950-TiDP24-C219	Provide access to telaprevir for subjects who were randomized to the control group in Study C216 who failed therapy for virologic reasons. The efficacy, safety, and tolerability of telaprevir in combination with Peg-IFN-alpha-2a/RBV will be evaluated. In addition, amino acid changes from baseline in the HCV NS3 protease domain will be evaluated.
VX08-950-110	Safety and tolerability of telaprevir, Peg-IFN, and RBV. The study is also designed to assess the efficacy of telaprevir, Peg-IFN, and RBV at Week 12 of dosing.

The SAE that led to death (Study C219) was an event of anterior myocardial infarction that occurred in a 69-year-old male with hypertension 5 days after the completion of the last dose of telaprevir. The subject was hospitalized and expired 42 days after the last dose of telaprevir. The investigator considered the anterior myocardial infarction possibly related to telaprevir, Peg-IFN-alfa-2a, and RBV.

In conclusion, there were no events reported in the 90-Day safety update that were qualitatively different from the types of events reported in the safety findings that were included in the original telaprevir NDA submission.

Table 46 Serious Adverse Events (Reporting Period 17 July 2010 through 31 October 2010)

Subject	Adverse Event	Day of Onset[a]	Reported Relationship	Study Drug Action Taken	Outcome
Study VX-950-TiDP24-C219					
0014	Myocardial infarction	90	T, P, R: Possibly related[b]	T: N/A; P, R: Discontinued	Fatal
0015	Anemia	55	T, P: Not related; R: Very likely related[b]	T, P: None; R: Reduced	Resolved
	Anemia	71	T, P: Not related; R: Very likely related[b]	T, P, R: None	Resolved
	Anemia	93	T, P: Not related; R: Very likely related[b]	T, P: None; R: Reduced	Resolved
0022	Anemia	57	T, P: Possibly related; R: Probably related[b]	T: none; P, R: Reduced	Resolved
	Anemia	85	T, P: Possibly related; R: Probably related[b]	T: N/A; P: None; R: Reduced	Resolved
0023	Anemia	83	T, R: Possibly related; P: Not related[b]	T: N/A; P: None; R: Interrupted	Ongoing
Study VX08-950-110					
105222	MRSA infection (painful lesion left naris)	27	T/Pbo: Unlikely related; P: Possibly related; R: Not related[b]	T/Pbo, P, R: None	Resolved
	MRSA facial cellulitis	30	T/Pbo: Unlikely related; P: Possibly related; R: Not related[b]	T/Pbo, P, R: None	Resolved
	MRSA maxillary facial abscess	30	T/Pbo: Unlikely related; P: Possibly related; R: Not related[b]	T/Pbo, P, R: None	Resolved
400225[c]	Jaundice	3	Related[d]	T/Pbo: Discontinued; P, R: None	Resolved
Study 0810010040					
1004	Depression	107	T, R: Not related; P: Related[b]	T: N/A; P: Interrupted; R: None	Resolved

N/A: not applicable; MRSA: Methicillin-resistant Staphylococcus aureus; P: Peg-IFN-alfa-2a; Pbo: Placebo; R: RBV; T: telaprevir.

[a] Day of onset is the time from date of first dose of study drug to the date of onset of the event/SAE.

[b] Reported relationship is the relationship to individual study drugs.

[c] This subject had an adverse event that led to the discontinuation of telaprevir/placebo (Reporting Period 17 July 2010 through 31 October 2010).

[d] Reported relationship is the relationship to study drug regimen, not the relationship to individual study drugs.

10 BENEFIT RISK SUMMARY

The principal benefits of treatment with a telaprevir-containing regimen over standard Peg-IFN/RBV treatment are substantially and significantly higher SVR rates in all populations studied, and 6-month shorter treatment duration for treatment-naive subjects and prior relapsers who achieve eRVR (HCV RNA undetectable at Weeks 4 and 12). The efficacy advantage is consistent across subgroups including those with cirrhosis.

The positive impact of a higher SVR rate cannot be overstated. Reduction in hepatic inflammation with regression of hepatic fibrosis has been demonstrated to result in improvements in quality of life, reductions in the risk of complications of portal hypertension (ascites, gastroesophageal varices, and portal systemic encephalopathy), hepatic decompensation, and hepatocellular carcinoma.[14-21] A recent study of more than 1000 prospectively followed subjects with advanced hepatic fibrosis due to HCV reported a 10-fold reduction in death/liver transplantation (2.2% versus 21.3%) and of liver-related mortality (2.7% versus 27.2%) in subjects who achieved SVR compared with subjects who failed combination therapy with Peg-IFN-alfa and RBV.[33,34]

Based on the safety and efficacy data from more than 40 clinical studies, telaprevir has the potential to offer many more subjects the benefits of achieving SVR.

10.1 Summary of Risks and Unanswered Risk Questions

The key risks of treatment with telaprevir are well-characterized AEs (notably severe rash and anemia), potential risks associated with viral resistance to telaprevir, including absence of data on the management of subjects who have failed a telaprevir containing regimen, and the potential but avoidable risks associated with DDIs.

This assessment of key risks is based primarily on a primary safety data pooling from the placebo-controlled Phase 2-3 studies in which 1346 subjects received a telaprevir based regimen with Peg-IFN/RBV and 764 subjects received a standard of care Peg-IFN/RBV regimen with placebo. A subsequent analysis of pooled safety data from the three Phase 3 studies (108, 111 and C216) confirms the conclusions from the primary safety data pooling.

Anemia and rash are the most common AEs associated with telaprevir treatment and the most likely to result in premature discontinuation of telaprevir. Both have been demonstrated to be manageable and reversible after treatment discontinuation. However, a minority of subjects will develop medically significant skin reactions or severe anemia and will not be able to complete treatment with the triple combination of T/PR; subjects who are not able to complete therapy are less likely to achieve SVR.

Most subjects who fail treatment with T/PR have telaprevir-resistant variants. In subjects unlikely to achieve SVR, stopping rules are being proposed to minimize the potential effects of toxicity and viral resistance associated with the regimen.

Although resistant variants are replaced with wild-type virus over time, there are no data on the re-treatment of subjects who have failed a telaprevir-containing regimen either with telaprevir or other direct acting antiviral agents.

An extensive Phase 1 program evaluated the potential for drug interactions with a broad spectrum of drugs that are likely to be co-administered in the target population and provided guidance for the management of observed and anticipated DDIs.

Finally, it is not known whether subjects in Child-Pugh Class B or Class C can be safely or effectively dosed with telaprevir because the results of a Phase 1 study in subjects with Child-Pugh score > 6 showed lower telaprevir exposures than anticipated.

It is important to note that telaprevir is dosed for 12 weeks and the associated profile of risks is well-characterized and easy to identify clinically or with routine laboratory monitoring. The potential risks associated with telaprevir may be averted or ameliorated with the proposed risk-management approach.

At the time of the NDA submission, Vertex had initiated or proposed several additional studies to characterize the safety and efficacy of telaprevir in special subject populations and with different dosing regimens, and to assess the long-term durability of the virologic response in subjects who achieved SVR during telaprevir-based treatment (Table 47).

Table 47 Proposed and On-Going Studies with Telaprevir

Study Number	Purpose of study
VX10-950-023	Characterize the sensory attributes of the 250-mg telaprevir pediatric chewable tablet formulation using the Flavor Profile method of descriptive sensory analysis
VX10-950-024	The effect of telaprevir on the steady-state PK parameters of buprenorphine.
VX09-222-103	Safety and tolerability of combination treatment with VX-222 and telaprevir administered for 12 weeks with and without Peg-IFN/RBV.
VX-950-TiDP24-C211	Assess the non-inferiority in sustained viral response (SVR24) of telaprevir administered as 1,125 mg twice daily (b.i.d.) versus 750 mg every 8 hours (q8h) in combination with Peg-IFN/RBV in treatment-naive subjects with chronic HCV genotype 1 infection.
VX-950-TiDP24-C219	Provide access to telaprevir for subjects who were randomized to the control group in Study C216 who failed therapy for virologic reasons. The efficacy, safety, and tolerability of telaprevir in combination with Peg-IFN-alpha-2a/RBV will be evaluated. In addition, amino acid changes from baseline in the HCV NS3 protease domain will be evaluated.
VX-950HEP1001	The effect of steady-state telaprevir 750 mg q8h on the steady-state PK parameters of raltegravir 400 mg b.i.d. and vice versa.
VX08-950-110	Safety and tolerability of telaprevir, Peg-IFN, and RBV. The study is also designed to assess the efficacy of telaprevir, Peg-IFN, and RBV at Week 12 of dosing.
VX08-950-112	Durability of virologic response in subjects who achieved an SVR following telaprevir-based treatment in a previous study and to evaluate changes in HCV variants over time in subjects who did not achieve an SVR following telaprevir-based treatment in a previous study.

In addition to the studies described above, Vertex has preliminary plans to further characterize telaprevir's safety and efficacy in special populations such as transplant subjects, subjects co-infected with HIV/HCV, and minorities. Vertex is also considering studies that would investigate the interactions of telaprevir with other drugs, both investigational and non-investigational. Vertex looks forward to presenting these protocols to the DAVP once final designs are available.

10.2 Dosing Recommendations and Total Treatment Duration

Dosing recommendations are as follows:

- Telaprevir: 750 mg taken 3 times a day (7-9 hours apart) with food (simulations demonstrate that a dosing schedule of 750 mg 3 times per day, with intervals of 7 to 9 hours, would result in exposures that are bioequivalent to the exposures achieved with dosing every 8 hours)
- Peg-IFN and RBV: dose recommendations are as described in the package inserts for Peg-IFN and RBV

Total treatment durations are recommended as follows:

- Response-guided therapy for treatment-naive subjects and subjects with prior relapse:
  - Patients with undetectable HCV RNA at Weeks 4 and 12 of treatment (eRVR): 24 weeks of total treatment duration with Peg-IFN/RBV
  - Patients who do not achieve eRVR: 48 weeks of total treatment duration with Peg-IFN/ RBV
- For prior partial and null responder patients: 48 weeks of total treatment duration with Peg-IFN/RBV

10.2.1 Overall Benefits/Risks

The addition of telaprevir to Peg-IFN/RBV results in significant and substantial increases in SVR for all groups of subjects from treatment-naive subjects to prior null-responders. The efficacy advantage is robust and consistent across a broad population of subjects with genotype 1 CHC including those who traditionally have a lower likelihood of achieving SVR (e.g., subjects who are black, Hispanic or Latino, have cirrhosis, have high baseline levels of HCV RNA, or had null or partial response to prior treatment with Peg-IFN/RBV).

The majority of treatment-naive and prior relapser subjects with undetectable HCV RNA levels at Week 4 and 12 may be effectively treated with just 24 weeks of total therapy, half the duration required for standard Peg-IFN/RBV, with 70% or higher cure rates. All subjects, even those requiring 48 weeks of total treatment, only need to take telaprevir as part of their regimen for the first 12 weeks. By Week 4 of treatment, it is possible to identify subjects who are unlikely to benefit from treatment and spare them the potential toxicity of the regimen and evolution of viral-resistant variants while being reassured that the vast majority of those who show a substantial response at this time point will achieve cure of CHC.

The safety profile of telaprevir has been well characterized during development and is consistent across populations. Treatment with Peg-IFN/RBV is known to be associated with a substantial toxicity profile, and the addition of telaprevir has been shown to increase the incidence and severity of certain AEs, notably rash and anemia. Both of these AEs are easily recognized, manageable, and reversible upon discontinuation of treatment. More than 90% of all rash cases are mild/moderate and non-progressive. Severe rash is well characterized. Management strategies were implemented and evaluated in Phase 3. Cases suggestive of severe cutaneous adverse reactions such as DRESS and SJS have been reported rarely (< 0.5%) in the telaprevir development program. Serious skin reactions including SJS are

also known to occur with Peg-IFN/ RBV. These reactions will require immediate and permanent discontinuation of telaprevir as well as Peg-IFN/RBV.

Although there is a higher discontinuation rate from telaprevir than placebo, premature discontinuation of telaprevir does not necessarily imply lack of benefit: data from 1 Phase 3 study in treatment-naive subjects (Study 108) demonstrated that an 8-week regimen, while slightly less efficacious than 12 weeks, was superior to comparator, and many subjects who discontinue telaprevir prematurely due to an AE go on to achieve SVR.

The data from the telaprevir development program demonstrate convincingly that the benefits greatly outweigh the risks. For every 100 subjects in a given population treated with T12/PR as compared with standard Peg-IFN/RBV treatment, an additional 31 treatment-naive, 60 prior-relapser, 45 prior partial-responder, and 25 null-responder subjects will be cured, even after accounting for those who will prematurely discontinue telaprevir because of an AE.

Taken together, the results of the clinical development program support the regimen of telaprevir in combination with Peg-IFN/RBV as first-line therapy for both treatment-naive and prior treatment-failure subjects with genotype 1 HCV.

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12 APPENDIX

12.1 Tabulation of Clinical Studies Showing Correlations Between Sustained Virologic Response (SVR) And Improvements In Clinical Outcomes After Treatment for CHC

Table 48 Correlations Between SVR and Improvements In Clinical Outcomes

Clinical Outcome	Reference
Reduced hepatic carcinoma incidence	Arase Y, et al. *Intervirology*. 2007;50(1):16-23. Braks RE, et al. *World J Gastroenterol*. 2007;13(42):5648-5653. Bruno S, et al. *Hepatology*. 2007;45(3):579-587. Imai Y, et al. *Ann Intern Med*. 1998;129(2):94-99. Okanoue Y, et al. *J Hepatol*. 1999;30(4):653-659. Shiratori Y, et al. *Ann Intern Med*. 2005;142(2):105-114. Yoshida H, et al. *Ann Intern Med*. 1999;131(3):174-181.
Reduced hepatic events	Bruno S, et al. *Hepatology*. 2007;45(3):579-587. Veldt BJ, et al. *Ann Intern Med*. 2007;147:677-684.
Reduced fibrosis	Yoshida H, et al. *Ann Intern Med*. 1999;131(3):174-181.
Prolonged survival	Arase Y, et al. *Intervirology*. 2007;50(1):16-23. Braks RE, et al. *World J Gastroenterol*. 2007;13(42):5648-5653. Bruno S, et al. *Hepatology*. 2007;45(3):579-587. Shiratori Y, et al. *Ann Intern Med*. 2005;142(2):105-114. Yoshida H, et al. *Gastroenterology*. 2002.123(2):483-491.

Source: FDA Guidance for Industry Chronic Hepatitis C Virus Infection: Developing Direct-Acting Agents for Treatment. September 2010.

12.2 Adverse Drug Reactions in Telaprevir Placebo-Controlled Phase 2-3 Studies—Telaprevir/Placebo Treatment Phase

12.2.1 Placebo-Controlled Phase 2-3 Studies—Telaprevir/Placebo Treatment Phase

Table 49 Placebo-Controlled Phase 2-3 Studies: Incidence of Adverse Drug Reactions of At Least Grade 2 in Severity – Telaprevir/Placebo Treatment Phase

System Organ Class Adverse Drug Reactions (Grouped Term), n (%)	T12/PR (750 mg q8h) n = 1,346	Pbo/PR n = 764
Any ADR of at least grade 2	745 (55.3)	188 (24.6)
Skin and subcutaneous tissue disorders		
Pruritus	219 (16.3)	32 (4.2)
Rash	216 (16.0)	37 (4.8)
Eczema	25 (1.9)	5 (0.7)
Swelling face	7 (0.5)	0
Drug rash with eosinophilia and systemic symptoms[a]	6 (0.4)	0
Urticaria	3 (0.2)	1 (0.1)
Exfoliative rash	2 (0.1)	0
Blood and lymphatic system disorders		
Anemia	282 (21.0)	65 (8.5)
Thrombocytopenia	44 (3.3)	8 (1.0)
Lymphopenia	17 (1.3)	2 (0.3)
Gastrointestinal disorders		
Nausea	128 (9.5)	43 (5.6)
Diarrhea	84 (6.2)	26 (3.4)
Hemorrhoids	56 (4.2)	3 (0.4)
Vomiting	54 (4.0)	18 (2.4)
Proctalgia	47 (3.5)	5 (0.7)
Anal pruritus	17 (1.3)	0
Rectal hemorrhage	10 (0.7)	3 (0.4)
Anal fissure	9 (0.7)	0
Proctitis	3 (0.2)	0
Metabolism and nutrition disorders		
Hyperuricemia	34 (2.5)	1 (0.1)
Hypokalemia	8 (0.6)	0
Gout	3 (0.2)	0
Nervous system disorders		
Dysgeusia	16 (1.2)	3 (0.4)
Syncope	13 (1.0)	3 (0.4)
Hepatobiliary disorders		
Hyperbilirubinemia	12 (0.9)	2 (0.3)
Infections and infestations		
Oral candidiasis	9 (0.7)	1 (0.1)
Endocrine disorders		
Hypothyroidism	5 (0.4)	0
General disorders and administration site conditions		
Edema peripheral	5 (0.4)	0
Eye disorders		
Retinopathy	3 (0.2)	0
Investigations		
Blood creatinine increased	2 (0.1)	0

[a] Incidence as derived from DEP assessment of suspected SCARs

Table 50 Placebo-Controlled Phase 2-3 Studies: Treatment-Emergent Laboratory Abnormalities of Grade 2 or Higher for Selected Parameters (Worst Grade) – *Telaprevir/Placebo Treatment Phase*

	T12/PR (750mg q8h)				Pbo/PR			
	At Least Grade 2		At Least Grade 3		At Least Grade 2		At Least Grade 3	
Laboratory parameter, n (%)	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**
Absolute lymphocyte count decrease	1332	395 (29.7)	1332	221 (16.6)	755	82 (10.9)	755	40 (5.3)
Creatinine increase	1318	14 (1.1)	1318	2 (0.2)	754	3 (0.4)	754	0
Hemoglobin decrease	1332	1055 (79.2)	1332	695 (52.2)	755	385 (51.0)	755	181 (24.0)
Hyperbilirubinemia	1332	233 (17.5)	1332	52 (3.9)	755	60 (7.9)	755	9 (1.2)
Hyperuricemia	1332	314 (23.6)	1332	76 (5.7)	755	24 (3.2)	755	4 (0.5)
Hypokalemia	1332	21 (1.6)	1332	0	755	2 (0.3)	755	0
Low density lipoprotein increase	1178	111 (9.4)	1178	30 (2.5)	731	18 (2.5)	731	3 (0.4)
Platelet count decrease	1331	364 (27.3)	1331	39 (2.9)	754	126 (16.7)	754	8 (1.1)
Total cholesterol increase	1222	212 (17.3)	1222	24 (2.0)	742	13 (1.8)	742	1 (0.1)

Table 51 Incidence of Adverse Drug Reactions - Laboratory Safety - Worst Toxicity Grades Telaprevir/Placebo Treatment Phase - Phase 3 Studies

	T12/PR (750mg q8h)		Pbo/PR	
	N	n (%)	N	n (%)
Absolute lymphocyte count				
Grade 1	1415	107 (7.6)	487	19 (3.9)
Grade 2	1415	173 (12.2)	487	28 (5.7)
Grade 3	1415	178 (12.6)	487	20 (4.1)
Grade 4	1415	69 (4.9)	487	3 (0.6)
Creatinine				
Grade 1	1381	50 (3.6)	486	4 (0.8)
Grade 2	1381	16 (1.2)	486	2 (0.4)
Grade 3	1381	1 (<0.1)	486	0
Haemoglobin				
Grade 1	1415	201 (14.2)	487	134 (27.5)
Grade 2	1415	359 (25.4)	487	132 (27.1)
Grade 3	1415	732 (51.7)	487	129 (26.5)
Grade 4	1415	22 (1.6)	487	0
Hyperbilirubinemia				
Grade 1	1414	307 (21.7)	487	87 (17.9)
Grade 2	1414	198 (14.0)	487	41 (8.4)
Grade 3	1414	53 (3.7)	487	8 (1.6)
Grade 4	1414	4 (0.3)	487	1 (0.2)
Hyperuricemia				
Grade 1	1414	621 (43.9)	487	102 (20.9)
Grade 2	1414	264 (18.7)	487	12 (2.5)
Grade 3	1414	86 (6.1)	487	3 (0.6)
Grade 4	1414	13 (0.9)	487	0
Hypokalemia				
Grade 1	1414	290 (20.5)	487	38 (7.8)
Grade 2	1414	32 (2.3)	487	1 (0.2)
Low density lipoprotein				
Grade 1	1225	146 (11.9)	466	13 (2.8)
Grade 2	1225	59 (4.8)	466	7 (1.5)
Grade 3	1225	17 (1.4)	466	0
Platelet count				
Grade 1	1414	330 (23.3)	486	101 (20.8)
Grade 2	1414	313 (22.1)	486	69 (14.2)
Grade 3	1414	43 (3.0)	486	5 (1.0)
Grade 4	1414	3 (0.2)	486	1 (0.2)
Total cholesterol				
Grade 1	1282	249 (19.4)	474	30 (6.3)
Grade 2	1282	157 (12.2)	474	4 (0.8)
Grade 3	1282	12 (0.9)	474	0

[a] Denominator derived from *denom* data set, no subset, the denominator class(es) are *LBTOXNM* x *ARM*
[b] Unique usubjids are counted.

12.3 Other Safety Analyses of Pooled Phase 3 Studies –

Table 52 Controlled and Uncontrolled Phase 3 studies: Summary of Adverse Events - 'Telaprevir/Placebo Treatment Phase'

n (%)	Any T/PR N = 1797	Pbo/PR N = 493
Number of subjects with:		
Adverse event	1773 (98.7)	474 (96.1)
Serious adverse event	99 (5.5)	11 (2.2)
Grade 2 adverse event	1289 (71.7)	300 (60.9)
Grade 3 adverse event	420 (23.4)	62 (12.6)
Permanent stop of TVR/Pbo	296 (16.5)	20 (4.1)
Permanent stop of All Study Drugs	119 (6.6)	17 (3.4)

Note: Studies 108, 111 and C216.

Table 53 Controlled and Uncontrolled Phase 3 studies: Summary of Most Common Adverse Events (≥20%)- 'Telaprevir/Placebo Treatment Phase'

n (%)	Any T/PR N = 1797	Pbo/PR N = 493
Any AE	1773 (98.7)	474 (96.1)
Blood and Lymphatic System Disorders		
Anemia	590 (32.8)	66 (13.4)
Gastrointestinal Disorders		
Diarrhea	458 (25.5)	86 (17.4)
Nausea	704 (39.2)	138 (28.0)
General Disorders and Administration Site Conditions		
Fatigue	998 (55.5)	245 (49.7)
Flu-Like Illness	516 (28.7)	127 (25.8)
Pyrexia	392 (21.8)	110 (22.3)
Nervous System Disorders		
Headache	657 (36.6)	171 (34.7)
Psychiatric Disorders		
Insomnia	458 (25.5)	116 (23.5)
Skin and Cutaneous Tissue Disorders		
Pruritus	840 (46.7)	137 (27.8)
Rash	597 (33.2)	86 (17.4)

Note: Studies 108, 111 and C216.

12.3.1 Phase 3 Studies—Telaprevir/Placebo Treatment Phase

Table 54 Incidence of Adverse Drug Reactions of At Least Grade 2 in Severity – Telaprevir/Placebo Treatment Phase; Phase 3 Studies

System Organ Class Adverse Drug Reactions n (%)	T12/PR (750 mg q8h) N = 1433	Pbo/PR N = 493
Number of subjects with an ADR of at least GR2	766 (53.5)	124 (25.2)
Blood and lymphatic system disorders		
Anaemia	326 (22.7)	49 (9.9)
Thrombocytopenia	44 (3.1)	7 (1.4)
Lymphopenia	21 (1.5)	2 (0.4)
Gastrointestinal disorders		
Nausea	137 (9.6)	24 (4.9)
Diarrhoea	87 (6.1)	13 (2.6)
Vomiting	56 (3.9)	10 (2.0)
Proctalgia	46 (3.2)	3 (0.6)
Rectal haemorrhage	8 (0.6)	2 (0.4)
Haemorrhoids	56 (3.9)	1 (0.2)
Anal fissure	8 (0.6)	0
Anal pruritus	11 (0.8)	0
Proctitis	5 (0.3)	0
Skin and subcutaneous tissue disorders		
Pruritus	221 (15.4)	21 (4.3)
Rash	214 (14.9)	20 (4.1)
Eczema	21 (1.5)	2 (0.4)
Urticaria	3 (0.2)	1 (0.2)
Drug rash with eosinophilia and systemic symptoms	4 (0.3)	0
Exfoliative rash	1 (<0.1)	0
Swelling face	6 (0.4)	0
Nervous system disorders		
Dysgeusia	15 (1.0)	2 (0.4)
Syncope	14 (1.0)	1 (0.2)
Hepatobiliary disorders		
Hyperbilirubinaemia	10 (0.7)	2 (0.4)
Infections and infestations		
Oral candidiasis	1 (<0.1)	1 (0.2)
Metabolism and nutrition disorders		
Hyperuricaemia	34 (2.4)	1 (0.2)
Gout	3 (0.2)	0
Hypokalaemia	14 (1.0)	0
Endocrine disorders		
Hypothyroidism	4 (0.3)	0
Eye disorders		
Retinopathy	3 (0.2)	0

Table 54 Incidence of Adverse Drug Reactions of At Least Grade 2 in Severity – Telaprevir/Placebo Treatment Phase; Phase 3 Studies

System Organ Class Adverse Drug Reactions n (%)	T12/PR (750 mg q8h) N = 1433	Pbo/PR N = 493
General disorders and administration site conditions		
Oedema peripheral	7 (0.5)	0
Investigations		
Blood creatinine increased	3 (0.2)	0

[a] Denominator derived from input data, no subset, the denominator class(es) are *ARM*
[b] Subset:(phasen=1 and not missing (adr) and AETOXGRN ≥ 2)
c Unique usubjids are counted.

Table 55 Controlled and Uncontrolled Phase 3 Studies: Summary of Most Common Laboratory Abnormalities, Worst Grade- Telaprevir/Placebo Treatment Phase (based on DAIDS Laboratory Grading Scale)

n (%)	Any T/PR N = 1797	Pbo/PR N = 493
Hematology		
Hemoglobin—Grade 3	903 (50.8)	129 (26.5)
Hemoglobin—Grade 4	24 (1.4)	0
WBC—Grade 3	139 (7.8)	25 (5.1)
WBC—Grade 4	5 (0.3)	0
Neutrophils—Grade 3	176 (9.9)	58 (11.9)
Neutrophils—Grade 4	33 (1.9)	14 (2.9)
Lymphocytes—Grade 3	199 (11.2)	20 (4.1)
Lymphocytes—Grade 4	73 (4.1)	3 (0.6)
Platelets—Grade 3	47 (2.6)	5 (1.0)
Platelets—Grade 4	4 (0.2)	1 (0.2)
Chemistry		
Glucose Increased—Grade 3	13 (0.8)	4 (0.8)
Creatinine—Grade 3	3 (0.2)	0
Uric Acid—Grade 3	104 (5.9)	3 (0.6)
Uric Acid—Grade 4	17 (1.0)	0
ALT—Grade 3	14 (0.8)	7 (1.4)
ALT—Grade 4	2 (0.1)	1 (0.2)
AST—Grade 3	21 (1.2)	8 (1.6)
AST—Grade 4	4 (0.2)	0
Total Bilirubin—Grade 3	66 (3.7)	8 (1.6)
Total Bilirubin—Grade 4	4 (0.2)	1 (0.2)
Lipids		
Total Cholesterol—Grade 3	16 (1.0)	0
LDL—Grade 3	20 (1.3)	0
Triglycerides—Grade 3	19 (1.7)	3 (0.6)
Triglycerides—Grade 4	6 (0.5)	4 (0.8)

Note: Studies 108, 111 and C216.