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APPLICATION NUMBER:

202258Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	202258
Priority or Standard	Priority
Submit Date(s)	November 10, 2010
Received Date(s)	November 15, 2010
PDUFA Goal Date	May 15, 2011
Division / Office	Division of Antiviral products/Office of Antimicrobial Products
Reviewer Name(s)	Poonam Mishra, M.D. Sarah Connelly, M.D.
Review Completion Date	April 15, 2011
Established Name	Boceprevir (SCH 503034)
(Proposed) Trade Name	VICTRELIS™
Therapeutic Class	Hepatitis C Virus NS3 Protease Inhibitor
Applicant	Schering-Plough Corp.
Formulation(s)	Capsules for oral use
Dosing Regimen	800 milligrams three times daily
Indication(s)	Treatment of chronic hepatitis C virus infection
Intended Population(s)	Adult patients (18 years and older) infected with chronic hepatitis C genotype1 infection

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, the approval of boceprevir is recommended for the treatment of chronic hepatitis C genotype 1 infection in combination with pegylated interferon and ribavirin. This recommendation is based on the efficacy and safety data presented in the marketing application which supports a favorable risk/benefit assessment for the use of boceprevir in pivotal trials.

The efficacy of boceprevir was demonstrated with the results of two randomized, double-blind, placebo-controlled Phase 3 trials (P05216 and P05101, see Section 5.3 for further description of these trials). Overall, in the treatment-naïve subjects (P05216), the sustained virologic response was 63% - 66% in boceprevir-containing arms versus 38% in the control arm; and in the treatment-failure subjects (P05101), the sustained virologic response was 59% - 66% in boceprevir-containing arms versus 21% in the control arm. The treatment difference was substantially and statistically significant for each trial based on the primary efficacy endpoint. Relapse rates were also lower in boceprevir-treated subjects, 9% in boceprevir-containing arms versus 22% in control arm in treatment-naïve subjects. In treatment-failure subjects, the relapse rate in boceprevir-containing arms was 12-14% versus 28% in the control arm. In these trials response-guided therapy approach was evaluated based on virologic response at early time points with a potential for a shorter duration of therapy in early responders. Please see Section 6.1.4 for a detailed description of the efficacy findings.

Overall, most of the reported adverse events have been well-characterized for pegylated interferon and ribavirin therapy. However, one important safety concern during the clinical development of boceprevir has been the incremental decrease in hemoglobin in addition to what is observed with standard of care therapy (pegylated interferon and ribavirin) alone. Anemia was reported as an adverse event in 49% of the subjects in the boceprevir containing arms versus 30% in the control arm. Management of anemia included use of erythropoietin in the boceprevir clinical development program. Erythropoiesis-stimulating agents (ESAs) are not FDA-approved for treatment of anemia in patients with chronic hepatitis C (CHC) and erythropoietin use in itself may potentially pose an additional safety risk, the extent of which has not yet been fully described. Another significant concern has been the other associated bone marrow suppression effects of boceprevir as evident by the increased frequency of neutropenia and thrombocytopenia in addition to anemia in boceprevir-treated subjects. An increased number of subjects reported psychiatric symptoms of suicidal and homicidal ideations in boceprevir-containing arms as compared to control; however, psychiatric adverse events are associated with pegylated interferon and ribavirin. This observation is of concern due to its potential life-threatening implications. In addition, dysgeusia was

reported in increased frequency in boceprevir-treated subjects as compared to control (37% in boceprevir-containing arms versus 16% in control arm); however, the majority of dysgeusia events were mild-moderate in intensity and were not treatment-limiting. Please see Section 7.3 for additional information regarding the boceprevir safety data.

In summary, based on the demonstrated superior efficacy to the current standard of care (i.e. significantly increased sustained virologic response) in both previously untreated and previous treatment failure adults with CHC genotype 1 infection and the supportive safety data, approval of boceprevir is recommended. Although the major safety concern with boceprevir use is anemia, it appears to have been effectively managed during the clinical trials. Further, the increased safety risk due to anemia may be mitigated in clinical practice by close monitoring and timely therapeutic interventions.

1.2 Risk Benefit Assessment

Based on the review of data presented in the application, the benefits of the demonstrated superior efficacy of boceprevir over placebo in combination with pegylated interferon and ribavirin therapy outweigh the currently identified risks including potential risk due to the significant anemia observed with the use of boceprevir. This favorable risk benefit assessment is made based on the key efficacy and safety findings.

Overall, the addition of boceprevir to pegylated interferon and ribavirin combination therapy resulted in a significant improvement in efficacy in both previously untreated (treatment-naïve) and previous treatment failure (treatment-experienced) subjects. The higher sustained virologic response was mainly driven by higher end of treatment response. Additionally, relapse rates were also substantially lower in boceprevir-treated subjects.

In treatment-naïve subjects (P05216), SVR rates in the response guided therapy arm were 63%, similar to SVR rates of 66% in triple therapy (BOC/PR48) arm. These results demonstrate superiority of boceprevir in combination with pegylated interferon and ribavirin ($p < 0.0001$) to the pegylated interferon and ribavirin (PR) control arm (SVR rate of 38%) demonstrating a robustness in the treatment effect. Efficacy of boceprevir was demonstrated in subjects regardless of race (non-black and black). In previous treatment-failure subjects (P05101), SVR rates in the response guided therapy arm were 59% compared to SVR rates of 66% in triple therapy (BOC/PR48) arm. These results demonstrate superiority of boceprevir in combination with pegylated interferon and ribavirin ($p < 0.0001$) to the PR control arm (SVR rate of 21%), demonstrating a robustness in the treatment effect in this difficult to treat population. Efficacy was demonstrated in both previous relapsers and the prior partial responders who had received at least 12 weeks of pegylated interferon and ribavirin therapy in the past. The data for primary endpoint analyses were highly statistically significant and the treatment effect was robust across all significant subgroups. However, efficacy was not

demonstrated in null responders to previous therapy in boceprevir trials as these subjects were not included in the trials.

The use of boceprevir was associated with an incremental decrease in hemoglobin above and beyond that observed with standard of care therapy (pegylated interferon and ribavirin) alone. The anemia appears to be part of an overall bone marrow suppressive effect of boceprevir as evidenced also by the increased frequency of neutropenia and thrombocytopenia in boceprevir-treated subjects compared to PR-treated controls.

Subjects treated with boceprevir had increased frequency of Grade 3 and 4 anemia. The potential risk associated with anemia can be mitigated in clinical practice by close monitoring of laboratory parameters and dose modification of ribavirin and/or adjunctive measures for the management of anemia. The use of erythropoietin was permitted in these trials, at the investigator's discretion, with or without ribavirin dose reduction as a supportive therapy for the management of anemia. Erythropoietin use has been associated with increased incidence in thromboembolic events in subjects receiving erythropoietin. There were few thromboembolic adverse events reported in these trials. However, the risk/benefit for use of erythropoietin in these trials cannot be fully assessed due to the presence of confounding factors and because erythropoietin use was open-label and was not randomized. Pure red-cell aplasia (PRCA) is a rare erythropoietin side effect, and was reported in one subject during the follow-up period; however, PRCA has also been associated with use of pegylated interferon and ribavirin.

Dysgeusia (alteration of taste) was a common adverse event reported at an increased frequency in boceprevir-treated subjects as compared to control (37% in boceprevir-containing arms versus 16% in control arm); however, the majority of dysgeusia events were mild-moderate in intensity and were not treatment-limiting. Gastrointestinal symptoms such as nausea, diarrhea, and vomiting (4%-6% difference compared to controls) also occurred at a somewhat increased frequency in boceprevir-treated subjects.

Adverse events of rash/skin eruption were observed at similar frequency in boceprevir-treated subjects compared to controls. No cases of Stevens-Johnson syndrome/toxic epidermal necrolysis were reported.

An advisory committee meeting has been scheduled on April 27, 2011 to discuss this application. The expert opinion and recommendations from the committee will be considered before the final regulatory decision is made regarding approval of boceprevir for treatment of patients with chronic hepatitis C.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The Applicant has proposed a Medication Guide only REMS and it is currently under review by Division of Risk Management (DRISK) in the FDA Office of Surveillance and Epidemiology (OSE).

1.4 Recommendations for Postmarket Requirements and Commitments

The pediatric studies to assess safety and activity of boceprevir for the treatment of CHC in pediatric subjects will be required under Pediatric Research Equity Act (PREA). Some of the issues under consideration at this time for additional post-marketing studies are:

- A trial of boceprevir in combination with PR in null responders to previous pegylated interferon/ribavirin therapy ($< 2 \log_{10}$ decline in HCV RNA at Week 12)
- A trial evaluating different durations of boceprevir/PR vs. PR alone in treatment-naïve subjects with IL28B C/C genotype.
- A randomized, controlled trial evaluating different durations of triple therapy for late responders in treatment-naïve population.
- Drug-drug interaction studies to address some of the unresolved issues.

Additional post-marketing commitments or requirements may be proposed at a later time based on the discussions and recommendations at the advisory committee meeting scheduled on April 27, 2011.

2 Introduction and Regulatory Background

Hepatitis C virus (HCV) is a small, enveloped, single-stranded ribonucleic acid (RNA) virus of the family Flaviviridae. HCV infection is the leading cause of chronic liver disease in the United States. The natural history of hepatitis C involves progression to cirrhosis, hepatocellular carcinoma, liver failure, and death. Globally, it is estimated that 175 million persons are infected with HCV, and it affects about 3.2 million people in the U.S. Genotype 1 HCV is the most prevalent genotype worldwide and accounts for 80% of the HCV infections in the US. Calculations based on a computer cohort simulation of the US population between 2010 and 2019 suggest that mortality related to HCV infection (death from liver failure or hepatocellular carcinoma) will continue to increase over the next two decades.

The current application requests approval of boceprevir, a new molecular entity, for the treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alpha and ribavirin, in adult patients (18 years and older) with compensated liver disease who are previously untreated or who have failed previous therapy. The

proposed treatment regimen is boceprevir 800 mg administered orally three times daily in combination with peginterferon alpha and ribavirin.

2.1 Product Information

Generic (trade) name:	Boceprevir (VICTRELIS™)
Chemical class:	New molecular entity
Pharmacological class:	HCV NS3 protease inhibitor
Proposed indication:	VICTRELIS is indicated for the treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alpha and ribavirin, in adult patients (≥18 years of age) with compensated liver disease who are previously untreated or who have failed previous therapy
Dosing regimens:	800 mg three times daily
Dosage form:	200 mg capsules

Boceprevir is a novel serine protease inhibitor of the ketoamide class which specifically inhibits hepatitis C virus (HCV) non-structural protein 3 (NS3) protease. HCV protease inhibitors block the NS3/4A protease-dependent cleavage of the HCV polyprotein, and thereby, inhibit viral replication in infected host cells.

The Applicant completed a clinical development plan to assess the efficacy and safety of boceprevir in patients with chronic hepatitis C infection. Boceprevir was evaluated clinically by the Applicant because of its potential for improving the sustained virologic response when given in combination with standard of care therapy and the potential for shorter duration of therapy leading to improvement in the tolerability of the current pegylated interferon and ribavirin therapies.

2.2 Tables of Currently Available Treatments for Proposed Indications

The current standard of care treatment for chronic hepatitis C is the combination therapy with peginterferon alfa-2a or alfa-2b plus ribavirin for a total duration of 24 or 48 weeks according to the genotype¹. The currently approved drugs for the treatment of HCV infection are listed in Table 1.

¹ Ghany MG et al. Hepatology. 2009 Apr;49(4)

Table 1: Currently Approved Drugs for the Treatment of Chronic Hepatitis C

Generic Name	Trade Name
Pegylated interferons	
Peginterferon alfa-2a	Pegasys®
Peginterferon alfa-2b	PegIntron®
Interferons	
Interferon alfa-2a	Roferon-A®*
Interferon alfa-2b	Intron-A®
Consensus interferon	Infergen®
Ribavirin	Rebetol®, Copegus®

* Voluntarily withdrawn from U.S. market 10/1/2007; not due to safety or efficacy concerns

The use of these therapeutic regimens has decreased the morbidity and mortality associated with HCV infection. However, the overall sustained viral response rate is only about 40% to 45% for HCV genotype 1 patients. It is imperative that patients be treated effectively, i.e. achieving a sustained response rate to minimize the impacts of this major public health problem. Therefore, the developments of new therapeutic modalities for the treatment of chronic HCV infection that are more efficacious are much needed and address an unmet need, particularly for those who have failed previous therapies with interferon alpha and ribavirin.

2.3 Availability of Proposed Active Ingredient in the United States

The proposed active ingredient is a new molecular entity and is not currently marketed in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

Boceprevir is a new molecular entity targeting a novel step in the life-cycle of HCV replication. Currently, no pharmacologically related products have received FDA approval and this is the first drug in the pharmacologic class of HCV NS3 protease inhibitor filed for the marketing licensure.

Another drug in the clinical development in the same class is telaprevir. Boceprevir and telaprevir are both linear ketoamide HCV-NS3/4A protease inhibitors. The Phase 3 trials have been completed and the marketing application has also been filed for telaprevir. The important safety issues reported with telaprevir are rash and anemia. The main cutaneous side effects reported with telaprevir have been rash, pruritus, skin eruption, and maculopapular exanthema including severe cases of rash. The data presented at the 18th Conference on Retroviruses and Opportunistic Infections (CROI) meeting 2011 shows that discontinuation due to rash is 7% in telaprevir trials. A case of drug rash with eosinophilia and systemic symptoms (DRESS) due to telaprevir (VX-950) has been

reported in literature². Authors noted that their observation suggests that potentially severe hypersensitivity reactions may belong to the spectrum of rashes induced by this drug.

Anemia is a concern with both the drugs; however, a major difference is that erythropoietin use was allowed for the management of anemia in boceprevir trials but was not used in telaprevir trials. Also, to be noted is that most of the trials for telaprevir have used pegylated interferon alfa-2a (PEG2a) in the backbone therapy; while the boceprevir clinical program used pegylated interferon alfa-2b (PEG2b) for the majority of the studies, with the exception of one recently completed study (P05685) using PEG2a. A head-to-head comparison of PEG2b and PEG2a (plus ribavirin) in the 3,070-subject IDEAL trial (P03471) demonstrated that there were no differences in efficacy and a similar safety profile when naïve subjects were treated with either peginterferon³. Study P05685 was conducted by the Applicant to formally study the combination of PEG2a/ribavirin plus boceprevir 800 mg TID. The Safety Update Report (SUR) contains a summary report from this recently completed trial; however, the full clinical study report and datasets have not been submitted to the NDA. The Applicant states that the safety data from Study P05685 have not revealed any unusual side effects or rates of adverse events obviously different from those seen with PEG2b/ribavirin plus boceprevir (See Section 7.5 for details). The Applicant concludes that together, these two trials support that boceprevir can be safely and effectively used in combination with either of the licensed peginterferons.

The proposed indication for boceprevir use is in combination with pegylated interferon and ribavirin; hence the safety profile of these drugs is discussed briefly in this section. Almost all patients treated with pegylated interferons and ribavirin experience one or more adverse events during the course of therapy. The most commonly reported adverse events are influenza- like side effects such as fatigue, headache, myalgia, fever and rigors. Other common adverse events are anorexia, nausea and vomiting, diarrhea, arthralgias, injection site reactions, alopecia, and pruritus. Neuropsychiatric side effects include depression, anxiety, insomnia, emotional lability, mood disorders, frank psychosis, suicidal ideation, actual suicide, and homicide. Adverse events are a major reason that patients decline or stop HCV therapy altogether. The currently approved alpha-interferon product labels carry Warnings and Precautions regarding potential toxicities in a substantial number of organ systems as shown in Table 2. All the approved interferon products carry a Pregnancy Category rating of C.

² Montaudie H, Passeron T, Cardot-Leccia N, Sebbag N, Lacour JP. Drug rash with eosinophilia and systemic symptoms due to telaprevir. *Dermatology* 2010;221(4):303-5.

³ McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N Engl J Med* 2009;361(6):580-593.

Table 2: Class Effects of alpha-Interferons in Combination with Ribavirin

Adverse Events (Warnings and Precautions)	
Neuropsychiatric	Suicide, suicidal/homicidal ideation, depression, relapse of drug addiction, drug overdose
Infections	Serious and severe infections (bacterial, viral, or fungal)
Bone marrow toxicity	Neutropenia, anemia, thrombocytopenia
Cardiovascular disorders	Hypotension, hypertension, supraventricular arrhythmias, chest pain, myocardial infarction
Cerebrovascular disorders	Ischemic and hemorrhagic cerebrovascular events
Hepatic failure and hepatitis exacerbations	Risk of hepatic decompensation in patients with cirrhosis
Hypersensitivity	Severe acute reactions, serious skin reactions (Stevens Johnson Syndrome, exfoliative dermatitis)
Endocrine disorders	Hypo- or hyperthyroidism, hypo- or hyperglycemia, diabetes mellitus
Autoimmune disorders	Myositis, hepatitis, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, psoriasis, rheumatoid arthritis, systemic lupus erythematosus, interstitial nephritis, thyroiditis
Pulmonary disorders	Dyspnea, pulmonary infiltrates, interstitial pneumonitis, bronchiolitis obliterans, pneumonia, pulmonary hypertension, sarcoidosis
Colitis	Ulcerative colitis, hemorrhagic/ischemic colitis
Ophthalmologic disorders	Macular edema, retinal artery/vein thrombosis, retinal hemorrhages and cotton wool spots, optic neuritis, papilledema, serous retinal detachment
Pancreatitis	Fatal and nonfatal pancreatitis

Source: US Package Inserts: Pegasys® and PegIntron®

The most common and concerning adverse events related to ribavirin are hemolytic anemia and rash. Ribavirin is genotoxic and teratogenic and is classified as Pregnancy Category X.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

An Investigational New Drug application (IND 69,027) was submitted by Schering Corporation on May 18, 2005. This was not first-in-human study and previous human experience was included in the IND submission. SCH 503034 had been administered to 71 healthy volunteers and 112 HCV infected subjects in single and multiple dose studies. After 30-day safety review, it was concluded that the Sponsor may proceed with the proposed clinical investigation.

The clinical development plan was reviewed by the FDA and the feedback was provided for the Phase 3 development program addressing the issues involving dose, durations, and optimization of treatment regimens prior to initiation of Phase 3 trials. Some of the key points included; 1) a 4 Week lead-in phase with pegylated interferon and ribavirin therapy for these studies; 2) a 48-week boceprevir treatment arm, as well as a short-term arm with response-guided parameters to be included in these studies; 3) futility criteria for treatment failures; and 4) long-term follow-up should be conducted for at least 3 years.

In January 2009, FDA notified all hepatitis C product sponsors of the Division's current position on the use of erythropoiesis-stimulating agents in hepatitis C clinical trials. On August 12, 2009 a meeting was held between Sponsor and the Division to discuss the study design for trial P06086, a trial proposed to evaluate the safety and efficacy of erythropoietin for the treatment of anemia associated with HCV therapy; and feedback was provided on the study design.

Pre-NDA Meeting:

A pre-NDA meeting was held on September 29, 2010. The following key points were made:

- FDA asked the Sponsor to perform and provide the combined analyses for Cohort 1 (Black) and Cohort (non-black) as the primary efficacy results for the Study P05216 in previously untreated subjects.
- FDA informed the Sponsor that (b) (4)
- FDA agreed that boceprevir met the criteria for Priority Review, accepted the schedule for a rolling NDA submission and agreed, that applicant can request a deferral and waiver of pediatric studies at the time of initial approval.

2.6 Other Relevant Background Information

The Day 80 assessment reports from European Medicines Agency (EMA) were obtained and reviewed to identify if there were any issues or concerns where the two agencies had different view points. Overall, FDA review team's assessment at this time seems to share similar concerns to those indicated in the EMA's preliminary assessment.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Site audits by Division of Scientific Investigations (DSI) were conducted for this NDA. The site selection process involved the boceprevir review team and Dr. Antoine El-Hage from DSI. Please refer to Dr. El-Hage's DSI review for further details. Four clinical sites were inspected (Table 3), because of enrollment of large numbers of study subjects at these sites. Two domestic and two foreign sites were selected as this is the first drug in a new class and some of the limited experience with this drug has been from foreign sites; it was desirable to include foreign sites in the DSI audits to verify the quality of conducted study.

The medical records reviewed from the two domestic sites disclosed no adverse findings that would reflect negatively on the reliability of the data. In general, the trial records reviewed were found to be in order and verifiable. Therefore, the available data from the inspected sites are acceptable in support of this NDA. The data from the two foreign sites, in Italy and France, are still pending at the time of this review.

Table 3: Listing of Division of Scientific Investigations Evaluation of Clinical Inspections

Name of CI and site #, if known	City, State/ Country	Protocol	Inspection Date	Final Classification
Jonathan McCone	Alexandria, VA	P05216	1/19-1/24/11	NAI
Stuart Gordon	Detroit, MI	P05101	1/12-1/20/11	NAI
	Italy			pending
	France			pending

Source: Division of Scientific Investigations Evaluation of Clinical Inspections for NDA 202-258 by Dr. Antoine El-Hage

CI = clinical investigator

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

3.2 Compliance with Good Clinical Practices

The protocol and informed consent documents were reviewed and approved by the Institutional Review Boards and Independent Ethics Committees for each of the investigational centers participating in the pivotal trials. The Applicant certified these trials were conducted in compliance with the ethical principles described in the Declaration of Helsinki and in compliance with International Conference on Harmonisation Good Clinical Practice guidelines. In addition, the FDA DSI inspected the clinical sites, and data from the available sites were considered acceptable (see Section 3.1). For a more detailed discussion of the DSI audit, please refer to the Clinical Inspection Summary, by Dr. Antoine El-Hage.

Table 4: Protocol Violations in Phase 3 Protocols P05101 and P05216

	P05101		P05216	
	Boceprevir-Containing Arms	PR Arm	Boceprevir-Containing Arms	PR Arm
# Subjects Randomized and Treated	323	80	734	363
Protocol deviation for enrollment – n (%)	24 (7.4)	4 (5.0)	37 (5.0)	19 (5.2)

Source: Clinical Study Report for Protocols P05101 and P05216

In summary, protocol violations were observed in approximately 5% subjects across treatment arms.

3.3 Financial Disclosures

The Applicant examined financial data regarding significant payments and equity for all participating Phase 2 and 3 investigators per 21 CFR Part 54. The Applicant provided a certification for the majority of investigators, indicating >90% of responding investigators had no financial arrangements. We additionally requested and reviewed investigator-signed financial disclosure forms (Form 3455) for all investigators reporting “significant payments of other sorts” in excess of \$25,000 and investigators not reporting payments of other sorts, but with evidence to the contrary based on disclosure forms signed by the Applicant. These payments primarily consisted of honorarium, consulting fees and contracts to the investigator’s institution. Our review found no significant conflicts of interest. Based on the low proportion of investigators with a financial interest and the double-blind nature of the Phase 3 protocols, the likelihood trial results were substantively biased based on financial interest is low.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please refer to Dr. Mark Seggel’s Chemistry review. Victrelis™ hard gelatin capsules contain 200 mg of boceprevir. The immediate release formulation also contains microcrystalline cellulose, lactose monohydrate, pregelatinized starch, croscarmellose sodium, sodium lauryl sulfate, and magnesium stearate. Sodium lauryl sulfate (SLS) is an anionic surfactant added to (b) (4)

(b) (4)

To reduce potential degradation the drug product is stored at 5°C before dispensing to patients. Stability at 25°C supports the storage of the product at room temperature for up to 3 months.

The Applicant has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period.

4.2 Clinical Microbiology

Please refer to Dr. Patrick Harrington's Review for detailed assessment. Key findings are summarized below.

Nonclinical Virology

Boceprevir is a small molecule drug that binds to the active site of the hepatitis C virus (HCV) NS3/4A protease and inhibits its enzymatic activity. Boceprevir inhibited the replication of an HCV genotype 1b (strain Con1) subgenomic replicon in Huh-7 cells with 50% and 90% effective concentration (EC₅₀ and EC₉₀) values of approximately 200 nM and 400 nM, respectively. A ~2-fold reduction in boceprevir antiviral activity was observed against the genotype 1a (H77) replicon relative to the genotype 1b (Con1) replicon.

Passage of HCV genotype 1b replicon-harboring cells in the presence of boceprevir resulted in the emergence of replicons with reduced susceptibility to boceprevir. Specific substitutions in the NS3 protease coding region of the HCV genome were detected in the boceprevir-selected replicons, including T54A, A156S, A156T, and V170A. These and other commonly observed boceprevir treatment-emergent substitutions (e.g., V36M, R155K, A156V) were shown to reduce boceprevir anti-HCV activity when re-introduced into the HCV genome by site-directed mutagenesis.

Any of the key boceprevir resistance-associated substitutions observed in cell culture or in clinical studies is predicted to confer at least some degree of cross-resistance to nearly every HCV NS3/4A protease inhibitor currently being studied under FDA IND.

Clinical Virology

Among boceprevir-treated subjects in P05216 or P05101 who did not achieve SVR, and for whom samples were analyzed, 52% (153/292) had one or more of the following post-baseline, treatment-emergent NS3 amino acid substitutions detected: V36A, V36M, T54A, T54S, V55A, V107I, R155K, R155T, A156S, A156T, A156V, V158I,

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significant portion of the HCV population for a long period of time following boceprevir/Peg-IFN α /RBV treatment failure. Among subjects with available data, one or more boceprevir treatment-emergent substitutions remained detectable in 25% of subjects after 2.5 years of follow-up using a population-based nucleotide sequence analysis method. The most common NS3 substitutions detected after 2.5 years of follow-up were T54S and R155K. Note that a population-based nucleotide sequencing assay typically cannot detect variants that comprise <20-25% of the total viral population in a given patient sample. Therefore, the lack of detection of an amino acid substitution by a population-based assay does not necessarily indicate that viral subpopulations carrying that substitution have declined to a background level that may have existed prior to treatment.

4.3 Preclinical Pharmacology/Toxicology

Please refer to Dr. Christopher Ellis' Pharmacology Toxicology review. The boceprevir nonclinical safety profile has been evaluated in safety pharmacology studies (rats, dogs and monkeys), acute and chronic toxicology studies (mice, rats and cynomolgus monkeys), fertility and pre- and post-natal developmental studies (rats), embryo-fetal developmental studies (rats and rabbits), neonatal/juvenile toxicology studies (rats), genetic toxicology studies (Ames, *in vitro* chromosomal aberration and *in vivo* mouse micronucleus assays), 2-year carcinogenicity studies (rats and mice; Section 7.6.1) and combination toxicology studies with ribavirin and PegIntron (rats and/or monkeys). Notable nonclinical findings include:

- Mild decreases in red blood cell count, hemoglobin and hematocrit along with increases in reticulocytes were observed in monkeys administered boceprevir at doses ~1.9-fold higher than the proposed human exposure. These effects did not progress over the three month duration. Additionally, boceprevir, when administered in combination with ribavirin and PegIntron in monkeys, did not exacerbate the hematological toxicity of ribavirin and PegIntron alone at boceprevir exposures up to 1.6-fold greater than exposures attained in subjects receiving boceprevir 800 mg TID.
- Liver toxicity was observed in mice, rats and monkeys at exposures similar to those attained in human subjects receiving the proposed clinical boceprevir 800 mg TID dose. In mice, higher liver weights with Kupffer cell hypertrophy and neutrophil infiltration was associated with AST and ALT elevations. In rats, liver findings were characterized by ALT elevations and enlarged multinucleated hepatocytes. In monkeys, liver findings were not observed at doses ~1.6-fold higher than the proposed clinical dose. The specific liver findings observed in each species were quite different and so a consistent mechanism for liver toxicity was not identified.

- Testicular degeneration occurred in rats at boceprevir exposures less than clinical boceprevir 800 mg TID exposures. Testicular findings were not associated with alterations in FSH, LH or testosterone, and the Sertoli cell appears to be the primary target. However, testicular findings were not observed in mice or monkeys administered boceprevir for 3 months at doses ~ 7- and 4-fold higher in mice and monkeys, respectively, than those in humans at the proposed boceprevir 800 mg TID dose. Further clinical evaluation of this nonclinical finding is discussed in Section 7.3.5.
- In female rats, fertility and early embryonic development were affected adversely at boceprevir doses ≥ 150 mg/kg; however, these effects were not observed at doses ~1.4-fold higher than the proposed human exposure. No adverse findings regarding embryo-fetal development were observed in rats or rabbits at boceprevir doses ~10 and 2-fold higher, respectively, than the proposed human exposure. The safety of the metabolite, SCH 629144, to the developing fetus has not been clearly established. No test article-related effects on maternal animal (F0) pregnancy, parturition and lactation, or on the F1 generation growth, viability, development or reproductive performance, or on the F2 generation survivability were reported in a rat prenatal and postnatal development study. The animal to human boceprevir exposure ratio at the high dose is 6.5.
- Boceprevir was not genotoxic as tested in the Ames assay, the *in vitro* chromosomal aberration assay in human peripheral blood lymphocytes and the *in vivo* mouse micronucleus assay. Two-year mouse and rat carcinogenicity studies were performed with boceprevir. Mice were administered doses of up to 500 mg/kg in males and 650 mg/kg in females, while rats were administered doses of up to 125 mg/kg in males and 100 mg/kg in females. Mice and rats were negative for boceprevir-related tumors at exposures either similar to (rats) or ~2 to 6-fold greater (for male and female mice, respectively) than those in humans at the recommended dose of 800 mg TID.
- Adverse testicular and thyroid findings were observed in a 3 month study in neonatal/juvenile rats at doses ≥ 75 mg/kg. Testicular findings were consistent with those in adult rats; however, minimal follicular hyperplasia of the thyroid has not been observed in adults. Additionally, femur length was reduced up to 3.3%. Reduced thyroid hormone exposure could cause the longitudinal bone growth reductions; however, they are more likely the result of body weight gain reductions.

4.4 Clinical Pharmacology

This section provides a brief summary of the clinical pharmacology of boceprevir. Please refer to the FDA Clinical Pharmacology Reviews by Dr. Ruben Ayala and Dr. Jeffry Florian for additional information.

4.4.1 Mechanism of Action

Boceprevir is an inhibitor of the HCV NS3/4A protease that is necessary for the proteolytic cleavage of the HCV encoded polyprotein into mature forms of the NS4A, NS4B, NS5A and NS5B proteins. Boceprevir covalently, yet reversibly, binds to the NS3 protease active site serine (S139) through a (alpha)-ketoamide functional group to inhibit viral replication in HCV-infected host cells. In a biochemical assay, boceprevir inhibited the activity of recombinant HCV genotype 1a and 1b NS3/4A protease enzymes, with K_i values of 14 nM for each NS3/4A subtype.

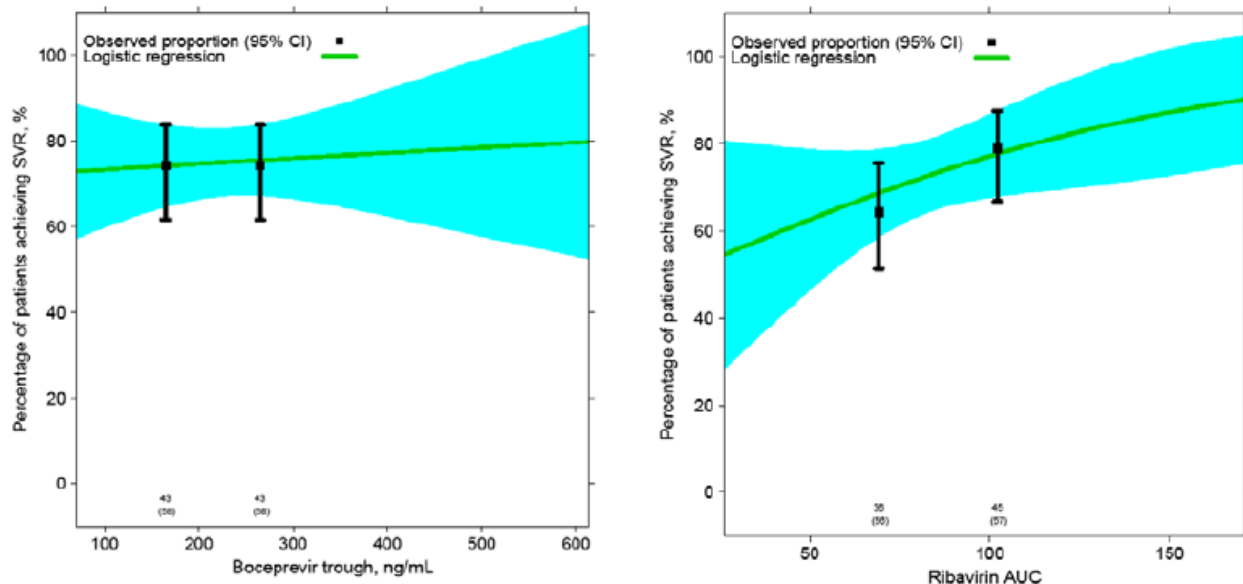
4.4.2 Pharmacodynamics

This section provides a brief summary of the FDA Pharmacometric Review of boceprevir. Please refer to the review by Dr. Jeffry Florian for additional information.

The Applicant's proposed boceprevir dose is based on Phase 2 trials in which doses lower than 800 mg three times daily were associated with lower efficacy rates. In the two pivotal Phase 3 trials, PK data were available for 67 of 734 treatment-naïve subjects (P05216) and 49 of 323 treatment experienced subjects (P05101). C_{trough} and AUC were estimated using sparse PK samples. At the 800 mg three times daily dose of boceprevir evaluated in these trials, a shallow and non-significant relationship was identified between boceprevir exposure and SVR (Figure 1, left). These results indicate that higher exposures to boceprevir are not expected to result in greater efficacy.

A non-significant but upward trending relationship between ribavirin steady-state AUC (AUC_{τ}) and SVR was observed in the same Phase 3 PK population (Figure 1, right). These results indicate that ribavirin exposure may be an important factor in achieving SVR in the setting of boceprevir treatment, despite dosing ribavirin based on weight.

Figure 1: Percentage of Subjects Achieving SVR from P05101 and P05216 Versus Boceprevir Trough Concentration (left) or Ribavirin Steady-State AUC (right)*



* Observations were grouped into two bins and plotted as the median bin value. The total number of subjects with SVR for each bin and total number of subjects per bin (in parentheses) are shown along the x-axis.

Source: FDA Pharmacometrics Reviewer

4.4.3 Pharmacokinetics

Boceprevir capsules contain a 1:1 mixture of two diastereomers, SCH534128 and SCH534129. In plasma the diastereomer ratio changes to 2:1, favoring the active diastereomer, SCH534128. Plasma concentrations of boceprevir described below consist of both diastereomers SCH534128 and SCH534129, unless otherwise specified.

In healthy subjects who received boceprevir 800 mg three times daily with food for 14 days, boceprevir exposure was characterized by a mean (SD) $AUC_{(0-8h)}$ of 4830 (± 1546) ng.hr/mL, C_{max} of 1680 (± 588) ng/mL, and C_{min} of 91 (± 29) ng/mL. Boceprevir pharmacokinetics were similar between healthy subjects and HCV-infected subjects.

Absorption

Boceprevir was absorbed following oral administration with a median T_{max} of 2 hours. Steady state AUC , C_{max} , and C_{min} increased in a less-than-dose-proportional manner and individual exposures overlapped substantially at 800 mg and 1200 mg, suggesting diminished absorption at higher doses. Accumulation is minimal (0.8 to 1.5-fold) and pharmacokinetic steady state is achieved after approximately 1 day of three times daily dosing. The absolute bioavailability of boceprevir has not been studied.

Food enhanced the exposure of boceprevir by up to 65% at the 800 mg three times daily dose when administered with a meal, relative to the fasting state. The bioavailability of boceprevir was similar regardless of meal type (e.g., high-fat vs. low-fat) or whether taken 5 minutes prior to eating, during a meal, or immediately following completion of the meal.

Distribution

Boceprevir has a mean apparent volume of distribution (Vd/F) of approximately 772 L at steady state in healthy subjects. Human plasma protein binding is approximately 75% following a single dose of boceprevir 800 mg. Boceprevir is administered as an approximately equal mixture of two diastereomers, SCH534128 and SCH534129, which rapidly interconvert in plasma. The predominant diastereomer, SCH534128, is pharmacologically active and the other diastereomer is inactive.

Metabolism

Studies *in vitro* indicate that boceprevir primarily undergoes metabolism through the aldo-ketoreductase (AKR)-mediated pathway to ketone-reduced metabolites that are inactive against HCV. After a single 800-mg oral dose of ¹⁴C-boceprevir, the most abundant circulating metabolites were a diasteriomic mixture of ketone-reduced metabolites with a mean exposure approximately 4-fold greater than that of boceprevir. Boceprevir also undergoes, to a lesser extent, oxidative metabolism mediated by CYP3A4/5.

Drug Interactions

Boceprevir is metabolized principally by aldoketo-reductase (AKR) enzymes and partially by CYP3A4. It is characterized as a potent inhibitor of CYP3A4 based on the results of *in vitro* assessments and the results of a drug-drug interaction (DDI) study conducted with oral midazolam, in which midazolam exposure increased over 5-fold with boceprevir coadministration. The Applicant assessed the impact of AKR inhibition (ibuprofen and diflunisal) and potent CYP3A4 inhibition (ketoconazole) on boceprevir pharmacokinetics *in vivo*; based on these results there is sufficient information to label boceprevir for safe use with inhibitors of AKR and CYP3A4. However, insufficient information is available to characterize the effect of boceprevir on other likely coadministered agents. Outstanding DDI issues at the time of the review include the following:

- DDI studies were not performed to assess the effect of boceprevir on methadone and buprenorphine PK, two important medications for the intended patient population. Although methadone is metabolized partially by CYP3A4, DDI studies with other potent inhibitors of CYP3A4, including ritonavir-boosted HIV protease inhibitors, have demonstrated unanticipated decreases in methadone exposure, possibly due to mixed inhibition and induction effects on CYP450 enzymes or uncharacterized transporter effects. Thus, the effect of boceprevir on methadone exposure cannot be accurately predicted based on *in vitro* experiments. Buprenorphine is less sensitive to interactions via CYP3A4, given

its alternative glucuronidation pathway; however, the impact of boceprevir on glucuronidation has not been characterized.

- A DDI study was not performed to characterize the effect of boceprevir on a sensitive P-glycoprotein (P-gp) substrate, such as digoxin. Based on *in vitro* experiments, boceprevir has the potential to inhibit P-gp, particularly in the gut, which may result in clinically significant increases in the exposure of digoxin and other sensitive substrates.
- The safety and efficacy of combined oral contraceptive (COC) use during boceprevir coadministration have not been sufficiently characterized. The completed DDI study conducted with Yaz® (ethinyl estradiol/drospirenone) showed a 24% decrease in ethinyl estradiol (EE) exposure and a 100% increase in drospirenone (DRSP) exposure during boceprevir administration. The magnitude of increase in DRSP exposure may increase the risk of adverse events, including hyperkalemia and thromboembolism. It is unknown if the doubling of exposure would necessarily occur with other progestational components (e.g. norgestimate or norethindrone). The 25% decrease in EE exposure may result in breakthrough bleeding and may theoretically impact COC efficacy, though there is limited information on which to draw a conclusion. Further, because of deficiencies in the design of the completed DDI study, reliability of the PK results and interpretation of the findings are in question. Because it may be challenging for women of child-bearing potential to rely on two barrier methods while on concomitant treatment with ribavirin, the safety and efficacy implications of boceprevir coadministration with COCs should be further characterized. The Applicant has acknowledged these concerns and plans to conduct a clinical DDI study with another progestin-containing COC. Please also refer to Section 7.5.5 for additional discussion regarding DDI with combined oral contraceptive (COC) use.
- *In vitro* experiments to evaluate the potential impact of boceprevir on liver and gut transporters OATP1B1, OATP1B3 and BCRP were not performed. The results of such experiments are important for characterizing possible DDIs with potential concomitant medications, including statins, angiotensin II receptor blockers (ARBs) and some antidiabetic agents.
- A DDI study was not conducted to assess the effect of boceprevir on antidepressant exposure. Unanticipated decreases in the exposure of selective serotonin reuptake inhibitors (SSRIs), including paroxetine, sertraline and escitalopram, have been observed in DDI studies conducted with other HCV and HIV protease inhibitors. Because the mechanism of these observed decreases have not been characterized, and given the importance of these agents in HCV patient care, an *in vivo* study is considered important to rule-out a potentially significant interaction.

Elimination

Boceprevir is eliminated with a mean plasma half-life ($t_{1/2}$) of approximately 3.4 hours. Boceprevir has a mean total body clearance (CL/F) of approximately 161 L/hr. Following a single 800 mg oral dose of ^{14}C -boceprevir, approximately 79% and 9% of the dose was excreted in faeces and urine, respectively, with approximately 8% and 3% of the dosed radiocarbon eliminated as boceprevir in faeces and urine. The data indicate that boceprevir is eliminated primarily by the liver.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Phase 1 Trials

A total of 20 Phase 1 trials were performed: 13 trials with all healthy volunteers, 5 trials with hepatitis C infected subjects, one renal impairment trial with both healthy volunteers and subjects with renal impairment, and one hepatic impairment trial with both healthy volunteers and subjects with hepatic impairment.

Table 5: Phase 1 Trials

	Population	Boceprevir Doses	Trial Objective	Treatment Duration	Enrolled Subjects
Healthy Volunteers					
P02727	Healthy Subjects	50, 100, 200, 400, 600, 800 mg	Single Ascending Dose	Single Dose	56/54 treated (36 boceprevir, 18 placebo)
P03521	Healthy Subjects	600 mg fed/fasting	Food effect	Single Dose x 2	23
P03533	Healthy Subjects	400 mg	Different formulations	Single Dose x 3-5 days	45
P03588	Healthy Subjects (all men)	^{14}C -Boceprevir 800 mg	Absorption, metabolism, excretion	Single Dose	12/10 treated
P04119	Healthy Subjects	600 mg	High Fat meal	Single Dose x 3	12
P04133	Healthy Subjects	400 mg	Food Effect	Single Dose x 4	12
P04486	Healthy Subjects	400, 800, 1200 mg TID, 800 mg BID or TID plus diflunisal	Effect of high dose boceprevir	Multiple Dose (up to 12 days)	39 (30 boceprevir, 9 placebo)
P04488	Healthy Subjects	200, 400, 800 mg TID	Race/Ethnic Origin Study	Multiple Dose (up to 8 days)	38/36 (20/18 Japanese, 18 Caucasian)
P04489	Healthy	800, 1200 mg	Thorough QT	Multiple Dose	36

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	Subjects	TID	Study	(up to 10 days)	
P04624	Healthy Subjects (all women)	400 mg BID or TID; diflunisal, ritonavir, clarithromycin	DDI	Multiple Dose (up to 15 days)	12
P04983	Healthy Subjects	800 mg	Different formulations	Single Dose x 2-4 days	48
P05351	Healthy Subjects (all men)	800 mg TID	Assess effect on Red Blood Cells	57 days	16 (8 boceprevir, 8 placebo)
P05880	Healthy Subjects	800 mg TID; midazolam, OCP, tenofovir, efavirenz	DDI	Multiple Dose (up to 14 days)	58
Hepatic/Renal Impairment					
P03747	Healthy and Hepatic Impaired Subjects	400 mg	Hepatic Impairment Study	Single Dose	24 (6 Healthy, 18 Hepatic Impairment)
P05579	Healthy and Renally Impaired Subjects	800 mg	Renal Impairment Study	Single Dose x 1 (healthy) or 2 (renal impairment)	14 (6 Healthy, 8 Renal Impairment)
HCV Infected Subjects					
P03516	HCV GT1, prior PEG nonresponders	100, 200, 400 mg BID, 400 mg TID or placebo	PK/PD, food effect	Multiple Dose (14 days)	92 (69 boceprevir, 23 placebo)
P03527	HCV GT1, prior PEG nonresponders	200, 400 mg TID, PEG	DDI, PK/PD	Multiple Dose (35 days, 21 days boceprevir)	26
P03648	HCV GT 2/3, treatment naïve	200, 400 mg BID, 400 mg TID or placebo	PK/PD	Multiple Dose (14 days)	39 (29 boceprevir, 10 placebo)
P04487	HCV GT1, prior PEG nonresponders	400 mg TID, 400, 600 mg QID, PEG	Different formulations, PK/PD	Multiple Dose (5 weeks, 4 weeks boceprevir)	30
P04531*	HCV GT1, prior PEG nonresponders	400 mg TID, PEG	PK/PD	Multiple Dose (20 weeks)	29

*P04531 is the long term maintenance protocol for subjects who completed P04487

PEG = pegylated interferon alfa

GT = genotype

Healthy Volunteer Trials

Fifteen Phase 1 trials enrolled 419 healthy volunteers, of whom 413 were treated: 377 were treated with boceprevir, 36 treated with placebo/comparator. The total daily

boceprevir dose ranged 50 to 3600 mg (single doses up to 800 mg and multiple doses up to 1200 mg TID) with 121 subjects receiving the proposed 800 mg TID dose. The maximum boceprevir treatment duration was 57 days.

Trials in Hepatitis C-Infected Subjects

Five Phase 1 trials enrolled 187 HCV infected subjects, of whom 180 were treated: 147 were treated with boceprevir, 32 treated with placebo and 1 treated with PEG2b alone. Of note, no subjects received the proposed clinical boceprevir dose of 800 mg TID. Four trials enrolled subjects with HCV GT1 who were previous treatment failures and one trial enrolled treatment naïve subjects with HCV genotype 2 or 3.

The Phase 2 and Phase 3 clinical trials analyzed for the assessment of the efficacy and safety are shown below in Table 6.

Table 6: Phase 2 and Phase 3 Clinical Trials

Study Number	Study Design	Treatment Regimen	No. of Subjects Randomized/ Treated
P03659 (RESPOND-1) Previous PR Treatment Failures	Phase 2, double-blind (to boceprevir and ribavirin), placebo-controlled study to determine the safe and effective dose range of boceprevir (100 to 800 mg) and PEG2b with or without RBV. Up to 49-wk treatment duration.	BOC (or placebo) 100, 200, 400, or 800 mg PO TID PEG2b 1.5 µg/kg QW RBV (or placebo) 800 to 1400 mg/day	357/357
P03523 (SPRINT-1) Treatment-naïve	Phase 2, open-label, two-part study. <u>Part 1</u> included five treatment arms with BOC/PR for 28 or 48 weeks, with and without a 4-week lead-in with PR. <u>Part 2</u> included exploration of BOC/P/low-dose RBV (400 to 1000 mg/day) for 48 weeks.	<u>Part 1</u> BOC 800 mg TID PEG2b 1.5 µg/kg QW RBV 800 to 1400 mg/day <u>Part 2</u> BOC 800 mg TID PEG2b 1.5 µg/kg QW RBV 400 to 1000 mg/day	Total: 598/595 Part 1: 520 treated Part 2: 75 treated
P05216	Phase 3, double-blind,	BOC 800 mg TID (or	1099/1097

(SPRINT-2) Treatment-naive	<p>placebo-controlled study comparing two regimens of boceprevir response-guided therapy (RGT) treatment paradigm of BOC/PR (28/48 wk) and BOC/PR (48 wk) to PR (48 wk). 4-week lead-in with PR.</p> <p>2 cohorts: Cohort 1 (white) and Cohort 2 (black)</p> <p>Randomization to 3 treatment arms (1:1:1) in each cohort.</p> <p>Stratified by HCV genotype 1a vs 1b and by viral load ($\leq 400,000$ IU/mL vs $> 400,000$ IU/mL) within cohort.</p>	<p>placebo) PEG2b 1.5 μg/kg QW RBV 600 to 1400 mg/day</p>	<p>Cohort 1: 938 nonblack treated subjects</p> <p>Cohort 2: 159 black treated subjects</p>
P05101 (RESPOND-2) Previous PR Treatment Failures	<p>Phase 3, double-blind, placebo-controlled study comparing two regimens of boceprevir response-guided therapy (RGT) treatment paradigm of BOC/PR (36/48 wk) and BOC/PR (48 wk) to PR (48 wk); 4-week lead-in with PR.</p> <p>Randomization to 3 treatment arms in a 1:2:2 ratio; Stratified by previous treatment in qualifying treatment regimen and by HCV genotype 1a vs 1b.</p>	<p>BOC 800 mg TID (or placebo) PEG2b 1.5 μg/kg QW RBV 600 to 1400 mg/day</p>	404/403
BOC=boceprevir; PEG2b=peginterferon alfa-2b; RBV=ribavirin; PR=peginterferon alfa-2b+ribavirin; TID = three times daily; QW= weekly			

5.2 Review Strategy

This reviewer, Dr. Poonam Mishra, is the primary clinical reviewer for this application. This review was performed in collaboration with two other clinical reviewers. Dr. Sarah Connelly, Medical Officer, reviewed the data from the Phase 1 trials, Phase 2 trials, and ongoing trials including the Safety Update Report. The findings of Dr. Connelly's review

are incorporated throughout this review in the relevant sections. Dr. Charles Cooper, Medical Officer, evaluated the safety data from the Phase 3 trials with regards to the special safety concern of anemia associated with boceprevir use. Dr. Cooper's review pertains specifically to the anemia observed in Phase 3 trials and is provided as a separate review document. Additionally, the FDA clinical and statistical reviewers collaborated extensively during the review process, and a number of the efficacy analyses were performed by the FDA statistician (Please refer to Statistical Review by Dr. Wen Zeng). In addition, there were significant interactions with the FDA clinical pharmacology, clinical microbiology, toxicology, and product evaluation groups. Their assessments are summarized in this document in the relevant sections, but complete descriptions of their findings are available in their respective discipline reviews.

Consultation was requested from the Division of Hematology Products to gain expert opinion and recommendations regarding bone marrow suppressive effects observed with boceprevir use and the issue of erythropoietin use for the management of anemia in the clinical trials. The pertinent findings, comments and recommendations from the consult review are incorporated in this document. Please refer to the Consult Review by Dr. Andrew Dmytrijuk dated March 07, 2011 for detailed assessment of their findings.

Consultation was also requested from the Division of Reproductive and Urologic Products (DRUP) relating to drug-drug interaction (DDI) studies already performed for boceprevir against combination oral contraceptives and possible recommendations concerning additional DDI studies. The key points are incorporated in this review. Please refer to the consult review by Dr. Gerald D. Willett dated March 21, 2011 for details.

5.3 Discussion of Individual Studies/Clinical Trials

The study designs of the individual trials and the pertinent results from some of the early phase trials are discussed in this section. Some of the key terms which were described by the Applicant and will be used throughout this review in the description of the trials are defined below:

Lead-In Period:

Lead-In phase refers to 4-weeks of therapy with pegylated interferon and ribavirin before the initiation of boceprevir. The Applicant's rationale for using lead-in is that it offers theoretical advantages over beginning all three drugs simultaneously. By having the lead-in with PR, viral load is reduced prior to the initiation of boceprevir, thereby decreasing the number of replicating virions exposed to boceprevir and potentially decreasing the likelihood for the development of resistance. In addition, by Week 4, ribavirin will have reached steady state, and the immunologic effects of interferon are also activated after the first few weeks of therapy, hence, when boceprevir is added at Week 4 all three drugs should be fully active at the same time. The Applicant further

states that this strategy may minimize any period of time when there is functional 'monotherapy' with a direct viral inhibitor.

An additional advantage noted by the Applicant is that by utilizing a 'lead-in' phase it may be possible to identify a population of subjects who should not receive boceprevir possibly due to insufficient interferon response. These are subjects who are expected to develop boceprevir resistance and achieve a low rate of SVR. Additionally a population with high responsiveness to PR who may not need the addition of boceprevir to obtain maximal SVR, or who may be treated for a shorter duration with the three-drug regimen, may be identified and thereby potentially increase the overall patient safety.

The following terms refer to the decline in HCV RNA from baseline to TW 4 and the subjects' interferon responsiveness:

- $< 1\text{-log}_{10}$ decline = poorly interferon responsive;
- $\geq 1\text{-log}_{10}$ decline = interferon responsive.

Reviewer's comment:

The use of a 4 week lead-in with standard of care therapy prior to initiation of boceprevir may help practicing clinicians to make early treatment decisions. A Lead-in period may help them identify patients who are not able to tolerate the pegylated interferon and ribavirin therapy in terms of side effect profile and thus may have to discontinue early. Hence, unnecessary exposure to protease inhibitor can be avoided.

Additionally, in patients who are poorly interferon responsive, further treatment decisions can be discussed with patients at an early time point. This Week 4 evaluation may minimize exposure to protease inhibitors in patients who are poorly interferon responsive and thus not jeopardize their future treatment options in terms of resistance variants.

Treatment Week 8 Response: Refers to virologic response after 8 weeks of treatment. In the two pivotal boceprevir trials, treatment decisions were prospectively based on the assessment of viral response at TW 8, which corresponds to 4 weeks of treatment on PR and 4 additional weeks of therapy consisting of boceprevir 800 mg PO TID plus PR (BOC/PR).

Based on achieving undetectable HCV RNA at TW 8, the terms 'early responders' (HCV RNA undetectable on or before TW 8) and 'late responders' (HCV RNA undetectable after TW 8) are used in the Phase 3 boceprevir trials.

Response Guided Therapy (RGT): Denotes a treatment paradigm in which subjects receive different therapies based on HCV RNA detectability at different timepoints evaluated during therapy.

- In Study P05216, subjects in the RGT arm with undetectable HCV RNA at all assays from TW 8 through TW 24 were eligible for the shorter treatment duration of 28 weeks and those with detectable HCV RNA at any assay from TW 8 up to TW 24, but undetectable HCV RNA at TW 24, were eligible for the longer treatment duration of 48 weeks (additional 20 weeks with placebo + PR).
- In Study P05101, subjects in the RGT arm with undetectable HCV RNA at TW 8 were eligible to receive shorter treatment duration (36 weeks), while those with detectable HCV RNA at TW 8, but undetectable HCV RNA by TW 12, were eligible for longer therapy for 48 weeks (additional 12 weeks with placebo + PR).

RGT treatment regimen is described further under individual study descriptions.

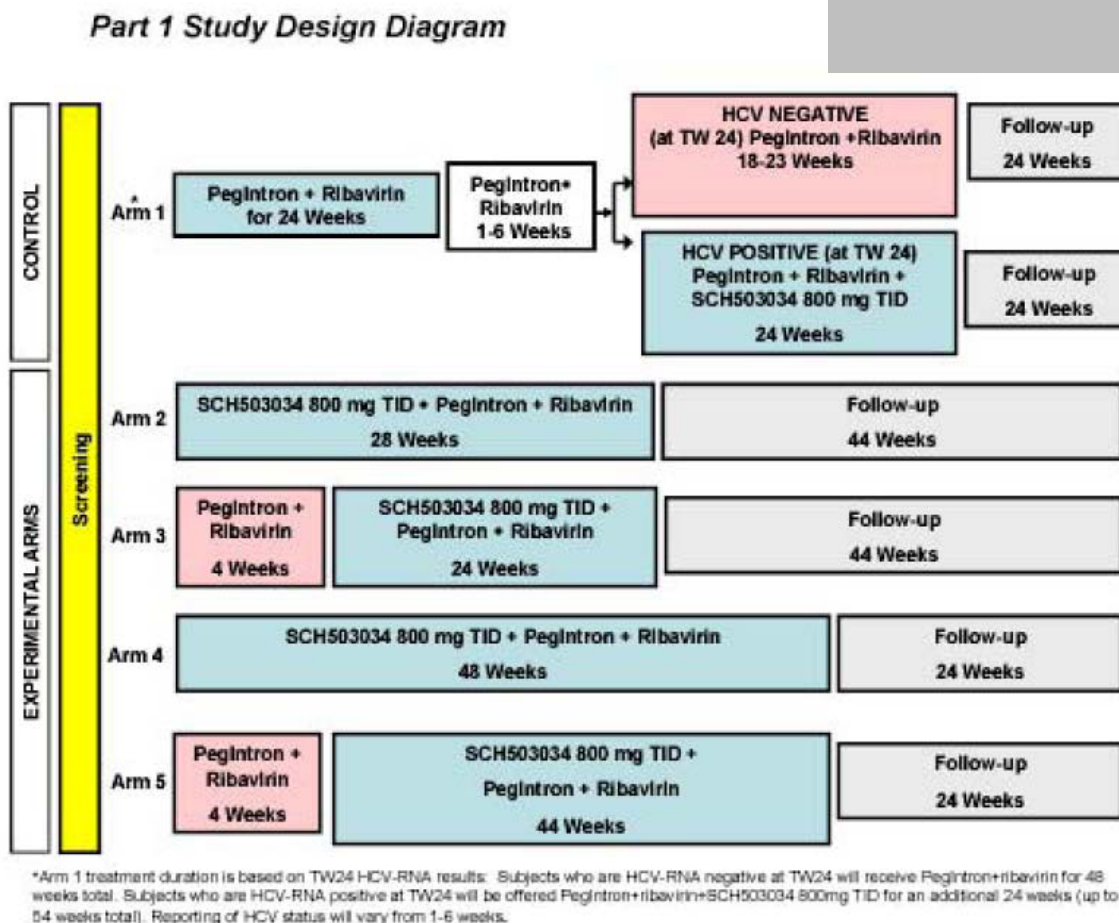
Phase 2 Trials

Protocol P03523: A Safety and Efficacy Study of SCH 503034 in Previously Untreated Subjects with Chronic Hepatitis C Infected with Genotype 1 (SPRINT-1)

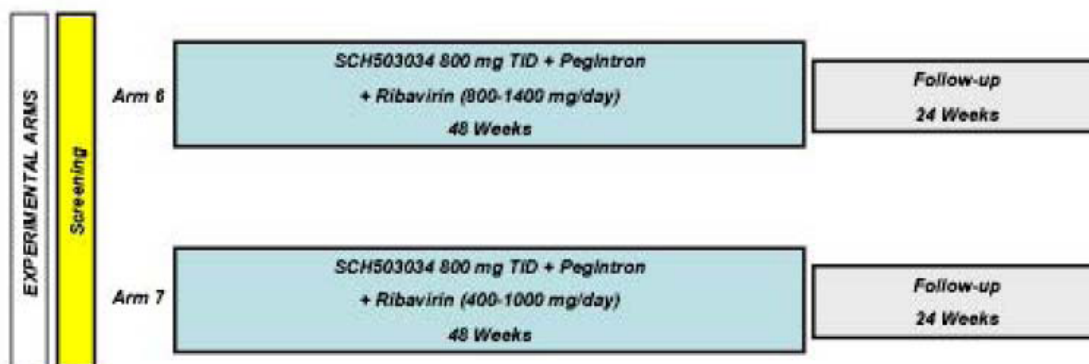
This Phase 2, open-label trial in HCV genotype 1 (GT1)-infected, treatment-naïve adult subjects was conducted in two parts. Part 1 included an active control arm receiving standard of care pegylated interferon alfa-2b plus ribavirin (PR) for 48 weeks and four experimental arms receiving PR plus boceprevir for 28 or 48 weeks, with or without a 4 week PR lead-in. Subjects were randomized in a 1:1:1:1:1 ratio into Arms 1 through 5 (Figure 2). Subjects were stratified at randomization by race (black or non-black) and by disease status (cirrhotic or noncirrhotic). A 28 week treatment arm was compared to 48 weeks of triple therapy to determine if improved virologic response could be attained with shorter treatment duration by adding boceprevir to PR (Arm 2 versus Arm 4). Arm 1 subjects with Week 24 detectable HCV RNA were considered treatment failures and offered boceprevir plus PR for an additional 24 weeks. In Part 2, subjects were randomized in a 4:1 ratio without stratification to treatment with pegylated interferon alfa-2b and boceprevir plus low-dose ribavirin (400 to 1000 mg/day) for 48 weeks or to PR-containing standard ribavirin doses of 800 to 1400 mg/day for 48 weeks. Low-dose ribavirin was explored to determine if anemia could be minimized while maintaining efficacy by addition of boceprevir. The primary efficacy endpoint was SVR, defined as plasma HCV RNA level below the lower limit of detection (LOD) at Follow-up Week 24 (FW 24). Relapse and viral breakthrough were defined differently than in the Phase 3 trials. Relapse was defined as having undetectable HCV RNA (< LOD) at End of Treatment (EOT) and detectable HCV RNA at FW 24. Only subjects with data at both EOT and FW 24 were included in the relapse rate calculations. Viral breakthrough was defined as undetectable HCV RNA with subsequent HCV RNA ≥ 2 log₁₀ elevation during treatment. The following figure shows the study design for P03523.

Figure 2: Protocol P03523 Trial Design

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Part 2 Study Design Diagram



Source: Clinical Study Report for Protocol P03523, p. 44

A total of 595 subjects, including 240 women (40%) and 355 men (60%) were randomized and received at least one study medication dose. Mean age was 49 years (18-60 years), 81% were Caucasian and 16% were African American/Black (14-17% Arms 1-5, 25-27% Arms 6 and 7). Using the (b) (4) data, 66% subjects were HCV genotype 1a (GT1a) and 31% were HCV genotype 1b (GT1b). A total of 7% subjects had cirrhosis. ESA use was 40% overall, with greater use in Arms 2-6 (39-51%). Median ESA use was 133 days. Most subjects (66%) completed the protocol-specified treatment phase, while 34% subjects discontinued investigational treatment early. The primary reasons for discontinuation were adverse events (13%). There were 36 Arm 1 subjects with detectable Week 12 HCV RNA who crossed over to triple therapy. Subject disposition in P03523 is shown in the following table.

Table 7: Protocol P03523 Subject Disposition

	Arm 1 PR	Arm 2 BPR-28	Arm 3 BPR-L/I- 28	Arm 4 BPR-48	Arm 5 BPR-L/I- 48	Arm 6 BPR-48	Arm 7 BPR-low dose RBV-48	Arm 1 Crossover
Treated	104	107	103	103	103	16	59	36
Completed Treatment Phase-n (%)	52 (50)	77 (72)	76 (74)	63 (61)	76 (74)	8 (50)	28 (47)	15 (42)
Discontinued Treatment Phase-n (%)	16 (15)	30 (28)	27 (26)	40 (39)	27 (26)	8 (50)	31 (53)	21 (58)
Adverse Event	8	12	15	20	9	4	7	2
Protocol defined clinical event	0	7	4	12	5	4	16	15
Lost to follow up	2	1	3	1	6	0	3	1
Other*	6	10	5	7	7	0	5	3

*Other = subject did not wish to continue for reasons unrelated to assigned study treatment, investigator deems it is not in the subject's best interest to continue, protocol non-compliance

P=pegylated interferon alfa 2b, R=ribavirin, B=boceprevir, L/I=lead-in, -28=28 week treatment duration, -48=48 week treatment duration

Source: DISPOS dataset for Protocol P03523

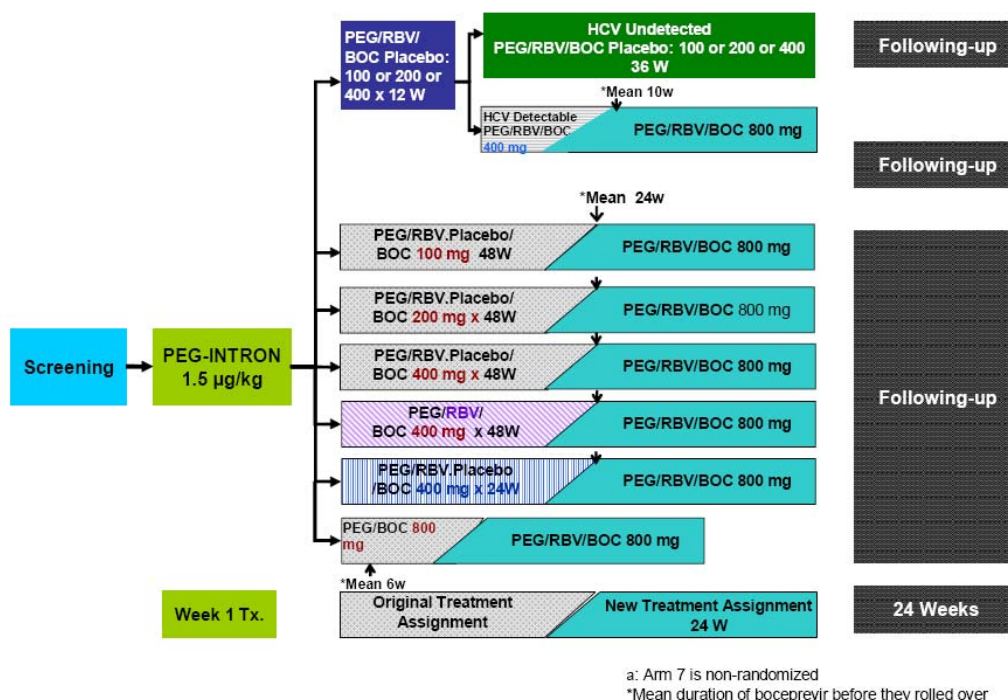
Protocol P03659: PegIntron/Rebetol vs PegIntron/SCH 503034 With and Without Ribavirin in Chronic Hepatitis C HCV-1 Peginterferon Alfa/Ribavirin Nonresponders: a SCH 503034 Dose-Finding Phase 2 Study (RESPOND-1)

This Phase 2 trial in HCV GT1 infected, noncirrhotic adult subjects who had previously failed PR treatment evaluated 100, 200, 400, and 800 mg TID BOC doses in combination with peginterferon alfa-2b and with/without ribavirin (800-1400 mg/day). This trial was initially designed as a six arm double blind (to boceprevir and ribavirin) trial in subjects who never achieved undetectable HCV RNA with a prior adequate PR

treatment course (≥ 12 weeks). Subjects with prior relapse following PR treatment were excluded. The trial design for P03659 is shown in Figure 3. Subjects received an initial peginterferon alfa-2b dose (Week 1), followed by randomization to one of six treatment arms: PR (Arm 1), ribavirin-sparing (Arms 2-4), triple therapy with 400 mg TID boceprevir (Arm 5), ribavirin-sparing and shorter 24 week duration (Arm 6). Subjects in the PR alone arm (Arm 1) with detectable Week 13 HCV RNA rolled over at Week 17 to add 400 mg TID boceprevir for an additional 24 weeks. The primary endpoint was SVR at 24 weeks after treatment cessation (defined as $< \text{LOD}$). An amendment later added a seventh non-randomized, open label 800 mg TID boceprevir plus peginterferon alfa-2b arm for a planned 24 week treatment course. Subsequent Data Review Advisory Board interim data review concluded lower boceprevir doses had poor anti-HCV activity and that viral resistance developed rapidly in ribavirin-sparing regimens; therefore, a second amendment (Amendment 2) made the following changes: (1) Arm 1 subjects with detectable Week 13 HCV RNA added 800 mg TID boceprevir at Week 17, (2) Arms 2-6 subjects with HCV RNV $\leq 10,000$ IU/mL increased boceprevir to 800 mg TID and added ribavirin (weight based dosing). If HCV RNA $> 10,000$ IU/mL, subjects discontinued from the trial, (3) Arm 7 all subjects added ribavirin independent of HCV RNA because mean treatment duration was < 7 weeks, (4) all eligible subjects received additional 24 weeks of triple therapy. In addition, the trial was unblinded and therefore was no longer able to meet the primary efficacy endpoint. The following figure shows the study design for P03659.

Figure 3: Protocol P03659 Trial Design

**Phase II, Boceprevir Dose-Finding Study Design
in PEG-Interferon + Ribavirin Non-Responders**



BOC = boceprevir; HCV = hepatitis C virus; PEG = 1.5 µg/kg/week; RBV = REBETOL.; Tx = treatment; W = week.

Source: Clinical Study Report for Protocol P03659, p. 37

A total of 357 subjects enrolled and received an initial peginterferon alfa-2b dose. Median age was 50 years (range 20-66 years). Most subjects were male (62%) and white (92%). African American or black subjects represented 5% of the population (Arms 1-6: <1%, Arm 7: 23%). Using the (b) (4) data, 57% were GT1a, 28% were GT1b, and the remaining subjects were not typeable or "other". Erythropoietin use was 4% prior to Amendment 2: 6% in Arm 1, <1% in the RBV-sparing Arms 2, 3, 4, 6, and 20% in the triple therapy Arm 5. Mean treatment duration prior to Amendment 2 ranged from 6.6 weeks in Arm 7 to 25.7 weeks in the PR control arm subjects who crossed over to add boceprevir 400 mg TID after failing two-drug therapy. The following table (Table 8) shows the subject disposition prior to rolling over to triple therapy with 800 mg TID boceprevir/PR:

Table 8: Protocol P03659 Subject Disposition, Prior to Amendment 2

	Arm 1 PR	Arm 2 100 B/P	Arm 3 200 B/P	Arm 4 400 B/P-48	Arm 5 400 B/P/R	Arm 6 400 B/P-28	Arm 7 800 B/P	Arm 1 Crossover
Treated	49	48	49	49	49	48	65	34
Completed Treatment Phase-n (%)	3 (6)	0	0	0	0	23 (48)	0	0
Discontinued Treatment Phase-n (%)	6 (40) [#]	44 (92)	40 (82)	42 (86)	28 (57)	18 (38)	4 (6)	6 (18)
Adverse Event	2	3	1	1	1	0	1	1
Treatment failure	0	37	35	38	24	17	0	4
Lost to follow up	0	1	0	1	1	0	0	0
Other*	4	3	4	2	2	1	3	1
Ongoing-n (%)	6 (40) [#]	4 (8)	9 (18)	7 (14)	21 (43)	7 (15)	61 (94)	28 (82)

[#]Arm 1: 15 subjects did not cross over to triple therapy, therefore the % is 6/15 = 40%

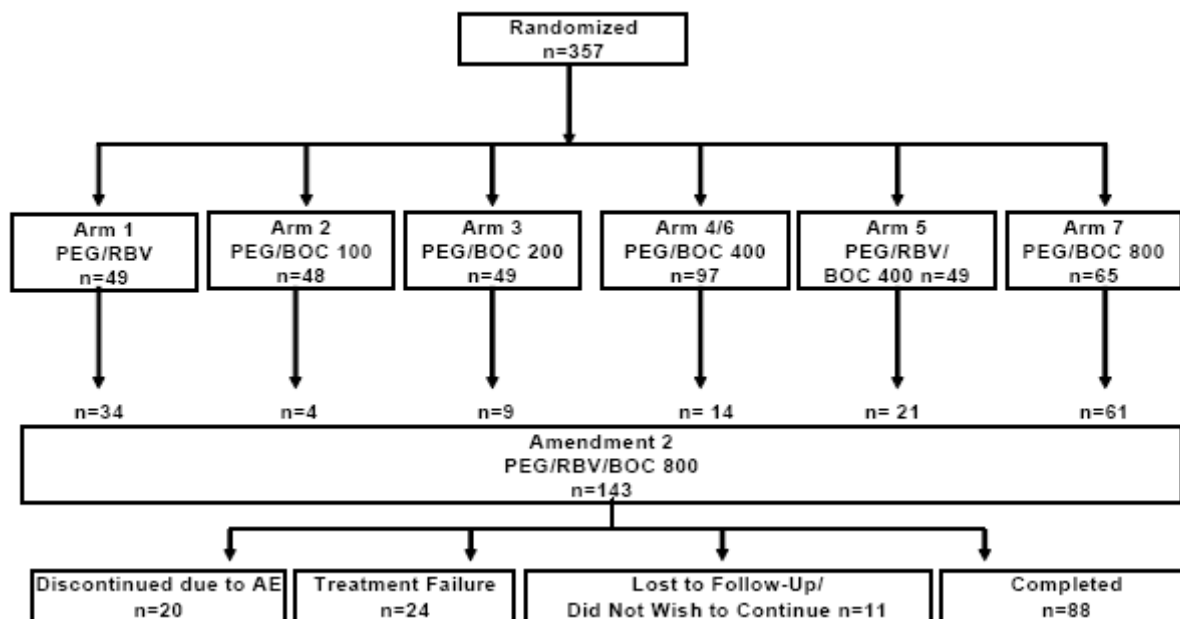
*Other = subject did not wish to continue for reasons unrelated to assigned study treatment, protocol non-compliance

P=pegylated interferon alfa 2b, R=ribavirin, B=boceprevir, -28=28 week treatment duration, -48=48 week treatment duration

Source: DISPOS and DISCON datasets for Protocol P03659

A total of 143 subjects (40%) were eligible to receive triple therapy following Amendment 2 (Figure 4), and the majority completed the amended trial (62%, 88/143).

Figure 4: Protocol P03659 Subject Disposition, Post-Amendment 2



Arms 4 and 6 are combined because most subjects received a mean 24 weeks of treatment.
Source: Clinical Study Report for Protocol P03659, p. 56

P03659 data interpretation is challenging because of lack of standard treatment lengths, lack of comparable treatment regimens, and timing differences for when subjects switched to the amended boceprevir/PR regimens. All eligible post-Amendment 2 subjects (N=143) were to receive the same 24 week triple therapy regimen; however, pre-Amendment 2 treatment durations were inconsistent, leading to a wide total treatment range for subjects both within and between arms. Mean 800 mg TID boceprevir/PR treatment duration was 19.3 weeks (range 1.9 to 26.9 weeks). Five subjects received more than 24 weeks of 800 mg TID boceprevir/PR, and no subject received more than 26 weeks.

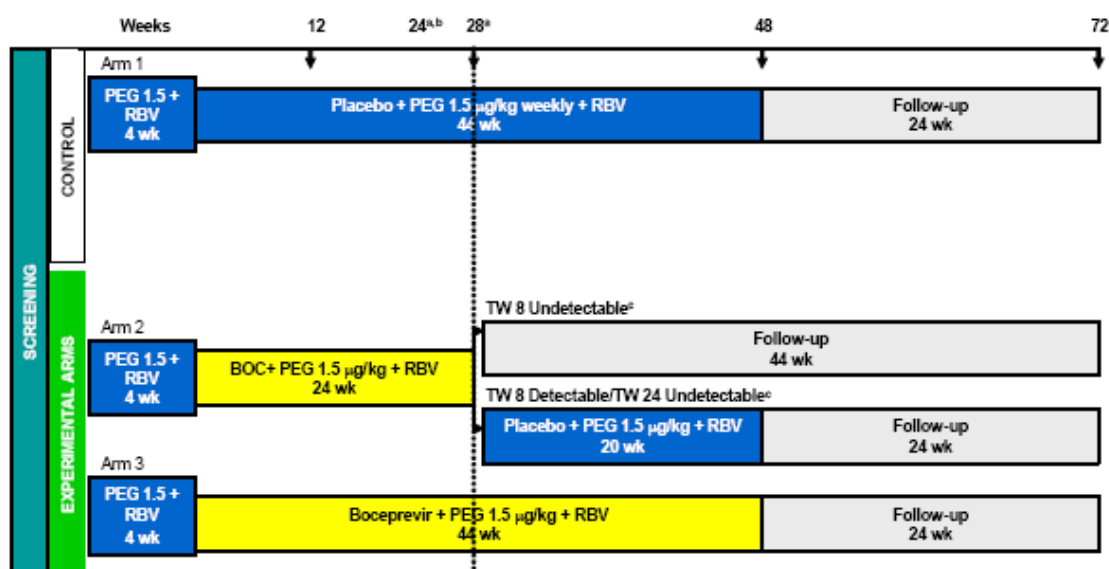
Phase 3 Trials

Protocol P05216: A Phase 3, Safety and Efficacy Study of Boceprevir in Previously Untreated Subjects with Chronic Hepatitis C Genotype 1.

This was a Phase 3, randomized, multicenter study, double-blinded for boceprevir or placebo in combination with open-label PR, in previously untreated adult subjects with CHC (HCV genotype 1). The study compared standard-of-care PR (PEG2b 1.5 µg/kg QW plus RBV 600 to 1400 mg/day [weight-based dosing]) for 48 weeks to two treatment paradigms containing boceprevir 800 mg TID plus PR for a total duration of 28 or 48 weeks, including a 4-week lead-in with PR. A response-guided therapy (RGT)

paradigm was used in Arm 2, whereby therapy was based on response at a specified time point on treatment. Thus, subjects randomized to Arm 2 received a 4-week PR lead-in followed by BOC/PR for 24 weeks; those with undetectable HCV-RNA at TW 8 through TW 24 completed therapy at TW 28 and entered follow-up, while those with detectable HCV-RNA at TW 8 or any subsequent assays and who did not discontinue for virologic futility at TW 24 received an additional 20 weeks of placebo plus PR, for a total treatment duration of 48 weeks. The switch from boceprevir to placebo occurred in a blinded fashion. Arm 3 consisted of a 4-week PR lead-in followed by 44 weeks of BOC/PR. The study design for P05216 is shown in the following Figure 5.

Figure 5: Protocol P05216 Trial Design



PEG + RBV= Peginterferon alfa-2b + ribavirin (weight-based dosing [WBD]); BOC=boceprevir 800 mg TID; TW=Treatment Week; wk=weeks.

Source: Adapted from Applicant's Figure1 in the Clinical Study Report (P05216)

Duration of Treatment:

- **Arm 1 (PR48 Control):** PEG2b 1.5 µg/kg + RBV (weight-based dosing [WBD]) for 4 weeks followed by placebo + PEG2b 1.5 µg/kg + RBV (WBD) for 44 weeks with 24 weeks post-treatment follow-up.
- **Arm 2 (RGT):** PEG2b 1.5 µg/kg + RBV (WBD) for 4 weeks followed by boceprevir + PEG2b 1.5 µg/kg + RBV (WBD) for 24 weeks. At the TW 28 visit, the interactive voice response system (b) (4) was to assign subjects to one of two groups based on their HCV RNA results on and after TW 8.

- At the TW 28 visit, subjects whose HCV RNA was undetectable at TW 8 and at all subsequent assays through TW 24 were to be instructed that they had completed their assigned treatment and were to proceed to the 44-week follow-up.
- At the TW 28 visit, subjects with detectable HCV RNA at TW 8 or at any subsequent assays through TW 24, were to be assigned by (b) (4) to continue therapy with placebo + PR for an additional 20 weeks, to complete a total of 48 weeks on treatment with 24 weeks post-treatment follow-up.

• **Arm 3 (BOC/PR48):** PEG2b 1.5 µg/kg + RBV (WBD) for 4 weeks followed by boceprevir + PEG2b 1.5 µg/kg + RBV (WBD) for 44 weeks with 24 weeks post-treatment follow-up.

Randomization was stratified by:

- HCV viral load: ≤400,000 IU/mL vs. >400,000 IU/mL at screening visit
- HCV-1 genotype: 1a vs. 1b (based on TRUGENE assay)

The futility Rule in trial P05216 was that subjects in any arm with detectable HCV RNA at TW 24 were to be considered treatment failures and were to discontinue treatment and advance to follow-up no later than the TW 28 visit.

Subjects in Arm 1 with detectable HCV RNA at TW 24 were to be eligible to participate in an expanded access trial (P05514) and receive boceprevir + PEG2b 1.5 µg/kg/week +RBV for up to 44 weeks. If they did not participate in the expanded access study, they were to proceed to the follow-up phase of this study.

Study Objectives:

Primary Objective

The primary objective of the Study P05216 was to compare the efficacy of two therapeutic regimens of boceprevir dosed 800 mg orally (PO) three times daily (TID) in combination with PEG2b 1.5 µg/kg SC once weekly (QW) plus weight-based dosing (WBD) with ribavirin (600 mg/day to 1400 mg/day) PO to therapy with PR alone (the active control) in previously untreated adult subjects with CHC (HCV genotype 1).

Secondary Objectives

The key secondary objective of this study was to compare the efficacy of two therapeutic regimens of boceprevir when used in combination with PR (WBD) with the standard of care (PR [WBD] alone) in the modified Intent-to-Treat (mITT) data set, which included all randomized subjects who received at least one dose of experimental study drug (placebo for the control arm and boceprevir for the experimental arms).

Other secondary objectives of the study were as follows:

- To evaluate the safety of boceprevir when used in combination with PR (WBD).
- To define predictors of SVR, such as epidemiologic factors, disease characteristics, and on-treatment response.
- To develop the relationship between steady-state pharmacokinetic parameters, obtained from a population-based pharmacokinetic model and responses in a subset of subjects.

Selection of Study Population

Adult subjects with chronic hepatitis C (CHC) HCV genotype 1, and with no previous treatment for CHC and HCV-RNA $\geq 10,000$ IU/mL prior to treatment and liver biopsy consistent with CHC were eligible for the study. Subjects who were co-infected with human immunodeficiency virus (HIV) or hepatitis B virus (HbsAg positive) were excluded from the study.

Key Protocol Amendment

Amendment #2 (P05216) was finalized on December 02, 2009 and included the following key change: a key secondary objective and endpoint were added to compare the SVR in the experimental arms only in those subjects who received boceprevir/placebo.

Safety Evaluation:

Clinical assessment and review of laboratory data were used to monitor safety and tolerability of study drugs. Safety assessments included, but were not limited to, the following; monitoring of adverse events (AEs) with particular interest in serious adverse events (SAEs); physical examinations, measurement of vital signs, and clinical laboratory tests. The following safety tests were conducted when clinically indicated during the study: chest x-rays; 12-lead ECGs; and ocular examinations.

The Applicant assessed the following as the key safety variables: dose modifications and study drug discontinuations due to AEs, treatment-related SAEs, neutrophil count $< 0.75 \times 10^9/L$, and Hgb < 10 g/dL. In addition, AEs of interest, including rash and rash-related AEs, cardiovascular AEs, and psychiatric AEs were also analyzed by the Applicant.

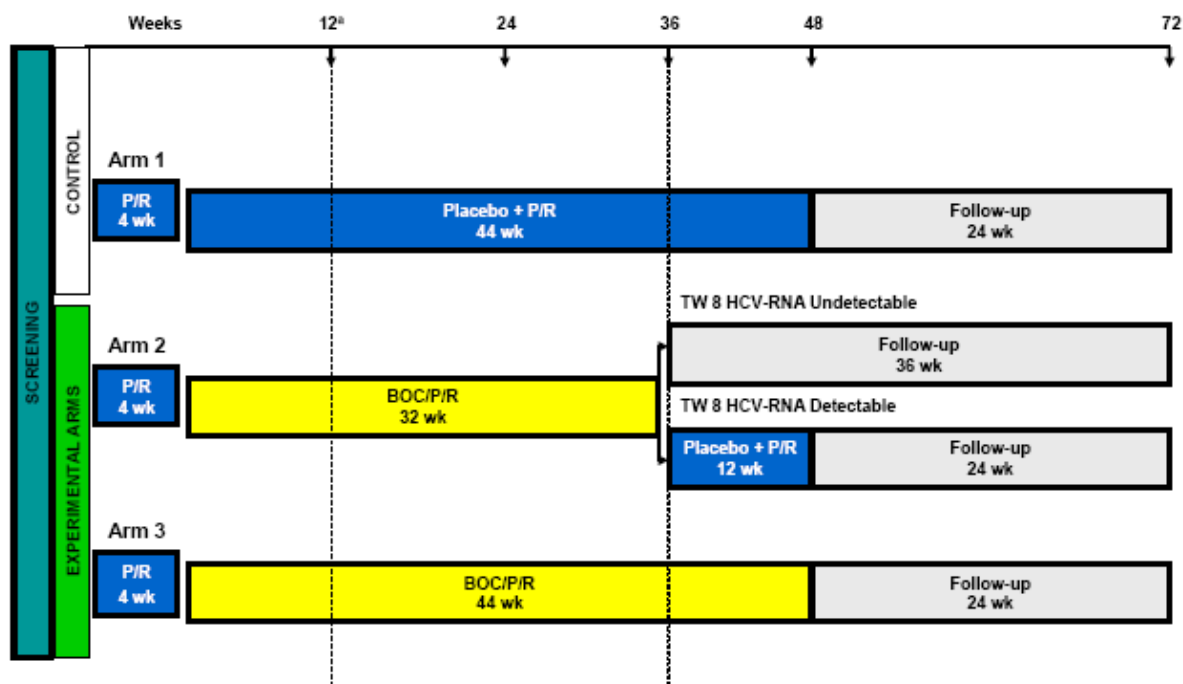
Data Monitoring Committee (DMC)

Safety results were reviewed on an ongoing basis at DMC meetings, which were held approximately semiannually.

Protocol P05101: A Phase 3 Safety and Efficacy Study of Boceprevir (SCH 503034) in Subjects With Chronic Hepatitis C Genotype 1 Who Failed Prior Treatment With Peginterferon/Ribavirin.

This was a randomized, parallel-group, multi-center study, double-blinded for boceprevir or placebo in combination with open-label PR, in adult subjects with chronic HCV genotype 1 who demonstrated interferon responsiveness but failed to achieve SVR on prior treatment with peginterferon/ribavirin. Subjects were randomized to 1 of 3 treatment arms on Day 1. At the time of randomization, subjects were stratified based on response to their previous qualifying regimen (relapser vs. nonresponder) and by HCV subtype (1a vs. 1b). The study design for P05101 is shown in the following Figure 6.

Figure 6: Protocol P05101 Trial Design



Source: Adapted from Applicant's Figure 2 in the Clinical Study Report (P5101)

Duration of Treatment:

PR Control (Arm 1): PR for 4 weeks followed by placebo + PR for 44 weeks, with 24 weeks post-treatment follow-up.

Response-Guided Therapy (RGT) (Arm 2): Subjects were assigned either a 36-week (a, below) or 48-week (b, below) course of therapy based on their HCV RNA status at TW 8.

PR for 4 weeks followed by BOC/PR for 32 weeks, then:

- a. 36-week regimen: subjects with undetectable HCV RNA at TW 8 completed treatment and entered 36 weeks of post-treatment follow-up.
- b. 48-week regimen: subjects with detectable HCV RNA at TW 8 were assigned an additional 12 weeks of placebo + PR (the switch from BOC to placebo occurred in a blinded fashion), followed by 24 weeks of post-treatment follow-up.

BOC/PR48 (Arm 3): PR for 4 weeks followed by BOC/PR for 44 weeks, with 24 weeks post-treatment follow-up.

A 12-week futility rule was followed for all arms, whereby all subjects with detectable HCV-RNA at Treatment Week (TW) 12 discontinued therapy and entered follow-up. Subjects in the RGT arm (Arm 2) and the BOC/PR48 arm (Arm 3) proceeded directly to the follow-up phase of this study. Sites and subjects remained blinded as to whether subjects had been in Arm 2 or Arm 3. Treatment failures in the PR control arm (Arm 1) were offered the opportunity to receive treatment with boceprevir plus PR (BOC/PR) via an expanded access study (P05514) or to proceed to the follow-up phase of this study.

Study Objectives:

Primary Objective

The primary objective of this study was to compare the efficacy of two therapeutic regimens of boceprevir 800 mg TID PO in combination with the current standard of care (PEG2b 1.5 µg/kg QW SC plus WBD with ribavirin 600 mg/day to 1400 mg/day [PR]) to therapy with 48 weeks of PR alone in adult subjects with CHC infected with HCV genotype 1 with demonstrated interferon responsiveness who failed prior treatment with peginterferon/ribavirin.

Secondary Objectives

The key secondary objective of this study was to compare the efficacy of two therapeutic regimens of boceprevir when used in combination with PR (WBD) with the standard of care (PR [WBD] alone) in randomized subjects who received at least one dose of experimental study drug (placebo for the control arm and boceprevir for the experimental arms; mITT).

Selection of Study Population

Adult subjects (men and women) ≥ 18 years of age with CHC genotype1 infection who failed to achieve an SVR on prior treatment with peginterferon alpha and ribavirin but demonstrated interferon responsiveness (a decrease in HCV-RNA viral load $\geq 2 \log_{10}$ by Week 12 or undetectable HCV RNA at end of treatment) were eligible for the study. Subjects who were co-infected with human immunodeficiency virus (HIV) or hepatitis B virus (HbsAg positive) were excluded from the study.

403 subjects were classified as either relapsers (n=259) or nonresponders (n=144) to previous therapy based on documentation of a minimum 12 weeks of treatment with peginterferon alpha/ribavirin (9 subjects withdrew prior to TW 4). Subjects were stratified by historical response as being either a nonresponder (never HCV RNA undetectable on previous therapy) or relapser (HCV RNA undetectable during therapy without SVR). Previous null-responders ($< 2 \log_{10}$ decline in viral load at TW 12) were excluded.

Reviewer's comments:

Null responders were excluded from the Phase 3 trial (Study P05101) in previous treatment-failure subjects. This was done by the Applicant based on the available data from the Phase 2 trial in the treatment-experienced population which provided insufficient support to initiate a larger trial for the null responder subgroup. The Phase 2 trial (P03659) enrolled previous treatment-failure subjects who never achieved undetectable HCV RNA while receiving pegylated interferon/ribavirin therapy, including null responders. However, because none of the subjects initially received the currently proposed dose of boceprevir (800 mg 3 times daily) and because of protocol amendments which required unblinding to treatment assignment, efficacy in that study cannot be fully assessed.

Safety evaluations were similar to the Study P05216.

6 Review of Efficacy

Efficacy Summary

Overall, the addition of boceprevir to pegylated interferon alfa-2b and ribavirin therapy resulted in a significant improvement in efficacy compared to the current standard of care therapy in both previously untreated (treatment-naïve) and previous treatment failure (treatment-experienced) subjects, including prior relapsers (defined as undetectable HCV RNA at end of treatment) and “non-responders” (defined by the applicant as decrease in HCV-RNA viral load $\geq 2 \log_{10}$ by Week 12 during previous therapy). The Applicant’s definition of “non-responders” would generally be considered the same as that used to define partial responders. Higher sustained virologic response was mainly driven by higher end of treatment response. Additionally, relapse rates were

also substantially lower in boceprevir-treated subjects. Efficacy was not demonstrated in null responders to previous therapy (defined as $< 2 \log_{10}$ decline in HCV RNA at week 12), as these subjects were not included in the Phase 3 boceprevir trials.

In treatment-naïve subjects (P05216), SVR rates in response guided therapy arm were 63% which were similar to SVR rates of 66% in triple therapy (BOC/PR48) arm. SVR was superior ($p < 0.0001$) in the boceprevir treatment arms compared to the PR control arm (SVR rate of 38%), demonstrating a robustness in the treatment effect.

- Efficacy of boceprevir was demonstrated in subjects regardless of race (non-black and black). However, the response rates for all arms in blacks were lower than that in non-black subjects. In Cohort 1(non-black): SVR in RGT arm was 67%; SVR in BOC/PR48 was 68% compared to 40% SVR in PR arm. In Cohort 2 (black): SVR in RGT arm was 42%, SVR in BOC/PR 48 was 53% compared to 23% SVR in PR48 arm. In blacks, considered a difficult to treat CHC population, response rates were numerically higher in 48 week triple therapy arm compared to RGT arm.
- For early responders (undetectable HCV RNA from TW8 through TW24), SVR rates in RGT arm (97%) were almost identical to SVR rates in BOC/PR48 arm (96%). For late responders (detectable HCV RNA at any time point from TW8-TW24 but undetectable at TW24, SVR rate in the RGT arm (66%) was lower than that in the BOC/PR48 arm (75%), but the difference was not statistically significant.
- SVR rates in subjects who were undetectable at TW4 were very high in PR control arm and similar to boceprevir treated subjects. *Whether the addition of boceprevir in these subjects offers any benefit by reducing the overall treatment duration should be further explored. However, these results should be interpreted with caution as the numbers in these subgroup analyses are small.*

In previous treatment-failure subjects (P05101), SVR rates in response guided therapy arm were 59% compared to SVR rates of 66% in triple therapy (BOC/PR48) arm. These results demonstrated superiority of boceprevir treatment arms ($p < 0.0001$) in comparison to the PR control arm (SVR rate of 21%), demonstrating a robustness in the treatment effect in this difficult to treat population.

- SVR rates were similar in both RGT and BOC/PR48 arms in early responders as well as late responders. However, duration of therapy was different in this trial for RGT arm (36 weeks compared to 28 weeks in treatment-naïve trial).
- Efficacy was shown in both previous relapser subjects (70-75%) and the prior partial responder (40-52%) subjects.

The data for primary endpoint analyses were highly statistically significant and the treatment effect was robust across all significant subgroups.

Summary data from the recently completed Phase 3 trial P05685 support use of boceprevir with pegylated interferon alfa 2a. The addition of boceprevir to PEG2a/RBV increased the SVR rate compared with PEG2a/RBV therapy alone (64% boceprevir arm versus 21% control arm).

6.1 Indication

The indication proposed by the Applicant is the following:

TRADENAME is a hepatitis C virus (HCV) protease inhibitor indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alpha and ribavirin, in adult patients (≥18 years of age) with compensated liver disease who are previously untreated or who have failed previous therapy.

Reviewer's comment:

Null responders to previous course of pegylated interferon and ribavirin therapy (defined as less than 2 log₁₀ decline in HCV RNA at week 12) were not included in the Phase 3 boceprevir trials. Applicant has provided data and rationale to support the use of boceprevir in this patient population. This issue will be discussed during the upcoming Advisory Committee meeting.

6.1.1 Methods

The efficacy data for the two Phase 3 pivotal trials, Protocol P05216 (SPRINT-2) and Protocol P05101 (RESPOND-2) were reviewed in support of the proposed indication.

As described in FDA Draft Guidance for Industry “Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Agents for Treatment” issued on September 13, 2010, the following definitions have been described to be used to define the treatment experience of chronic hepatitis C patients, which are based on previous responses to Peg-Interferon/RBV.

Naïve: received no prior therapy for HCV (including interferon or pegylated interferon monotherapy)

Null Responder: less than 2 log₁₀ reduction in HCV RNA at week 12 of a Peg Interferon/RBV

Partial Responder: greater than or equal to 2 log₁₀ reduction in HCV RNA at week 12, but not achieving HCV RNA undetectable at end of treatment with a Peg-Interferon/RBV

Responder Relapser: HCV RNA undetectable at end of treatment with a pegylated interferon-based regimen, but HCV RNA detectable within 24 weeks of treatment follow-up.

As also mentioned in the draft guidance, other definitions for null response have been proposed, such as less than 1 log₁₀ IU/mL decline in HCV RNA at week 4 of treatment. However, failure to achieve a greater than 2 log₁₀ IU/mL HCV RNA decline at week 12 has typically been used as a treatment futility criterion and use of a null response definition of viral reduction less than 1 log₁₀ IU/mL at week 4 causes a gap in classification for individuals with a viral load reduction greater than 1 log₁₀ at week 4 but less than 2 log₁₀ reduction at week 12.

Statistical Methods

This section describes the statistical methods used by the applicant and the FDA for the efficacy analysis. All statistical comparisons for the primary and key secondary efficacy analyses were carried out using the two-sided Cochran-Mantel Haenszel (CMH) chi-square test (adjusted for the baseline stratification factors).

Some of the key concepts used in the analysis are described below:

Subgroup analysis and comparison between RGT and BOC/PR48 (arms receiving PR lead-in for 4 weeks, then BOC/PR for 44 weeks): Refers to subgroups of subjects with similar virologic response (e.g., HCV RNA undetectable or detectable at TW 8) in the RGT and BOC/PR48 (48-week) arms. The goal of this subgroup analysis is to compare efficacy of RGT vs. BOC/PR48.

Comparison of the early responders: This is a comparison of SVR for those subjects with early virologic response who received shorter treatment duration in the RGT arm with matched subjects in the BOC/PR48 arm who received the 48-week, fixed-duration treatment. The goal of this analysis is to assess whether shorter treatment duration (28 or 36 weeks in previously untreated and previous treatment failure subjects, respectively) is as efficacious as a 48-week fixed duration.

Comparison of the late responders: This is a comparison of SVR for those subjects with later virologic response who received longer treatment duration in the RGT arm. The goal of this analysis is to assess whether triple therapy is needed for 44 weeks or whether PR may be used for the last 20 or 12 weeks (in treatment-naïve and previous treatment-failure subjects, respectively) for the late responders who require a total of 48 weeks of treatment.

Comparison of the early and late responders was done by the applicant using the following two types of analyses:

Per protocol: includes only subjects with assigned treatment duration by the interactive voice response system ((b) (4) (RGT-28 or RGT-36 for treatment-naïve and previous treatment-failure subjects, respectively, or RGT-48). In the per protocol analysis; subjects with an unassigned treatment duration and those who discontinued treatment for any reason prior to TW 28/36 are not included.

Based on TW 8 response: includes all subjects with TW 8 HCV RNA results (undetectable or detectable). Subjects with missing TW 8 HCV RNA results are not included.

FDA analyses for the comparison of early and late responders differed from the applicant's analyses and included both the HCV RNA results at TW8 and the total duration of the treatment received. FDA analyses also exclude the subjects who were assigned to the incorrect treatment duration based on the HCV RNA results at different time points. These analyses were done using the following methods:

Early/late responders in P05216 study:

- Early responder: a subject who had undetectable HCV RNA at TW8 through TW24, and completed 28 weeks of therapy in RGT arm; in BOC/PR48 arm, the subject who had undetectable HCV RNA at TW8 through TW24 and received more than 31 weeks of therapy;
- Late responder: a subject who had detectable HCV RNA at TW8, but undetectable HCV RNA at TW24 and completed 48 weeks of therapy in RGT arm; in BOC/PR48 arm, the subject who had had detectable HCV RNA at TW8, but undetectable HCV RNA at TW24 and received more than 31 weeks of therapy;

Early/late responders in P05101 study:

- Early responder: a subject who had undetectable HCV RNA at TW8 and TW12, and completed 36 weeks of therapy in RGT arm; in BOC/PR48 arm, the subject who had undetectable HCV RNA at TW8 through TW12 and received more than 39 weeks of therapy;
- Late responder: a subject who had detectable HCV RNA at TW8, but undetectable HCV RNA at TW12 and completed 48 weeks of therapy in RGT arm; in BOC/PR48 arm, the subject who had had detectable HCV RNA at TW8, but undetectable HCV RNA at TW12 and received more than 39 weeks of therapy;

In order to control the type 1 error for the two comparisons (BOC/PR48 vs. Control, and RGT vs. Control) for the primary efficacy analysis, a step down approach was carried out for hypothesis testing. First, the 48-week experimental arm (BOC/PR48) was to be compared against the PR48 control arm using the two-sided CMH chi-square test, controlling for the baseline stratification factors. If this p-value was less than 0.05, efficacy of 48 weeks of treatment with BOC/PR over the PR48 control arm was to have

been established and the next comparison was to be carried out, i.e., the RGT arm (Arm 2) was to be compared against the PR48 control arm using the same CMH test. If this p-value was less than 0.05, then the efficacy of the RGT arm was also to have been established.

To account for multiplicity between the primary and key-secondary analyses, the step down to the key secondary analyses was to occur only if the significance of the primary comparisons was established. A step-down approach was also used to control the type 1 error for the two key secondary comparisons.

To assess the effect of the two boceprevir treatment regimens on the primary efficacy outcome, the difference in the SVR rate between the RGT and BOC/PR48 arms was summarized using a 95% confidence interval of the difference of proportions (obtained using Normal approximation for binary data).

The FDA statistical reviewer calculated an exact 95% confidence interval of the difference in the SVR rate between the RGT and BOC/PR48 arms using two one-sided tests. Please refer to FDA Statistical Review by Dr. Wen Zeng for detailed assessment.

6.1.2 Demographics

P05216

A total of 1099 subjects were randomized; 1097 subjects received at least one dose of any study medication (PR or BOC), and 1048 subjects received at least one dose of boceprevir or placebo. The study population was mainly males (60%), majority were white (82%), mean age of 49 years and the mean body mass index (BMI) of 28. Majority of subjects had high viral load HCV RNA $\geq 400,000$ IU/mL. About 5% of subjects had cirrhosis at baseline. (Table 9).

**Table 9: Demographic and Baseline Characteristics Study P05216 (FAS)
Combined Cohort 1 and 2**

Subgroup	PR48	RGT	BOC/PR48
N	363	368	366
Race Group			
BLACK	52 (14.3%)	52 (14.1%)	55 (15.0%)
NON-BLACK	311 (85.7%)	316 (85.9%)	311 (85.0%)
Gender			
F	157 (43.3%)	139 (37.8%)	145 (39.6%)
M	206 (56.7%)	229 (62.2%)	221 (60.4%)
Age (Year)			
Mean (SD)	48.58 (10.0)	49.80 (9.2)	48.85 (8.7)
Age Group			
<40 yr	57 (15.7%)	48 (13.0%)	53 (14.5%)
≥45-<65	291 (80.2%)	308 (83.7%)	306 (83.6%)
≥65 yr	15 (4.1%)	12 (3.3%)	7 (1.9%)
Weight Group			
<75 Kg	146 (40.2%)	131 (35.6%)	131 (35.8%)
≥75 Kg	217 (59.8%)	237 (64.4%)	235 (64.2%)
BMI			
MEAN (SD)	27.19 (4.5)	27.84 (4.9)	27.85 (5.5)
Baseline Platelets Count			
<150,000/uL	27 (7.4%)	33 (9.0%)	38 (10.4%)
≥150,000/uL	336 (92.6%)	335 (91.0%)	328 (89.6%)
Baseline Log ₁₀ of HCV Viral Geometric Mean (IU/mL)			
Mean (SD)	6.54 (0.6)	6.52 (0.6)	6.53 (0.6)
Baseline HCV Viral Category (IU/mL)			
≤200,000	13 (3.6%)	18 (4.9%)	14 (3.8%)
>200,000-400,000	13 (3.6%)	14 (3.8%)	11 (3.0%)
>400,000-800,000	29 (8.0%)	22 (6.0%)	28 (7.7%)
>800,000	308 (84.8%)	314 (85.3%)	313 (85.5%)
Metavir Fibrosis Score			
0	17 (4.7%)	20 (5.4%)	10 (2.7%)
1	246 (67.8%)	238 (64.7%)	246 (67.2%)
2	65 (17.9%)	61 (16.6%)	57 (15.6%)
3	11 (3.0%)	18 (4.9%)	18 (4.9%)
4	13 (3.6%)	16 (4.3%)	24 (6.6%)
Missing	11 (3.0%)	15 (4.1%)	11 (3.0%)
Liver Cirrhosis at Baseline			
N	339 (96.3%)	337 (95.5%)	331 (93.2%)

Y	13 (3.7%)	16 (4.5%)	24 (6.8%)
HCV-1 Subtype (b) (4)			
1	60 (16.5%)	55 (14.9%)	46 (12.6%)
1a	177 (48.8%)	179 (48.6%)	187 (51.1%)
1b	126 (34.7%)	134 (36.4%)	133 (36.3%)
HCV-1 Subtype (b) (4)			
1a	228 (65.0%)	234 (65.2%)	237 (66.8%)
1b	121 (34.5%)	124 (34.5%)	117 (33.0%)
Region			
EU	99 (27.3%)	79 (21.5%)	86 (23.5%)
LA	10 (2.8%)	12 (3.3%)	10 (2.7%)
NA	254 (70.0%)	277 (75.3%)	270 (73.8%)
Location (US vs. International)			
US	225 (62.0%)	245 (66.6%)	239 (65.3%)
International	138 (38.0%)	123 (33.4%)	127 (34.7%)

SD stands for standard deviation.
Source: FDA Statistical Reviewer

Baseline and demographic characteristics were well-balanced between the treatment arms and is generally representative of the chronic hepatitis C genotype 1 treatment naïve subjects.

P05101

A total of 404 subjects were randomized; 403 subjects received at least one dose of any study medication (PR or BOC), and 394 subjects received at least one dose of boceprevir or placebo. The study population was mainly males (67%), white (85%), mean age of 53 years and a mean BMI of 28. Approximately 12% of the subjects were black. Majority of subjects (88%) had high viral load at baseline (>800,000 IU/mL). There were about 13% of subjects with liver cirrhosis at baseline. Baseline demographics and disease characteristics were well balanced across treatment arms (Table 10).

Table 10: Demographic and Baseline Characteristics Study P05101 (FAS)

Subgroup	PR48	RGT	BOC/PR48
N	80	162	161
Race Group			
BLACK	12 (15.0%)	18 (11.1%)	19 (11.8%)
NON-BLACK	68 (85.0%)	144 (88.9%)	142 (88.2%)
Gender			

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F	22 (27.5%)	64 (39.5%)	49 (30.4%)
M	58 (72.5%)	98 (60.5%)	112 (69.6%)
Age (Year)			
Mean (SD)	52.90 (8.0)	52.89 (7.4)	52.30 (7.7)
Age Group			
<40 yr	4 (5.0%)	5 (3.1%)	7 (4.3%)
>=45-<65	70 (87.5%)	146 (90.1%)	146 (90.7%)
>=65 yr	6 (7.5%)	11 (6.8%)	8 (5.0%)
Weight Group			
<75 Kg	17 (21.3%)	42 (25.9%)	44 (27.3%)
>=75 Kg	63 (78.8%)	120 (74.1%)	117 (72.7%)
BMI			
Mean (SD)	28.16 (4.3)	28.76 (4.6)	28.23 (4.6)
Baseline Platelets Count			
<150,000/uL	10 (12.5%)	21 (13.0%)	19 (11.8%)
>=150,000/uL	70 (87.5%)	141 (87.0%)	142 (88.2%)
Baseline Log ₁₀ of HCV Viral Geometric Mean (IU/mL)			
Mean (SD)	6.52 (0.659)	6.63 (0.530)	6.69 (0.574)
Baseline HCV Viral Category (IU/mL)			
<=200,000	2 (2.5%)	2 (1.2%)	3 (1.9%)
>200,000-400,000	4 (5.0%)	5 (3.1%)	4 (2.5%)
>400,000-800,000	9 (11.3%)	8 (4.9%)	13 (8.1%)
>800,000	65 (81.3%)	147 (90.7%)	141 (87.6%)
Metavir Fibrosis Score			
0	5 (6%)	8 (5%)	5 (3%)
1	43 (54%)	79 (49%)	78 (48%)
2	13 (16%)	30 (19%)	36 (22%)
3	5 (6%)	15 (9%)	9 (6%)
4	10 (13%)	17 (10%)	22 (14%)
Missing	4 (5%)	13 (8%)	11 (7%)
Liver Cirrhosis at Baseline			
N	66 (86.8%)	132 (88.6%)	128 (85.3%)
Y	10 (13.2%)	17 (11.4%)	22 (14.7%)
Previous Peginterferon Type Used			
PEG2A	42 (52.5%)	79 (48.8%)	68 (42.2%)
PEG2B	38 (47.5%)	83 (51.2%)	93 (57.8%)
Previous Response (b) (4)			
Never Negative	30 (37.5%)	59 (36.4%)	59 (36.6%)
Some Negative	50 (62.5%)	103 (63.6%)	102 (63.4%)
Previous Response (Inform)			
NON-RESPONDER	41 (51.3%)	75 (46.6%)	72 (44.7%)
RELAPSER	39 (48.8%)	86 (53.4%)	89 (55.3%)

HCV-1 Subtype (b) (4)			
1	6 (7.5%)	13 (8.0%)	17 (10.6%)
1a	38 (47.5%)	74 (45.7%)	77 (47.8%)
1b	36 (45.0%)	75 (46.3%)	67 (41.6%)
HCV-1 Subtype (b) (4)			
1a	46 (57.5%)	96 (59.3%)	97 (61.0%)
1b	34 (42.5%)	66 (40.7%)	61 (38.4%)
Region			
EU	29 (36.3%)	46 (28.4%)	42 (26.1%)
LA	0	1 (0.6%)	0
NA	51 (63.8%)	115 (71.0%)	119 (73.9%)
Location (US vs. International)			
US	43 (53.8%)	92 (56.8%)	97 (60.2%)
International	37 (46.3%)	70 (43.2%)	64 (39.8%)

SD stands for standard deviation.
Source: FDA Statistical Reviewer

Certain differences were noted between the treatment-naïve and previous PR treatment-failure study populations in terms of age, weight, degree of fibrosis, baseline platelet count, and length of exposure to HCV. The mean age of the treatment-naïve subjects was slightly lower than that in previous PR treatment failures. The mean weight of previous treatment failure subjects was approximately 3 to 4 kg higher than that in treatment-naïve subjects.

Reviewer's comment:

Demographic and baseline characteristics that have been shown to predict a lower SVR rate with standard of care treatment include a high viral load at baseline, advanced disease on histology (bridging fibrosis and cirrhosis), obesity, older age, and African American race. A genetic polymorphism near the IL28B gene is a strong predictor of SVR in patients receiving therapy with Peginterferon and ribavirin. Numerous studies have demonstrated that patients who carry the variant alleles (C/T and T/T genotypes) have lower SVR rates than individuals with the C/C genotype.

6.1.3 Subject Disposition

Study P05216

In Study P05216, 49 (4%) subjects discontinued treatment during PR lead-in phase. Out of these, 34 subjects discontinued due to AEs. Discontinuations due to AEs in the treatment phase after adding BOC/placebo were 12% in the PR arm, 10% in the RGT arm and 14% in BOC/PR48 arm. Discontinuations due to treatment failure in the treatment phase after adding BOC/placebo were 34% in the PR arm, 16% in the RGT

arm and 13% in BOC/PR48 arm. Subject disposition at the end of treatment phase is shown below in Table 11.

Table 11: Subject Disposition at the End of Treatment Phase in Study P05216 (FAS)

	Arm 1 (PR48) N=363 n (%)	Arm 2 (RGT) N=368 n (%)	Arm 3 (BOC/PR48) N=366 n (%)
Completed Treatment	159 (44)	229 (62)	215 (59)
Not Completed Treatment	204 (56)	139 (38)	151 (41)
Adverse Event	57 (16)	45 (12)	60 (16)
Treatment Failure	117 (32)	55 (15)	47 (13)
Lost to Follow-up	10 (3)	7 (2)	7 (2)
Subject withdrew consent	5 (1)	3 (<1)	3 (<1)
Did not wish to continue (unrelated)	9 (3)	14 (4)	17 (5)
Did not wish to continue related to treatment	2 (<1)	10 (3)	12 (3)
Non-compliance with Protocol	4 (1)	5 (1)	5 (1)

BOC=boceprevir 800 mg PO TID; PR=peginterferon alfa-2b+ribavirin; RGT=response-guided therapy;
Arm 1 (PR48) = PEG2b + RBV (PR) for 48 weeks

Arm 2 (RGT) = PR lead-in for 4 weeks, then BOC/PR for 24 weeks (if undetectable HCV-RNA at TW 8) or BOC/PR for 24 weeks followed by placebo/PR for 20 weeks (if detectable HCV-RNA at TW 8).

Arm 3 (BOC/PR48) = PR lead-in for 4 weeks, then BOC/PR for 44 weeks.

Source: FDA Statistical Reviewer

Study P05101

In Study P05101, 9 (2%) subjects discontinued treatment during PR lead-in phase. Out of these, 5 subjects discontinued due to AEs. Discontinuations due to AEs in the treatment phase after adding BOC/placebo were 1% in the PR arm, 6% in the RGT arm and 12% in BOC/PR48 arm. Discontinuations due to treatment failure in the treatment phase after adding BOC/placebo were 63% in the PR arm, 23% in the RGT arm and 18% in BOC/PR48 arm. Subject disposition at the end of treatment phase is shown below in Table 12.

Table 12: Subject Disposition at the End of Treatment Phase in Study P05101 (FAS)

	Arm 1 (PR48) N=80 n (%)	Arm 2 (RGT) N=162 n (%)	Arm 3 (BOC/PR48) N=161 n (%)
Completed Treatment	23 (29)	104 (64)	105 (65)
Not Completed Treatment	57 (71)	58 (36)	56 (35)
Adverse Event	2 (3)	13 (8)	20 (12)
Treatment Failure	49 (61)	36 (22)	29 (18)
Lost to Follow-up	-	1 (<1)	-
Subject withdrew consent	-	4 (3)	1 (<1)
Did not wish to continue (unrelated)	4 (5)	1(<1)	4 (3)
Did not wish to continue related to treatment	2 (3)	1 (<1)	1 (<1)
Non-compliance with Protocol	-	1 (<1)	1 (<1)

BOC=boceprevir 800 mg PO TID; PR=peginterferon alfa-2b+ribavirin; RGT=response-guided therapy;
Arm 1 (PR48) = PEG2b + RBV (PR) for 48 weeks

Arm 2 (RGT) = PR lead-in for 4 weeks, then BOC/PR for 32 weeks (if undetectable HCV-RNA at TW 8) or BOC/PR for 32 weeks followed by placebo/PR for 12 weeks (if detectable HCV-RNA at TW 8).

Arm 3 (BOC/PR48) = PR lead-in for 4 weeks, then BOC/PR for 44 weeks.

Source: FDA Statistical Reviewer

6.1.4 Analysis of Primary Endpoint(s)

The goal of HCV therapy is to prevent complications and death from HCV infection. Due to the infeasibility of conducting a long term, randomized clinical trial to assess the clinical outcomes of chronic hepatitis C disease progression, treatment response is defined by a virological parameter. The most important virological parameter for treatment of chronic hepatitis C is the sustained virological response (SVR), defined as the absence of HCV RNA from serum by a sensitive PCR assay 24 weeks following discontinuation of therapy. The attainment of SVR has been proven to be a reliable predictor of long-term clearance of hepatitis C infection and is generally regarded as a “virological cure”. SVR has also been linked with improvement in quality of life, histologic improvement demonstrated by reduction of the rate of fibrosis progression, decreased risk of hepatocellular carcinoma, and overall reduced liver-related mortality. Short-term outcomes can be measured biochemically (normalization of serum ALT levels), virologically (absence of HCV RNA from serum by a sensitive PCR-based assay), and histologically (point improvement in necroinflammatory score with no worsening in fibrosis score).

The primary efficacy endpoint was the achievement of SVR; defined as undetectable HCV RNA (< 10 IU/mL) measured 24 weeks after the end of therapy. However, the Division asked the Applicant to use an HCV RNA cutoff of < 25 IU/mL for defining SVR because of issues with false positive HCV RNA using the LOD (< 10 IU/mL) post-treatment. As shown in Table 13 below this change did not alter the overall efficacy results; hence, for all further FDA analyses for this review, HCV RNA cutoff of < 25 IU/mL was used for primary endpoint analyses. Relapse was defined as achieving end of treatment response defined as HCV RNA undetectable (<10 IU/mL), but failing to subsequently achieve SVR.

The primary efficacy analysis was based on the full analysis set (FAS), defined as all randomized subjects who received at least one dose of any study medication (PEG2b, RBV, or boceprevir/placebo). If a subject was missing data at FW 24 after having had undetectable HCV RNA at FW 12, the subject was to be considered to have achieved an SVR. This was considered acceptable by the Division based on the available data which supports this imputation.

Primary Efficacy Results in Study P05216

In trial P05216, subjects in both boceprevir containing arms had a higher rate of SVR than those who received PR48 alone. SVR rates in response guided therapy arm were 63% which were similar to SVR rates of 66% in triple therapy (BOC/PR48) arm. These were superior ($p<0.0001$) to SVR rate of 38% in the PR control arm demonstrating a robustness in the treatment effect.

Table 13: Primary Efficacy Results in Study P05216 (Combined Cohort 1 and 2-FAS)

Efficacy Parameter	PR 48 N=363	RGT N=368	BOC/PR 48 N=366
<u>Sustained Virologic Response</u>			
SVR at EOF (HCV RNA <10 IU/mL)			
SVR Rate (%)	137/363 (38)	233/368 (63)	242/366 (66)
Difference in SVR	-	25	28
95% CI for Diff.	-	[18.4, 32.3]	[21.4, 35.1]
P_value	-	<0.0001	<0.0001
SVR at EOF (HCV RNA <25 IU/mL)			
SVR Rate (%)	138/363 (38)	233/368 (63)	242/366 (66)
Difference in SVR	-	25	28.0
95% CI for Diff.	-	[18.2, 32.0]	[21.1, 34.8]
P_value	-	<0.0001	<0.0001
<u>Relapse Rates</u>			
HCV RNA <10 IU/mL at EOT and >25 IU/mL at EOF			

Relapse Rate (Cohort 1 and 2)	39/176 (22)	24/257 (9)	24/265 (9)
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FAS= full analysis set, defined as all randomized subjects who received at least one dose of study medication; RGT=response-guided therapy

BOC=boceprevir 800 mg PO TID; PR=peginterferon alfa-2b+ribavirin;

EOF= end of follow-up; EOT= end of treatment

SVR= sustained virologic response at 24 weeks after the end of treatment. HCV RNA was imputed from follow-up week 12 if week 24 data was missing.

Source: FDA Statistical Reviewer

Table 14: Primary Efficacy Results in Study P05216 by Cohorts (FAS)

Efficacy Parameter	PR 48	RGT	BOC/PR 48
Cohort 1			
<u>Sustained Virologic Response</u>			
SVR Rate n/N(%)	126/311 (40.5)	211/316 (66.8)	213/311 (68.5)
Difference in SVR	-	26.2	28.0
95% CI for Diff	-	[18.7, 33.6]	[20.6, 35.4]
P_value	-	<0.0001	<0.0001
<u>Relapse Rates</u>			
Relapse Rate	37/162 (23)	21/232 (9)	18/230 (8)
Cohort 2			
<u>Sustained Virologic Response</u>			
SVR Rate n/N(%)	12/52 (23.1)	22/52 (42.3)	29/55 (52.7)
Difference in SVR	-	18.8	27.8
95% CI for Diff	-	[0.9, 36.8]	[10.1, 45.5]
P_value	-	0.0440	0.0035
<u>Relapse Rates</u>			
Relapse Rate	2/14 (14)	3/25 (12)	6/35 (17)

FAS= full analysis set, defined as all randomized subjects who received at least one dose of study medication; RGT=response-guided therapy

BOC=boceprevir 800 mg PO TID; PR=peginterferon alfa-2b+ribavirin;

EOF= end-of-follow up

SVR= sustained virologic response at 24 weeks after the end of treatment. HCV RNA was imputed from follow-up week 12 if week 24 data was missing.

Relapse Rate - HCV RNA <10 IU/mL at EOT and >25 IU/mL at EOF

Source: FDA Statistical Reviewer

Efficacy of boceprevir was demonstrated in subjects regardless of race (non-black and black). Although SVR rates were numerically lower in Cohort 2 (black) subjects who received boceprevir (42% to 53%), these rates were significantly higher than the SVR rate for the PR48 control (23%). Additionally, Cohort 2 (blacks) subjects in Arm 3 (BOC/PR 48) achieved numerically higher SVR rates compared to RGT arm (53% vs. 42% respectively); although this difference (11%) was not statistically significant.

Sustained Virologic Response based on Response Guided Therapy in P05216

Subjects in both boceprevir/PR treatment arms had a higher rate of SVR than those who received PR48 alone. However, as shown in the Table 15, SVR was numerically higher in the BOC/PR48 Arm 3 than the RGT Arm 2 in subjects who were late responders and thus received longer durations of therapy. In late responders, subjects who received 4 weeks PR followed by 24 weeks boceprevir/PR followed by 20 weeks PR, SVR was numerically approximately 9% lower than subjects in Arm 3 who received the 44 weeks boceprevir/PR after the 4 week PR lead-in phase. This difference was not statistically significant, but the trial was not designed to detect differences in this subgroup. If this finding represents a true difference, it would probably be considered clinically relevant. Note that this analysis excludes the 14 “late responder” subjects in Arm 2 who received the “wrong” duration of therapy because of detectable HCV RNA results that were not confirmed with a second analysis.

Table 15: Sustained Virologic Response for Early and Late Responders (P05216-Cohort 1 and 2 Combined)

	RGT (Arm 2) n/N (SVR %)	BOC/PR48 (Arm 3) n/N (SVR %)	Treatment Difference Arm 2-Arm 3 [95% CI two sided]
Overall	233/368 (63.3)	242/366 (66.1)	2.8 [-9.8, 4.1]
*Early Responders	156/161 (96.9)	155/161 (96.3)	0.6 [-3.8, 5.2]
#Late Responders	45/68 (66)	55/73 (75)	-9.2 [-24.4, 6.3]

*Early Responders: Undetectable HCV RNA treatment Week 8 through 24 (In RGT arm, early responders received BOC/PR through treatment Week 28).

#Late Responders: Detectable HCV RNA Week 8, but undetectable by Week 24 (In RGT arm, late responders received 28 weeks BOC/PR, followed by 20 weeks of PR for total of 48 weeks).

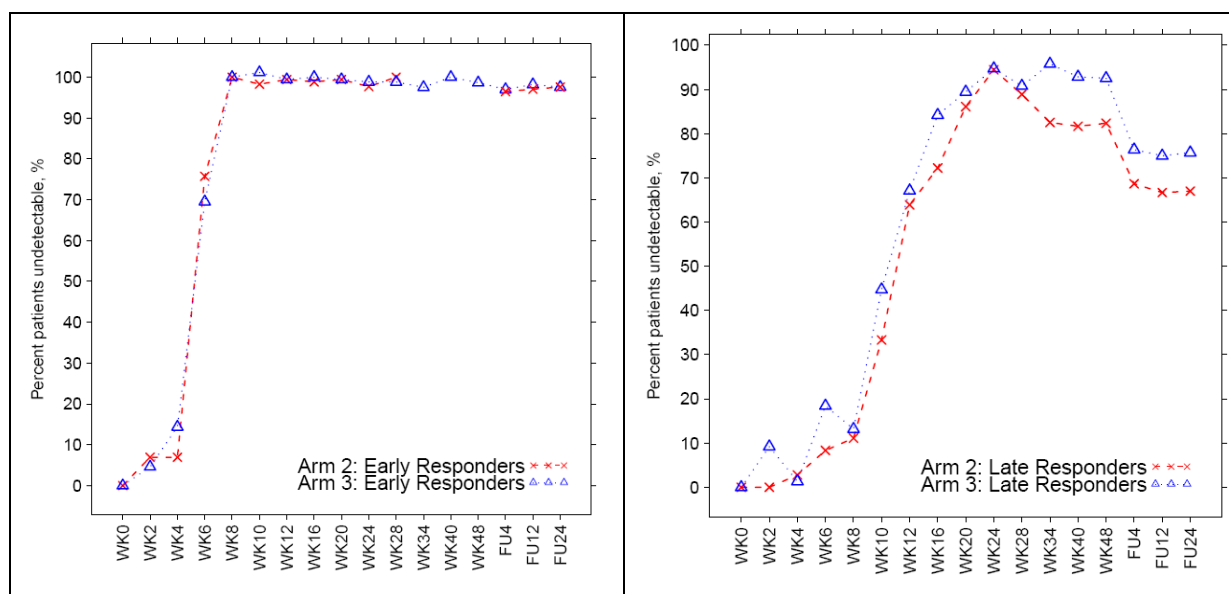
Subjects were discontinued for futility at Week 24 in all treatment arms if HCV RNA was detectable.

Source: FDA Statistical Reviewer

This numeric difference in SVR between late responders in Arm 2 and 3 (and the similar SVR between Arm 2 and 3 early responders) was further investigated by evaluating the percentage of subjects with undetectable HCV RNA at each visit. Any subject that discontinued treatment prior to Week 28 was removed from the analysis, as all subjects received the same treatment during that period. There were four groups of subjects based on whether the viral load was detectable at Week 8 and through Week 24 (Arm 2 early responders: n = 161; Arm 2 late responders: n=68; Arm 3 early responders: n=161; Arm 3 late responders: n=73). For early responders, there was no difference between shorter (Arm 2) and longer (Arm 3) treatment with SVR of 97% and 96%, respectively (Figure 7, Left). Therefore, an additional 20 weeks of triple therapy did not increase efficacy in early responders.

In contrast, there was an observable difference between Arm 2 and Arm 3 late responders starting at Week 28, which corresponds to administration of PR only in Arm 2. More subjects receiving longer boceprevir therapy (Arm 3) were undetectable at the end-of-treatment (93%) compared to subjects receiving shorter boceprevir therapy (Arm 2 late responders: 82%). There was a modest difference in SVR between the two groups; Arm 2 late responders: SVR-66% (n/N= 45/68); Arm 3 late responders: SVR-75% (n/N= 55/73). It appears that this difference can be attributed largely to virologic breakthrough while on PR after stopping boceprevir (Figure 7, Right).

Figure 7: Percentage of Treatment-Naïve Subjects with Undetectable Viral Load at Different Treatment Time Points for Early Responders (Left) or Late Responders (Right) for Study P05216



Source: FDA Pharmacometrics Reviewer

FDA analyses suggest that treatment-naïve subjects with detectable HCV RNA at Treatment Week 8 but undetectable at Week 24 (i.e., late responders not meeting futility rule) may benefit from receiving a longer duration (for example, 36 or 48 weeks) of boceprevir plus PR rather than boceprevir plus PR through Week 28, followed by PR alone to Week 48.

One treatment option would be 48 weeks of triple therapy (44 weeks of boceprevir) for this group. This treatment was studied during P05216 and demonstrated numerically higher SVR compared to boceprevir plus PR through Week 28, followed by PR alone to Week 48. However, a potentially higher SVR with this duration may come at the cost of prolonged anemia. Another option could be giving treatment-naïve late responders a total of 32 weeks of boceprevir followed by PR alone for 12 weeks, as was studied in the treatment-experienced trial (P05101). This approach may allow for improved SVR

while limiting the duration of anemia compared to a full 48 weeks of triple therapy. This approach is further discussed in detail in Section 6.1.8.

Relapse rates were similar in early responders who received either 24 weeks of triple therapy in RGT arm or 44 weeks of triple therapy in BOC/PR 48 arm. There was also no difference in the late responders in the RGT arm who received 24 weeks boceprevir/PR followed by 20 weeks PR compared to the 44 weeks of triple therapy in BOC/PR 48 arm (Table 16). All subjects received 4 weeks of PR lead-in.

Table 16: Relapse Rates for Early and Late Responders (P05216-Cohort 1 and 2 Combined)

Relapse Rates*			
Treatment-Naïve Trial (P05216)	PR48	RGT	BOC/PR48
Overall	39/176 (22)	24/257 (9)	24/265 (9)
Early Responders**	-	4/160 (3)	2/157 (1)
Late Responders**	-	7/52 (13)	9/64 (14)

*HCV RNA < 10 IU/mL at EOT and > 25 IU/mL during follow up

**based on HCV RNA results treatment week 8-24.

Primary Efficacy Results in Study P05101

SVR was higher in both boceprevir-containing arms compared to the PR control arm in this previous treatment-failure population. However, SVR was numerically (7%) higher (difference not statistically significant) in Arm 3 than in the RGT arm in this population. The Applicant reported that the 7% difference in SVR between the two arms was due to differences observed while subjects in each arm were receiving identical therapy prior to Week 36, and may be due to differences in responses in the subgroup of subjects with cirrhosis. In FDA's analysis, in the subgroup of cirrhotic subjects, 2/17 (12%) in Arm 2 (RGT) and 14/22 (64%) in Arm 3 (BOC/PR48) had an undetectable HCV RNA at TW 8 and reached TW 36 while receiving triple therapy. The difference in response prior to Week 36 between these subgroups remains unexplained.

Table 17: Primary Efficacy Results in Study P05101 (FAS)

Efficacy Parameter	PR 48 N=80	RGT N=162	BOC/PR 48 N=161
<u>Sustained Virologic Response</u>			
SVR at EOF (HCV RNA <10 IU/mL)			
SVR Rate (%)	17/80 (21)	95/162 (59)	107/161 (66.5)
Difference in SVR	-	37.3	45.2
95% CI for Diff	-	[25.8, 48.8]	[33.7, 56.6]
P_value	-	<0.0001	<0.0001
SVR at EOF (HCV RNA <25 IU/mL)			
SVR	18/80 (23)	96/162 (59)	107/161 (66.5)
Difference in SVR	-	36.6	43.9
95% CI for Diff	-	[25.0, 48.2]	[32.3, 55.5]
P_value	-	<0.0001	<0.0001
<u>Relapse Rates</u>			
Relapse Rate	7/25 (28)	16/111 (14)	14/121 (12)

FAS= full analysis set, defined as all randomized subjects who received at least one dose of study medication; RGT=response-guided therapy

EOF= end of follow-up; EOT= end of treatment

SVR= sustained virologic response at 24 weeks after the end of treatment. HCV RNA was imputed from follow-up week 12 if week 24 data was missing.

Relapse Rate - HCV RNA <10 IU/mL at EOT and >25 IU/mL at EOF

Source: FDA Statistical Reviewer

Sustained Virologic Response based on Response Guided Therapy in P05101

In trial P05101, SVR in the subset of early responders (undetectable HCV RNA at TW8 and TW12) in the RGT arm who completed treatment after 36 weeks of therapy (4 weeks PR lead-in followed by 32 weeks boceprevir in combination with PR) was similar to that observed in early responders in the BOC/PR48 arm who received boceprevir in combination with PR for 44 weeks after the 4 week PR lead-in phase. SVR in the subset of late responders (detectable HCV RNA at TW8, but undetectable at TW12) was 27/34 (79%) in the RGT arm who received 12 additional weeks of PR after receiving 32 weeks boceprevir in combination with PR (4 weeks PR lead-in followed by 32 weeks triple therapy) compared to 29/40 (73%) in subjects who received boceprevir in combination with PR for 48 weeks (4 weeks PR lead-in followed by 44 weeks triple therapy).

Table 18: Sustained Virologic Response for Early and Late Responders (P05101)^a

Treatment Group	RGT (Arm 2) n/N (SVR %)	BOC/PR48 (Arm 3) n/N (SVR %)
* Early Responders	62/68 (91%)	68/70 (97%)
# Late Responders	27/34 (79%)	29/40 (73%)

^a Subjects who had treatment duration of less than 36 weeks were removed from this analysis.

* Early Responders: undetectable HCV RNA at Week 8 and Week 12

Late Responders: detectable HCV RNA at Week 8, but undetectable at Week 12
Arm 2 (RGT) = PR lead-in for 4 weeks, then BOC/PR for 32 weeks (if undetectable HCV-RNA at TW 8) or BOC/PR for 32 weeks followed by placebo/PR for 12 weeks (if detectable HCV-RNA at TW 8).

Relapse rates were similar in late responders who received either 32 weeks of triple therapy followed by 12 weeks PR in RGT arm or 44 weeks of triple therapy in BOC/PR 48 arm. However, the relapse rate was somewhat higher in the early responders in the RGT arm who received 32 weeks triple therapy compared to the 44 weeks of triple therapy in BOC/PR 48 arm. It should be noted, however, that the numbers in the subsets are small (Table 19). All subjects received 4 weeks of PR lead-in.

Table 19: Relapse Rates for Early and Late Responders (P05101)

Treatment-Experienced Trial (P05101)	Relapse Rates*		
	PR48	RGT	Boc/PR48
Overall	7/25 (28)	16/111 (14)	14/121 (12)
Early Responders**	-	5/66 (8)	0/68 (0)
Late Responders **	-	6/33 (18)	7/36 (19)

*HCV RNA < 10 IU/mL at EOT and > 25 IU/mL during follow up

**based on HCV RNA results at treatment week 8

6.1.5 Analysis of Secondary Endpoints(s)

Modified Intent-to-Treat (mITT) Analysis Set– All randomized subjects who received at least one dose of boceprevir (experimental arms) or placebo (control arm). This population was analyzed for the key secondary objective in the pivotal Phase 3 studies (P05216 and P05101). The Applicant's goal of analyzing efficacy results using the mITT set was to provide an estimate of the experimental treatment effect of adding boceprevir to PR standard of care.

Other secondary efficacy endpoints analyzed were:

- The proportion of subjects with early virologic response (eg, undetectable HCV-RNA at TW 2, 4, 8, or 12).
- The proportion of subjects with early virologic response (eg, undetectable HCV-RNA at TW 2, 4, 8, or 12) who achieved SVR.
- The proportion of subjects with undetectable HCV-RNA at FW 12.
- The proportion of subjects with undetectable HCV-RNA at 72 weeks after randomization

Some of these results have been discussed in different sections of the review. Please refer to FDA Statistical Review for details of other analyses performed.

6.1.6 Other Endpoints

Several exploratory analyses were done by the FDA Reviewers using the different time-points of HCV-RNA measurements and virologic response to predict SVR. Please refer to FDA Clinical Pharmacology and Statistical Reviews.

6.1.7 Subpopulations

P05216 (Treatment-Naïve)

Overall the response rates in boceprevir-containing arms were higher compared to the PR control arm in every significant subgroup of study population. In the subset analysis, within the boceprevir treatment arms no differences in SVR were observed for gender or age (Table 20). As discussed earlier in Section 6.1.4, although SVR rates were numerically lower in Cohort 2 (black) subjects who received boceprevir (42% to 53%), these rates were significantly higher than the SVR rate for the PR48 control (23%). Additionally, Cohort 2 (blacks) subjects in Arm 3 (BOC/PR 48) achieved numerically higher SVR rates compared to the RGT arm (53% vs. 42% respectively); although this difference (11%) was not statistically significant.

Table 20: Sustained Virologic Response in Subgroups based on Baseline Characteristics (Study P05216 –Cohort 1 plus Cohort 2- FAS)

Efficacy Parameter	PR 48 n/N (%)	RGT n/N (%)	BOC/PR 48 n/N (%)
Overall SVR	138/363 (38)	233/368 (63)	242/366 (66)
Race Group			
Black	12/52 (23)	22/52 (42)	29/55 (53)
Non-Black	126/311 (41)	211/316 (67)	213/311 (69)
Gender			
Female	65/157 (41)	84/139 (60)	97/145 (67)
Male	73/206 (35)	149/229 (65)	145/221 (66)
Age Group			
≤ 40 year	35/67 (52)	37/51 (73)	41/59 (70)
> 40 year	103 /296 (35)	196 /317 (62)	201/307 (66)
Baseline Platelet Count			
<150,000/UL	9/27 (33)	18/33 (55)	20/38 (53)
≥150,000/UL	129 /336 (38)	215/335 (64)	222/328 (68)
Baseline HCV Viral Category (IU/mL)			
≤400,000	21/26 (81)	25/32 (78)	22/25 (88)
>400,000	117/337 (35)	208/336 (62)	220/341 (65)
Metavir Fibrosis Score Group			
0/1/2	124/328 (38)	213/319 (67)	211/313 (67)
3/4	9/24 (38)	14/34 (41)	22/42 (52)
Liver Cirrhosis at baseline			

Efficacy Parameter	PR 48 n/N (%)	RGT n/N (%)	BOC/PR 48 n/N (%)
No	127/339 (38)	222/337 (66)	223/331 (67)
Yes	6/13 (46)	5/16 (31)	10/24 (42)
HCV-1 Subtype (b) (4)			
1a	78/228 (34)	139/234 (59)	147/237 (62)
1b	48/121 (40)	88/124 (71)	85/117 (73)
Region			
EU	44/99 (44)	54/79 (68)	56/86 (65)
LA	4/10 (40)	10/12 (83)	8/10 (80)
NA	89/254 (35)	169/277 (61)	178/270 (66)
Week 4 Responsiveness			
<1-log ₁₀ Decline	3/83 (4)	27/97 (28)	36/95 (38)
≥1-log ₁₀ Decline	134/260 (52)	203/252 (81)	200/254 (79)

Source: FDA Statistical Reviewer

SVR was higher in subjects with baseline HCV RNA ≤ 400,000 IU/mL than in those with baseline > 400,000 IU/mL, in subjects with HCV subtype 1b than in those with subtype 1a, in subjects with a baseline platelet count ≥150,000/μL than those with platelet count <150,000/ μL, in subjects with a lower fibrosis score (Metavir F0, F1, and F2 combined) than in those with higher fibrosis score (Metavir F3 or F4 combined), and in subjects without cirrhosis at baseline compared to those with cirrhosis at baseline (as assessed by the investigator). In summary, SVR rates were higher in subjects with a low baseline HCV viral load, less fibrosis, greater platelet count and non-black race. Higher SVR rates were seen in subjects with genotype 1b.

Interferon-responsiveness (as defined by ≥1-log₁₀ decline in viral load at TW4) was predictive of SVR. Boceprevir-treated subjects who demonstrated interferon responsiveness by TW4 achieved SVR rates of 79-81% compared to 52% in subjects treated with PR. In subjects with <1-log₁₀ decline in viral load at TW4 (poor interferon-responsiveness), treatment with the combination of boceprevir with PR resulted in SVR rates of 28-38%, respectively, compared to 4% in subjects treated with PR alone. Further, in subjects who had undetectable HCV RNA at TW 4 had an SVR rate of 97% (29/30) in control arm and 90% in boceprevir containing arms (RGT 17/19 (90%) and BOC/PR48 18/20 (90% respectively).

P05101 (Treatment-Failure)

As seen in treatment-naïve population, overall the response rates in boceprevir-containing arms were higher compared to the PR control arm in every significant subgroup of study population (Table 21).

Table 21: Sustained Virologic Response in Subgroups based on Baseline Characteristics (Study P05101- FAS)

Efficacy Parameter	PR 48 n/N (%)	RGT n/N (%)	BOC/PR 48 n/N (%)
Overall SVR	18/80 (23)	96/162(59)	107/161(67)
Race Group			
Black	1/12 (8)	11/18 (61)	10/19 (53)
Non-Black	17/68 (25)	85/144 (59)	97/142 (68)
Gender			
Female	4/22 (18)	37/64 (58)	32/49 (65)
Male	14/58 (24)	59/98 (60)	75/112 (67)
Age Group			
≤ 53 year	8/40 (20)	54/89 (61)	52/82 (63)
> 53 year	10/40 (25)	42/73 (58)	55/79 (70)
Baseline Platelet Count			
≤150,000/UL	2/10 (20)	8/21 (38)	13/19 (68)
150,000-200,000/UL	5/16 (31)	20/37 (54)	27/45 (60)
>200,000/UL	11/54 (20)	68/104 (65)	67/97 (69)
Baseline HCV Viral Category (IU/mL)			
≤400,000	3/6 (50)	7/7 (100)	5/7 (71)
>400,000	15/74 (20)	89/155 (57)	102/154 (66)
Baseline HCV Viral Category (IU/mL)			
≥800,000	6/15 (40)	13/15 (87)	16/20 (80)
>800,000	12/65 (19)	83/147 (57)	91/141 (65)
Metavir Fibrosis Score Group			
0/1/2	14/61 (23)	78/117 (67)	81/119 (68)
3/4	3/15 (20)	14/32 (44)	21/31 (68)
Liver Cirrhosis at baseline			
No	17/66 (26)	86/132 (65)	85/128 (66)
Yes	0/10 (0)	6/17 (35)	17/22 (77)
HCV-1 Subtype (b) (4)			
1a	12/46 (26)	52/96 (54)	62/97 (64)
1b	6/34 (18)	44/66 (67)	43/61 (71)
Region			
EU	8/29 (28)	24/46 (52)	28/42 (67)
NA	10/51 (20)	72/115 (63)	79/119 (66)
Week 4 Responsiveness			
<1-log ₁₀ Decline	0/12 (0)	15/46 (33)	15/44 (34)
≥1-log ₁₀ Decline	18/67 (27)	81/110 (74)	90/114 (79)
PEG Type used during Previous Treatment			
PEG2a	10/42 (24)	45/79 (57)	42/68 (62)
PEG2b	8/38 (21)	51/83 (61)	65/93 (70)
Previous Treatment Response			
Never Negative	2/29 (7)	23/57 (40)	30/58 (52)
Some Negative	16/51 (31)	73/105 (70)	77/103 (75)

Source: FDA Statistical Reviewer

Black and non-black subjects were not enrolled in separate cohorts in study P05101, as was done in P05216. As shown in the table 21, SVR in the subset of black subjects in this trial was similar in the RGT arm to that observed in non-blacks who received RGT, but SVR was somewhat lower in blacks than in non-black subjects in the BOC/PR48 arm. As the subset of black subjects in this study is relatively small, results of this subgroup analysis should be interpreted with caution. However, in both subsets, SVR was higher in both boceprevir arms than in the control arm.

In FDA subset analyses, within the boceprevir treatment arms, subjects who were previous relapsers, those with lower baseline HCV RNA ($\leq 800,000$ IU/mL), and HCV subtype 1b, had higher response rates (SVR) than those who were previous partial responders, with higher baseline HCV RNA ($> 800,000$ IU/mL), HCV subtype 1a; while no significant difference in SVR was observed with gender and age. No difference in SVR was noted in the subjects who had lower Metavir fibrosis scores (F0/1/2) compared to higher Metavir scores (F3/4) in the BOC/PR 48 arm; however, in the RGT arm subjects with lower Metavir scores (F0/1/2) did better compared to those with higher Metavir scores (F3/4). These results should be interpreted with caution as the numbers in this subset analyses are small.

Boceprevir-treated subjects who demonstrated interferon responsiveness by TW4 achieved SVR rates of 74-79% compared to 27% in subjects treated with PR. In subjects with $< 1\text{-log}_{10}$ decline in viral load at TW4 (poor interferon-responsiveness), treatment with the combination of boceprevir with PR resulted in SVR rates of 33-34%, compared to 0% in subjects treated with PR alone.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The Applicant used Phase 2 trial data to support Phase 3 lead-in strategy (P03523) and dose-selection (P03659).

P03523

Boceprevir 800 mg TID added to the PR standard of care for treatment of HCV GT1 infected treatment-naïve subjects increased SVR in both the 28-week (54-56%) and 48-week (67-75%) regimens compared to PR alone (38%). The 48-week BOC-containing arms had higher SVR and lower relapse compared to the 28-week BOC-containing arms (Table 22). SVR in the Arm 1 crossover subjects (N=36) was 25%. The low-dose ribavirin Arm 7 had similar SVR compared to PR control and was associated with increased relapse and virologic breakthrough.

Table 22: Sustained Virologic Response Rates (P03523)

	Arm 1 PR N=104*	Arm 2 BPR-28 N=107	Arm 3 BPR-L/I- 28 N=103	Arm 4 BPR-48 N=103	Arm 5 BPR-L/I- 48 N=103	Arm 6 BPR-48 N=16	Arm 7 BPR- low dose RBV-48 N=59
SVR-n (%)	39 (38)	58 (54)	58 (56)	69 (67)	77 (75)	8 (50)	21 (36)
Relapse-n (%)**	12 (24)	24 (30)	18 (24)	5 (7)	2 (3)	1 (11)	6 (22)
Breakthrough-% (N)	0	7 (7)	4 (4)	12 (12)	5 (5)	4 (25)	16 (27)
Incomplete Responder- % (N)	1 (1)	2 (2)	1 (1)	1 (1)	0	0	1 (2)
Nonresponder- % (N)	52 (50)	16 (15)	22 (21)	16 (16)	19 (18)	3 (19)	15 (25)
Genotype (b) (4)							
1a							
SVR-% (N)	24 (36)	38 (49)	35 (54)	37 (57)	49 (71)	4 (50)	15 (37)
Relapse-% (N)	8 (25)	20 (34)	12 (26)	4 (10)	1 (2)	1 (20)	6 (29)
1b							
SVR-% (N)	10 (31)	19 (73)	22 (61)	29 (85)	26 (81)	2 (33)	4 (25)
Relapse-% (N)	4 (29)	3 (14)	5 (19)	1 (3)	1 (4)	0	0

P=pegylated interferon alfa 2b, R=ribavirin, B=boceprevir, L/I=lead-in, -28=28 week treatment duration, -48=48 week treatment duration

*N=36 in Arm 1 rolled over to BPR; therefore, counted as nonresponders

**The denominator for relapse comprises subjects with EOT (PCREOFN) and FW24 (PCREOT) data.

Source: (b) (4) dataset for P03523

Higher SVR occurred in the 48-week lead-in treatment arm (Arm 5, 75%) compared with the 48-week no lead-in treatment arm (Arm 4, 67%). In addition, lower virologic breakthrough occurred in both the 28- and 48-week arms containing a lead-in (Arm 3, 4%; Arm 5, 5%) compared to arms with no lead-in (Arm 2, 7%; Arm 4, 12%). However, P03523 was an open-label trial, and it should be noted that although SVR was higher in the lead-in arms, treatment compliance was also higher in these arms. Therefore, if SVR analysis is limited to 100% treatment compliant subjects (Table 23), the advantage of the lead-in arms over the non lead-in arms disappears, with comparable SVR between the 48-week lead-in (Arm 5, 94%) and 48-week no lead-in arms (Arm 4, 98%). A similar effect is seen with relapse in the 48-week treatment arms, 0% in the 48-week lead-in arm versus 2% in the 48-week no lead-in arm. Furthermore, no fully compliant subjects experienced virologic breakthrough. While this analysis challenges the lead-in strategy, it is a *post hoc* analysis of only the fully compliant subject subgroup and should be viewed as exploratory.

Table 23: Sustained Virologic Response Rates in 100% Treatment Compliant Subjects (P03523)

	Arm 1 PR	Arm 2 BPR-28	Arm 3 BPR-L/I- 28	Arm 4 BPR-48	Arm 5 BPR-L/I- 48	Arm 6 BPR-48	Arm 7 BPR-low dose RBV- 48
All Randomized and Treated Subjects							
N	104	107	103	103	103	16	59
SVR-%	38	54	56	67	75	50	36
Relapse-%	24	30	24	7	3	11	22
Subjects with 100% Compliance							
N	44	57	64	44	52	6	21
SVR-%	66	75	73	98	94	100	71
Relapse-%	28	24	18	0	2	0	17

P=pegylated interferon alfa 2b, R=ribavirin, B=boceprevir, L/I=lead-in, -28=28 week treatment duration, -48=48 week treatment duration

Source: (b) (4) dataset for P03523 using DCOMP variable for treatment duration compliance

The Applicant reasoned the lead-in strategy may decrease overall viral load and the pool of pre-existing HCV quasiespecies prior to the introduction of boceprevir, thereby limiting selection and emergence of resistant variants. These theoretical advantages coupled with P03523's efficacy data supported the lead-in approach for the subsequent Phase 3 boceprevir trials.

P03659

As noted in Section 5.3, the original P03659 trial design in HCV infected GT 1 treatment-experienced subjects resulted in overall poor HCV antiviral activity with the lower doses of boceprevir used initially, and viral resistance developed in the RBV-sparing arms. These findings led to Amendment 2, a major protocol change requiring unblinding to treatment and switching all eligible subjects to the currently proposed BOC-containing treatment regimen, 800 mg TID BOC plus PR, for 24 weeks. From the original 357 subjects in Arms 1-7, 143 subjects (40%) continued triple therapy for an additional 24 weeks. Of these 143 subjects, 88 (62%) completed the amended trial, 20 (14%) discontinued due to AE, 24 (17%) were treatment failures, and 11 (8%) were lost to follow-up/did not wish to continue. The following table 24 presents SVR results (1) based on the original protocol design, and (2) based on the 143 subject subset following Amendment 2.

Table 24: Sustained Virologic Response Rates (P03659)

	Arm 1 PR	Arm 2 100 B/P	Arm 3 200 B/P	Arm 4 400 B/P	Arm 5 400 B/P/R	Arm 6 400 B/P-28	Arm 7 800 B/P
All Treated Subjects	49	48	49	49	49	48	65
SVR-n (%)	1 (2)	1 (2)	6 (12)	4 (8)	7 (14)	1 (2)	3 (5)

Post-Amendment 2*							
N	-	4	9	7	21	7	61
SVR-n (%)	-	1 (25)	6 (66)	4 (57)	7 (33)	1 (14)	3 (5)
Relapser-n (%)	-	1 (25)	1 (11)	1 (14)	3 (14)	2 (29)	11 (18)
Nonresponder-n (%)	-	0	0	0	0	0	1 (2)

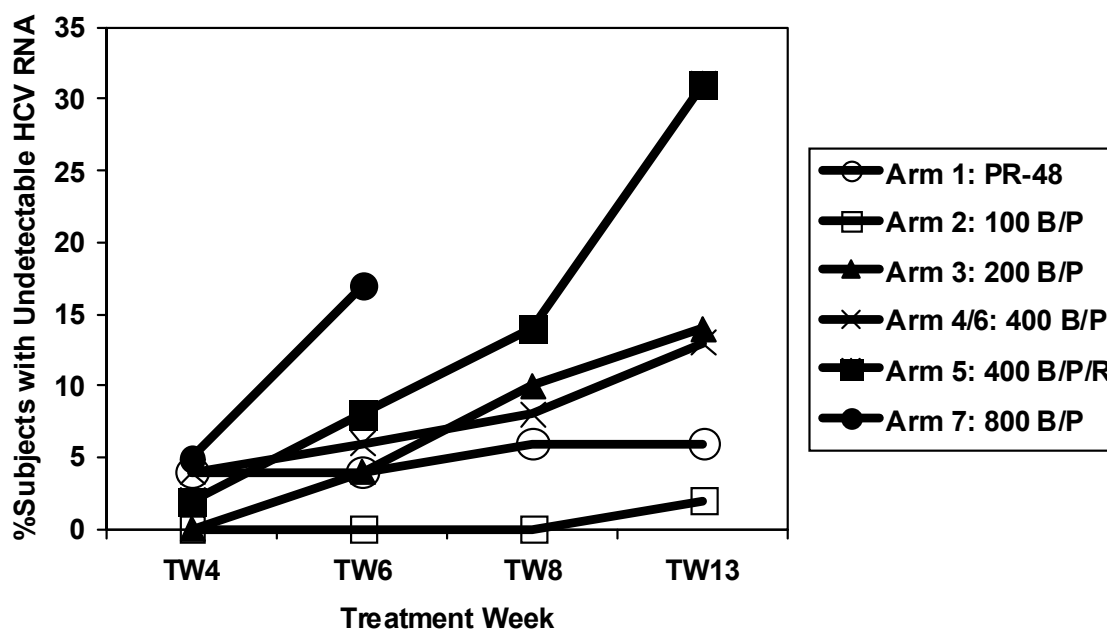
*N=34 additional Arm 1 subjects are not included in this table. These subjects were virologic failures (detectable Week 13 HCV RNA) who rolled over to add boceprevir.

P=pegylated interferon, R=ribavirin, B=boceprevir, P=pegylated interferon alfa 2b, -28=28 week treatment duration, -48=48 week treatment duration

Source: (b) (4) dataset for Protocol P03659

Prior to Amendment 2, there was some evidence of dose-response pertaining to HCV RNA undetectable status (Figure 8). More subjects receiving 400 mg TID BOC achieved undetectable HCV RNA by Week 13. Arm 7 had >15% subjects with undetectable HCV RNA at Week 6 supporting the Phase 3 BOC 800 mg TID dose selection: subsequent Arm 7 dose-response comparisons are not possible due to the Amendment 2 addition of RBV.

Figure 8: P03659 Percentage of Subjects with Undetectable HCV RNA by Treatment Week, Prior to Amendment 2



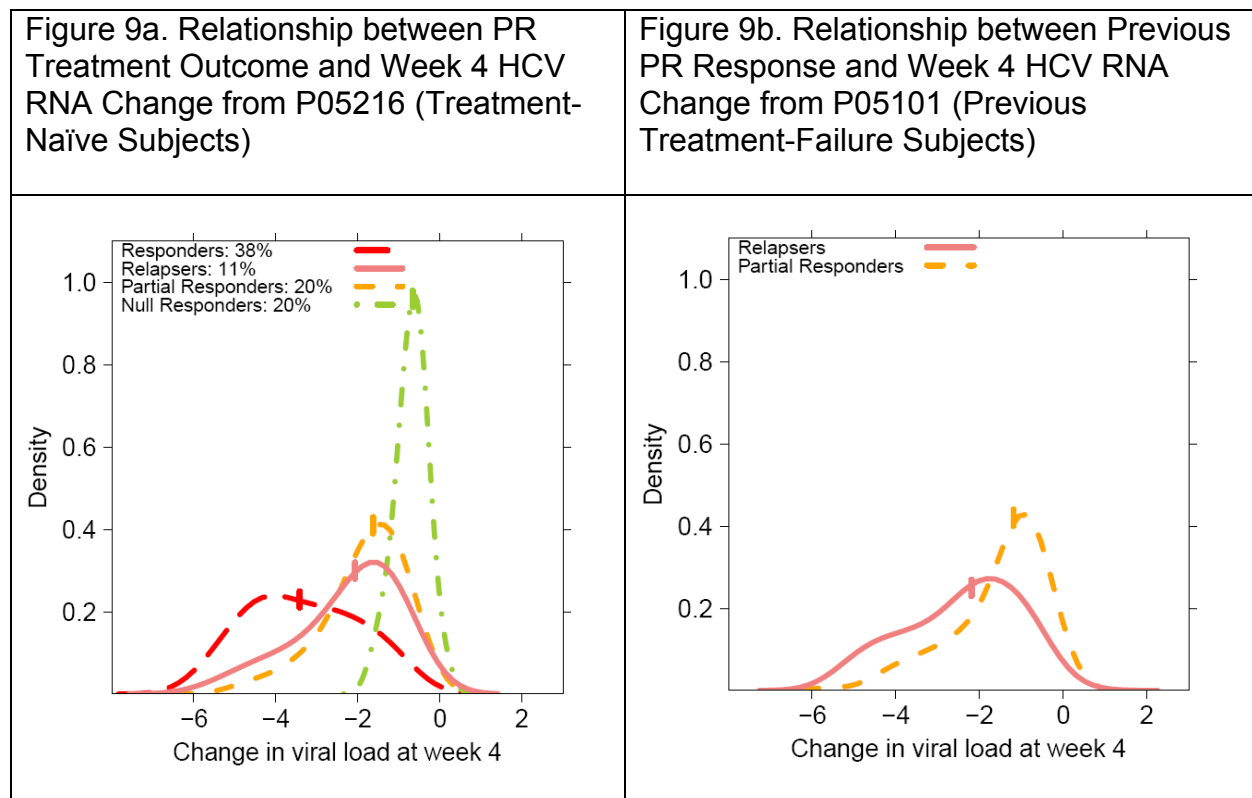
Source: (b) (4) dataset for Protocol P03659

FDA Analysis Exploring Longer Duration of Boceprevir Therapy in Late Responders in Previously Untreated Population (Treatment-Naïve)

Data from studies P05216 and P05101 were bridged to support a 32 week duration of boceprevir treatment (i.e. through Week 36) followed by PR alone for late responders in treatment-naïve population. This “bridging” analysis demonstrates that late responders among the treatment-naïve population are fairly similar in characteristics to that of previously-treated partial responders, and relapsers (i.e., those subjects enrolled in P05101).

The following figures provide the relationship between Week 4 HCV RNA change and treatment outcome for the treatment-naïve population who received PR in P05216, and the relationship between Week 4 HCV RNA change and previous response for the treatment-experienced population from P05101. Clearly, treatment-naïve subjects with large viral load decreases (median=3.4 log₁₀ decrease) at Week 4 are more likely to be SVR responders and those with smaller Week 4 viral load changes (median=0.7 log₁₀ decrease) are more likely to be null responders to PR (<2 log₁₀ decline at Week 12) (Figure 9a). The relapser (median=2.1 or 2.2 log₁₀ decreases) and partial responder (median=1.6 or 1.2 log₁₀ decreases) populations also demonstrate similar viral load decreases as expected, for both treatment-naïve (Figure 9a) and treatment-experienced (Figure 9b) populations, respectively. Hence, the Week 4 response is a good predictor of PR treatment outcome in treatment-naïve subjects and a similar PR Week 4 response is maintained if subjects classified as relapsers or partial responders are retreated with PR.

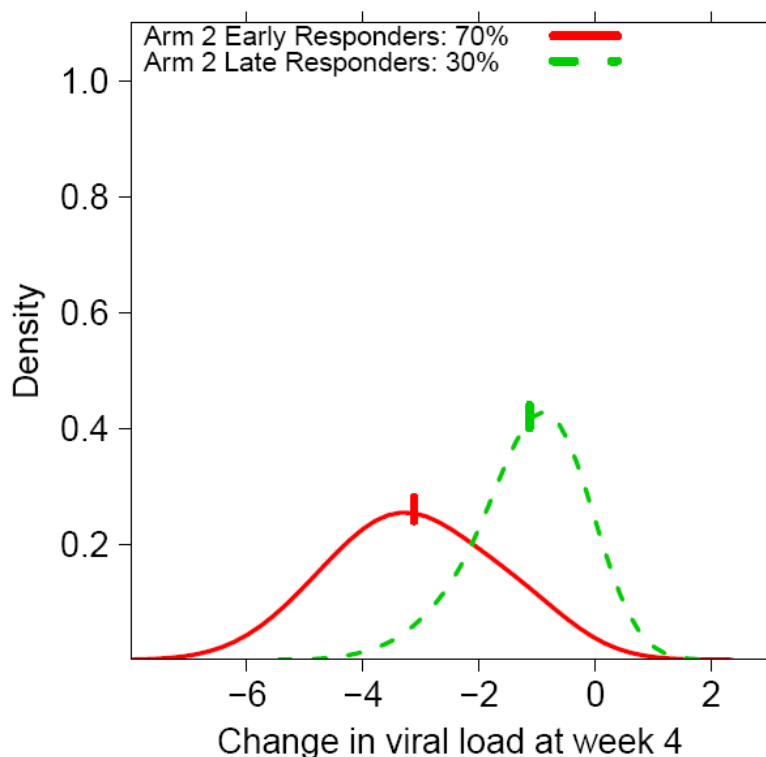
Figure 9: Relationship between PR Treatment Outcome and Week 4 HCV RNA Change in Study P05216 (Treatment-Naïve Subjects) and Study P05101 (Previous Treatment-Failure Subjects)



Source: FDA Pharmacometrics Reviewer

An additional analysis of the boceprevir RGT arm in P05216 based on Week 4 response identified those subjects with $>2.0 \log_{10}$ decrease at Week 4 as comprising $>75\%$ of the early responder population who received 4 weeks of PR followed by 24 weeks triple therapy, as shown in the following Figure (Figure 10). In contrast, late responders in Arm 2 receiving the full 48 week treatment duration (4 weeks PR, followed by 24 weeks triple therapy, then 20 weeks PR) were those subjects with smaller changes in HCV RNA at Week 4. For example, 50% (34/68) of subjects receiving 48 weeks of therapy in Arm 2 from P05216 had $<1.0 \log_{10}$ decrease at Week 4; and 91% (62/68) of subjects receiving 48 weeks of therapy in Arm 2 from P05216 had $<2.0 \log_{10}$ decrease at Week 4. Therefore, the late responder treatment arms from P05216 are predominantly comprised of subjects that would have failed PR treatment.

Figure 10: Relationship between Response Guided Treatment Arm Assignment and Week 4 HCV RNA Change (P05216)



Source: FDA Pharmacogenomics Reviewer

While the late responders in Arm 2 from P05216 had numerically lower SVR rates than late responders in Arm 3, the late responders in the treatment-experienced trial (P05101) exhibited a similar response for the two boceprevir treatment arms (Section 6.1.4). Taken together, these analyses indicate that 28 weeks duration of boceprevir was not sufficient in late responders based on P05216, while P05101 suggests that 36 weeks may be sufficient in this group. However, this analysis is not conclusive as P05101 did not include previous null responders. The issue about the duration of boceprevir necessary to achieve optimal SVR rates in these patients is currently unresolved and will be discussed at the upcoming AC meeting.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

A 3 year long term follow up study (P05063) is ongoing. The goals of this study are to examine the durability of SVR, the long-term safety and the natural history of resistance-associated variants over time in subjects treated with boceprevir. Please refer to Section 7.4.5 for details.

6.1.10 Additional Efficacy Issues/Analyses

Efficacy in Null Responders

Null responders were not eligible for enrollment in the Phase 3 previous treatment-failure trial P05101. However, Applicant is proposing that null responders not be excluded from the indication. Multiple previous studies have shown that null responders to previous therapy with pegylated interferon and ribavirin generally do not respond as well as relapsers or partial responders to re-treatment with pegylated interferon/ribavirin.

An important concept for consideration is the view that treatment-naïve patients are comprised of a spectrum of potential responders and nonresponders (i.e. null or partial responders). In fact it can be predicted that more than half of treatment-naïve patients will eventually be proven to be pegylated interferon plus ribavirin nonresponders, some of whom will be null responders. The Applicant's principal argument is that "would-be" null responders have already been studied in their Phase 3 naïve trial and that the lead-in period of the trial allows one to predict and identify patients who are intrinsically null responders among the treatment-naïve population. In other words, the Applicant contends that a poor ($< 1 \log_{10}$ HCV RNA decline) response to pegylated interferon and ribavirin at 4 weeks, as observed during the lead-in period, is a surrogate definition for null response.

In support of using the week 4 virologic response to predict null responders, the Applicant provided a retrospective analysis of their IDEAL trial. They evaluated whether there was a correlation between treatment week 4 virologic response and week 12 HCV RNA levels, and between treatment week 4 virologic response and SVR.

The IDEAL trial (P0347) was a randomized trial which evaluated 3 different pegylated interferon plus ribavirin treatment arms in 3070 treatment-naïve subjects with genotype 1. Subjects were randomized 1:1:1 to either: peginterferon alfa-2b 1.5 µg/kg/wk or peginterferon alfa-2b 1.0 µg/kg/wk, both with weight-based dosing of ribavirin (800-1400 mg/day), or to peginterferon alfa-2a 180 µg/kg/wk plus ribavirin 1000-1200 mg/day. Subjects with a $< 2.0 \log_{10}$ decline in HCV RNA at treatment week 12 discontinued due to futility.

In IDEAL, 678 subjects had a $< 2 \log_{10}$ decline at treatment week 12. Subjects with a $< 1.0 \log_{10}$ decline in HCV RNA at treatment week 4 had SVRs ranging from 3-5% among the 3 treatment arms; and thus approximately 96% subjects who failed to achieve at least a $1 \log_{10}$ decline in HCV RNA by week treatment week 4 did not achieve SVR. In addition in boceprevir trials P05216 (treatment-naïve) and P05101 (previous treatment failures), subjects in the PR control arms with a $< 1.0 \log_{10}$ decrease in HCV RNA after 4 weeks PR lead-in therapy had SVR rates of 5%, and 0%, respectively. These data show that patients receiving PR who have a $< 1 \log_{10}$ response at week 4 have a very low probability of SVR.

Furthermore, based on their analysis of the IDEAL study, the Applicant found that a $< 1 \log_{10}$ decline in HCV RNA at treatment week 4 correlated with $< 2.0 \log_{10}$ decline in HCV RNA at treatment week 12. The correlation coefficient ranged from $r = 0.73$ to 0.78 for the 3 treatment arms in the Applicant's logistic regression analysis. Additionally, a Classification and Regression Tree (CART) analysis found that a $< 1.0 \log_{10}$ decline in HCV RNA at treatment week 4 closely corresponded to a $< 2.0 \log_{10}$ decline at treatment week 12.

The Applicant concluded that virologic response at either timepoint (week 4 or 12) could be used to predict which subjects are unlikely to achieve SVR, and that treatment week 4 response to PR therapy could be used to predict SVR, and could be considered a surrogate for null response ($< 2 \log_{10}$ HCV RNA decline at treatment week 12).

There are some limitations in the Applicant's contention that boceprevir efficacy has been sufficiently characterized in prior PR null responders, based on using PR lead-in response as a surrogate for prior treatment history. Although both on-treatment measures ($< 1 \log_{10}$ at Week 4, $< 2 \log_{10}$ at Week 12) during standard PR therapy have a robust negative predictive value for SVR, these populations are not necessarily the same. Based on the Applicant's analysis of PR virologic response data from the IDEAL trial, while 679 subjects had a $< 2 \log_{10}$ decline in HCV RNA at treatment Week 12, 146 (21%) of these subjects had a $\geq 1 \log_{10}$ decline in HCV RNA at Week 4. Similarly, 705 subjects had a $< 1 \log_{10}$ decline in HCV RNA at treatment Week 4, but 172 (24%) of these subjects had a $\geq 2 \log_{10}$ decline at treatment Week 12.

Analysis of PR lead-in responses in the Phase 3 trial (P05101) in treatment-experienced subjects also raises questions about using PR lead-in responsiveness as a surrogate for prior treatment history. Although this trial specifically excluded prior PR null responders (based on the $< 2 \log_{10}$ at Week 12 definition), 25% (102/403) of all subjects enrolled achieved a $< 1 \log_{10}$ HCV RNA decline at treatment Week 4 (end of PR lead-in). Of the 102 subjects who achieved a $< 1 \log_{10}$ HCV RNA decline at treatment Week 4, 46 (45%) were prior relapsers. In other words, the Applicant's proposed surrogate indicator of PR "null responder" does not adequately differentiate prior partial responders and relapsers from prior null responders.

Reviewer's comment:

Whether the treatment week 4 response to pegylated interferon and ribavirin during the current therapy correlates with the historical 12 week response during the previous therapy needs further exploration. This issue will be discussed at the upcoming AC meeting.

Although the overall SVR was lower for subjects who were poorly interferon responsive across arms, the difference in treatment effect for boceprevir remained consistent for

patients across a range of interferon responsiveness, including those predicted to be null responders (i.e. poorly interferon responsive).

Post hoc Efficacy Analysis based on IL28B Pharmacogenetics

A genetic polymorphism, rs12979860, near the IL28B gene (encoding interferon-lambda 3; hereafter referred to as “IL28B genotype”) is a strong predictor of sustained viral response (SVR) in subjects receiving therapy with pegylated interferon and ribavirin (PR). Numerous studies have demonstrated that subjects who carry the variant alleles (C/T and T/T genotypes) have lower SVR rates than individuals with the C/C genotype.

In the two Phase 3 trials (P05216, treatment-naïve; P05101, treatment-failure), DNA samples were collected on a voluntary basis. In these trials, IL28B testing was not included in the original protocols. However, as originally planned in the protocols, DNA samples were collected for exploratory pharmacogenomic assays on an optional basis if approved by the IRB or IEC at each site; and protocols were later amended to include IL28B genotype testing. Treatment responses were evaluated according to IL28B genotype for 62% and 66% of the modified intent-to-treat populations of P05216 and P05101, respectively. Some prognostic imbalances were observed, although SVR rates and treatment effects in the IL28B substudy were similar to the overall population.

The Applicant’s genetic substudy confirms previous reports of IL28B genotype effects on PR responses (Table 25). In treatment-naïve subjects with the C/T and T/T genotypes, boceprevir-containing regimens resulted in significantly higher SVR rates than PR alone, whereas SVR rates did not differ significantly between the boceprevir-containing arms and PR alone in the C/C genotype subgroup (genotype x treatment interaction $P=0.005$). Among C/T and T/T subjects, the number-needed to treat (NNT) with boceprevir to achieve one additional SVR was approximately 3 to 4 depending on the boceprevir regimen; among C/C subjects the NNT was 27 for boceprevir response-guided therapy (RGT) and 53 for boceprevir/PR48. In treatment-failure subjects, IL28B genotype effects were less pronounced and thus treatment effects did not differ significantly based on IL28B genotype (genotype x treatment interaction $P=0.60$). However, the lack of significant genotype effects within the P05101 treatment arms may be related to the smaller sample size and enrichment for prior PR partial responders and relapsers.

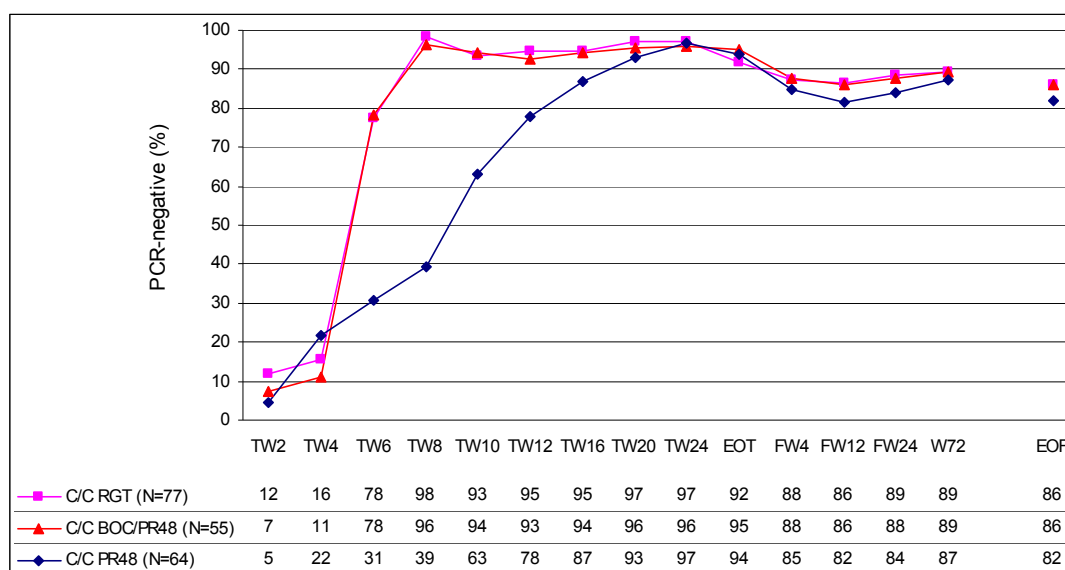
Table 25: Treatment Comparisons by IL28B Genotype and Treatment

Trial	IL28B Genotype	N	SVR, n/N (%)		
			Arm 1 PR	Arm 2 RGT	Arm 3 Boc/PR48
P05216 (naïve)	C/C	196	50/64 (78)	63/77 (82)	44/55 (80)
	C/T	334	33/116 (28)	67/103 (65)	82/115 (71)
	T/T	123	10/37 (27)	23/42 (55)	26/44 (59)
P05101 (failure)	C/C	63	6/13 (46)	22/28 (79)	17/22 (77)
	C/T	157	5/29 (17)	38/62 (61)	48/66 (73)
	T/T	39	5/10 (50)	6/11 (55)	13/18 (72)

Source: FDA Pharmacogenomics Reviewer

While SVR rates were similar for boceprevir-containing regimens and PR48 in treatment-naïve C/C subjects, responses to boceprevir occurred more rapidly in subjects with the C/C genotype in arms 2 and 3 relative to PR48 (Figure 11). The majority of C/C subjects treated with boceprevir had undetectable HCV-RNA by Treatment Week 8, whereas similar response rates were not achieved until Treatment Week 24 for those treated with PR48. These data suggest that IL28B C/C genotype subjects could potentially benefit from a shorter course of boceprevir/PR therapy and still achieve SVR. This hypothesis has not been tested.

Figure 11: Virologic Response over Time by Genotype and Treatment in Treatment-Naïve Subjects (P05216)



Source: FDA Pharmacogenomics Reviewer

Overall, the findings of these retrospective substudies suggest that IL28B genotype is a major contributor to variable treatment responses. Properly controlled trials (e.g., enriched, stratified randomization) will be important to understand the role of IL28B genotyping in patient management.

Some other efficacy issues which remain unanswered at this time are:

- There were insufficient numbers of subjects age 65 and older in the clinical studies to determine whether this population responds differently from younger patients.
- No efficacy or safety data is available in patients in HIV/HCV co-infected subjects (Study is ongoing and discussed in Section 7.4.5).
- Study to compare the SVR rates based on the management of anemia; erythropoietin use verses ribavirin dose reduction is ongoing and is discussed in Section 7.4.5.
- Optimum duration of therapy in late responders in the treatment-naïve population. This was discussed in Section 6.1.8.
- No efficacy or safety data is available in posttransplant patients thus there still exists an unmet need for this population.

7 Review of Safety

Safety Summary

Overall, most of the adverse events reported in these trials have been well-described for pegylated interferon and ribavirin therapy.

The most important safety concern during the clinical development of boceprevir has been the decrease in hemoglobin above and beyond that observed with pegylated interferon and ribavirin alone. The anemia appears to be part of an overall bone marrow suppressive effect of boceprevir as evidenced by the increased frequency of neutropenia and thrombocytopenia in boceprevir-treated subjects compared to PR-treated controls. Subjects treated with boceprevir had increased frequency of Grade 3 and 4 anemia. The use of erythropoietin was permitted in these trials, at the investigator's discretion, with or without ribavirin dose reduction as a supportive therapy for the management of anemia. Erythropoietin use has been associated with increased incidence in thromboembolic events in subjects receiving erythropoietin. There were few thromboembolic adverse events reported in these trials including one case of arterial thrombosis. However, no definite causality assessment or benefit risk assessment can be made due to the presence of confounding factors and also erythropoietin use was not randomized and was open-label. Pure red-cell aplasia (PRCA) is a rare erythropoietin side effect, and was reported in one subject during the follow-up period.

Another potential safety signal is the increased number of subjects with reported psychiatric symptoms of suicidal and homicidal ideations in boceprevir-containing arms as compared to control. Although these psychiatric adverse events are known to be associated with pegylated interferons, they are potentially life-threatening, and could have important implications for boceprevir use in combination with PR in a larger population.

Dysgeusia (alteration of taste) was a common adverse event reported at an increased frequency in boceprevir-treated subjects as compared to control (37% in boceprevir-containing arms versus 16% in control arm); however, the majority of dysgeusia events were mild-moderate in intensity and were not treatment-limiting. Gastrointestinal symptoms such as nausea, diarrhea, and vomiting (4%-6% difference compared to controls) also occurred at a somewhat increased frequency in boceprevir-treated subjects.

Adverse events of rash/skin eruption were observed at similar frequency in boceprevir-treated subjects compared to controls. No cases of Stevens-Johnson syndrome/toxic epidermal necrolysis were reported.

7.1 Methods

Safety data for this NDA was submitted by the Applicant as final study reports, clinical safety summary, an integrated summary of safety and electronic datasets. Narrative summaries were provided for all subjects who died, developed a serious adverse event (SAE), developed an adverse event of special interest or discontinued from the study because of an adverse event (AE).

Summary results of the integrated safety analysis are presented in the following sections. Minor differences between the Applicant's results and FDA's results can be attributed to the differences in the methods for conducting the analyses and do not significantly alter the final conclusions. Medical Dictionary for Regulatory Activities (MedDRA) terms are used in the analyses of the adverse event tables in this review; however American English spelling is used in the tables and text of this review instead of British English spelling. The Applicant's categorization of closely related events and coding of adverse event verbatim terms to preferred terms was assessed and was found to be appropriate.

Each AE is listed only once in summary tables, regardless of the number of times it occurred for the subject. A subject may report more than one AE; therefore, the total number of AEs reported may be greater than the number of subjects in the study. Adverse events and laboratory abnormalities were graded using the modified WHO grading scale.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Pivotal Data

The safety data derived from the Phase 2b trial (P03523) and the two pivotal phase 3 trials (P05216 and P05101) constitutes the primary safety population and FDA analyses of key safety signals were performed using this integrated dataset. Data from the two treatment-naïve trials, P03523 and P05216, were pooled by combining data from the two standard-of-care (PR) arms and then combining data from all arms including boceprevir therapy (BOC/PR). All three trials were randomized but trial P03523 was an open label trial; whereas the two phase 3 trials were double-blind, placebo-controlled trials. However, all subjects in these three trials received the proposed recommended dose (800 mg TID) of boceprevir in combination with PR. In these key trials, 547 subjects in the PR arms and 1548 subjects in the BOC/PR arms received at least one dose of any study medication. Data from Study P03659, a Phase 2 dose-finding trial, were not pooled, as the dose and duration of boceprevir differed from the proposed dose for the indicated use.

Supporting Data

The data from Phase 1 trials, Phase 2 trial (P03659) and other ongoing trials constitutes the supporting safety data and has been discussed in relevant sections of this review.

7.1.2 Categorization of Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA), version 13.0 was used for AE coding. Adverse events were summarized by MedDRA System Organ Class and Preferred Term. A treatment-emergent AE was defined as any AE that began on or after the treatment start date up to 30 days after the treatment stop date.

A serious adverse event (SAE) is any event that results in any one of the following outcomes: death; life-threatening AE; persistent or significant disability/incapacity; required in-patient hospitalization or prolonged hospitalization; congenital anomaly or birth defect; other important medical events that may jeopardize the subject and may require medical or surgical intervention to prevent one of the above outcomes.

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

Although Trial P03523, evaluated boceprevir in different treatment durations arms (28 or 48 weeks), with and without a 4-week lead-in with PR and lower RBV dose in one arm (400 to 1000 mg/day), it is considered appropriate for pooling with the other 2 Phase 3 trials given that study designs (other than duration of treatment) were similar, many characteristics of the patient populations were similar, the boceprevir dose evaluated were the same, most AEs manifest within the first 24-28 weeks of treatment, and available data suggest safety profiles are similar across treatment-naïve and previous

treatment failure subjects. However, when evaluating the hematology parameters (hemoglobin, neutrophils count and platelet counts), only the data from two phase 3 trials was pooled to exclude any effect due to variations in treatment durations and regimens and lower ribavirin dose used in part 2 of the Study P03523.

7.2 Adequacy of Safety Assessments

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

A total of 2098 subjects with chronic hepatitis C were exposed to at least one dose of boceprevir in the unblinded phase 2/3 studies (P03523, P05216, P05101, P03659, P05514 and P06086). In these studies, the total dose of boceprevir ranged from 300 mg up to 2400 mg. Most of the subjects (1900/2098, 91%) received 2400 mg boceprevir daily as 800 mg TID, the proposed dose for marketing approval. Sixty-six percent of subjects (1251/1900) who received boceprevir 800 mg TID were treated for >24 weeks. In the pooled safety data, 370 subjects received at least 44 weeks of boceprevir.

A total of 547 subjects in the PR arms and 1548 subjects in the BOC/PR arms of the pooled studies received at least one dose of any study medication (BOC/PR total excludes 36 PR subjects in Study P03523 who were allowed to crossover to BOC/PR because of treatment failure). In the 1541 subjects who received at least one dose of boceprevir in the key studies, the total exposure to boceprevir was 839.7 person years. Actual treatment durations ranged from one to 362 days (median exposure 201 days in the BOC/PR arms), including any PR lead-in phase.

In Study P05101 (previous treatment-failure subjects), exposure to PR control was much less than exposure to BOC/PR. The median treatment duration in the PR control arm was 104 days compared to 253 days in the BOC/PR arm. In Study P05216 (treatment-naïve subjects), however, the difference in the treatment exposure was minimal. The median treatment duration was 216 days in PR control arm vs. 197 days in BOC/PR arm. The Applicant noted that this difference between study populations may be explained by the earlier virologic futility rule and the stopping rule in previous treatment failures compared with treatment-naïve subjects, thereby limiting exposure among PR-treated subjects in previous treatment failures.

Due to the virologic futility rules, the percentage of the treatment-naïve subjects receiving treatment, decreased from 85% at TW 24 to 66% TW 28 in the PR control arms, and from 80% at TW 24 to 73% at TW 28 in the BOC/PR arm; while in Study P05101, the percentage of subjects decreased from 94% at TW 12 to 55% at TW 16 in the PR control arms, and from 95% at TW 12 to 87% at TW 16 in the BOC/PR arm (Table 26).

Table 26: Distribution of Treatment Duration in the Key Studies: Interval From Beginning to End of Treatment

Treatment Duration ^b	Number (%) of Subjects					
	Treatment Naïve P03523/P05216		PEG/R Treatment Failure P05101		All Subjects	
	PR ^a n=467	BOC/PR n=1225	PR n=80	BOC/PR n=323	PR ^a n=547	BOC/PR n=1548
Received Any Treatment	467 (100)	1225 (100)	80 (100)	323 (100)	547 (100)	1548 (100)
TW 2	467 (100)	1225 (100)	80 (100)	323 (100)	547 (100)	1548 (100)
TW 4 ^c	449 (96)	1189 (97)	79 (99)	318 (98)	528 (97)	1507 (97)
TW 6	446 (96)	1164 (95)	78 (98)	315 (98)	524 (96)	1479 (96)
TW 8	441 (94)	1140 (93)	77 (96)	312 (97)	518 (95)	1452 (94)
TW 10	436 (93)	1125 (92)	75 (94)	311 (96)	511 (93)	1436 (93)
TW 12	433 (93)	1108 (90)	75 (94)	307 (95)	508 (93)	1415 (91)
TW 16	423 (91)	1067 (87)	44 (55)	280 (87)	467 (85)	1347 (87)
TW 20	411 (88)	1019 (83)	26 (33)	243 (75)	437 (80)	1262 (82)
TW 24	399 (85)	974 (80)	25 (31)	238 (74)	424 (78)	1212 (78)
TW 28	306 (66)	897 (73)	23 (29)	231 (72)	329 (60)	1128 (73)
TW 30	242 (52)	528 (43)	23 (29)	229 (71)	265 (48)	757 (49)
TW 36	227 (49)	498 (41)	23 (29)	224 (69)	250 (46)	722 (47)
TW 42	219 (47)	482 (39)	23 (29)	148 (46)	242 (44)	630 (41)
TW 48	214 (46)	467 (38)	23 (29)	140 (43)	237 (43)	607 (39)

BOC=boceprevir 800 mg PO TID; P=peginterferon alfa-2b; PEG=peginterferon alfa; PR=peginterferon alfa-2b+ribavirin; QW=once weekly; R=ribavirin; SD=standard deviation; TW=treatment week.

^a 36 subjects in Study P03523 crossed over from Arm 1 (PR) to BOC/PR.

^b Duration is based on treatment begin date and treatment end date and does not take into account possible dosing interruptions and subject noncompliance. Each week in the table represents an interval of days.

^c All treatment arms in P05101 and P05216, and 3 of 7 arms in P03523 included a 4-week PR lead-in (Arms 2, 4, 6, and 7 in P03523 did not have PR lead-in).

Source: Adapted from Applicant's Table Integrated Summary of Safety

The three key studies (P03523, P05216, and P05101) were conducted mainly in the US, Canada, and Europe. Demographics and baseline disease characteristics were well balanced across treatment groups in the pooled safety population. The majority of subjects were males (61%) and the study population was predominately white (82%). The proportion of Black/African American subjects was 15%. The median age was 50 years (range: 18 to 76 years), with only 3% of the subjects 65 years or older. Majority of subjects (65%) were ≥ 75 kg in weight. The cohort had a mean viral load of $6.5 \log_{10}$ IU/L with a majority of subjects (93%) having a pretreatment HCV RNA ($\geq 400,000$ IU/mL). Subjects with HCV genotype 1a were 63% (HCV subtype as determined by

(b) (4) assay based on sequencing of domain p329bp in the NS5B polymerase gene). Few subjects (8%) in the key trials had advanced liver fibrosis (Metavir F3-F4).

The subjects in Study P05101 (previous treatment failures) were slightly older, had increased body weight, and more subjects had advanced fibrosis/cirrhosis than in Studies P03523/P05216 (treatment-naïve), as expected of a chronic hepatitis C patient population.

Reviewer's comments:

Overall, an adequate number of subjects and duration of drug exposure was obtained for the patient population under study. However, there was an underrepresentation of Black/African American subjects and those with advanced fibrosis. These subgroups represent a harder to treat population with lower sustained virologic response rates.

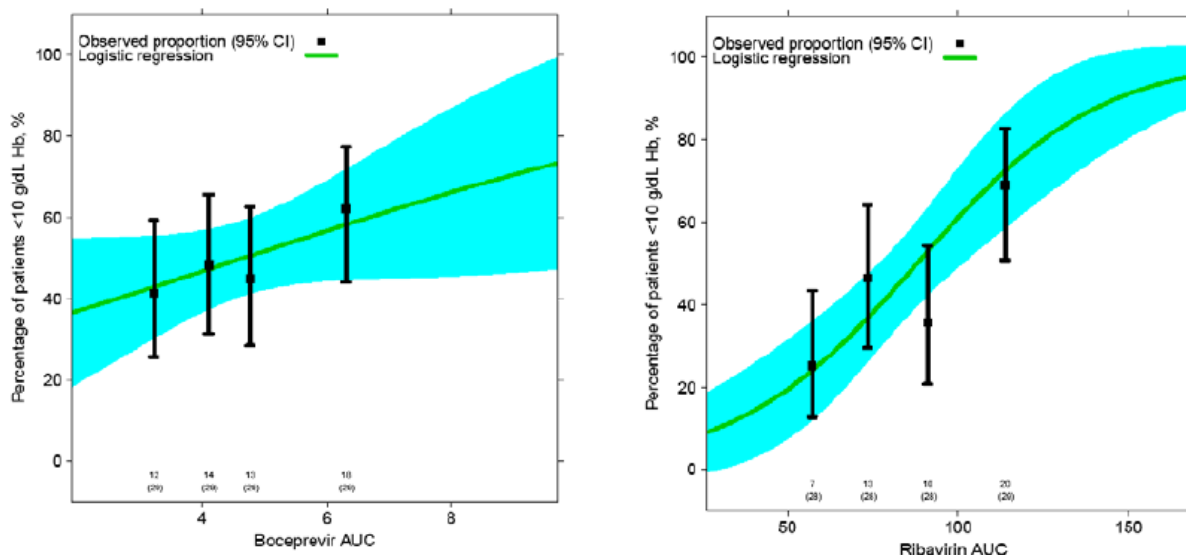
7.2.2 Explorations for Dose Response

A non-significant upward trend of increasing incidence of anemia (Hgb < 10 g/dL) was observed with increasing boceprevir AUC_T in the Phase 3 PK population (Figure 12, left). Boceprevir AUC_T was used as the PK parameter for the exposure-response safety analysis; however, similar relationships were identified between C_{trough} or C_{max} and incidence of anemia. The model predicted that the incidence of anemia for the median boceprevir exposure (4.3 µg·hr/mL) was 48%. Similarly, the predicted incidence of anemia at the lowest and highest exposure quartiles (3.2 and 6.3 µg·hr/mL) was 43% and 58%, respectively. Higher doses of boceprevir are anticipated to further increase the incidence of anemia without an expected benefit in efficacy, as described below.

A significant relationship between incidence of anemia and ribavirin AUC_T was observed in the Phase 3 PK population receiving triple therapy (n=113; $p < 0.0001$) (Figure 12, right). This finding is not unexpected, given ribavirin's known hematological effects, with an observed incidence rate of ~30% in the standard of care (SOC) population. Indeed, a similar exposure-response relationship is observed if the analysis is performed for subjects randomized to SOC (n=51; $p = 0.001$). The relationships between ribavirin exposure and efficacy and ribavirin exposure and safety may explain, in part, why higher SVR rates were observed in subjects who develop anemia.

Given the steeper exposure-response safety relationship between ribavirin exposure and incidence of anemia compared to boceprevir exposure, it would be appropriate to dose reduce ribavirin as a strategy for managing anemia with no accompanying dose reduction for boceprevir.

Figure 12: Percentage of Subjects with Anemia from P05101 and P05216 Versus Boceprevir (left) or Ribavirin Steady-State AUC (right).*



*Observations were binned as quartiles and plotted at the median quartile value. The total number of subjects with hemoglobin <10 g/dL for each quartile and total number of subjects per quartile bin (in parentheses) are shown along the x-axis.
Source: FDA Pharmacometrics Reviewer

These data suggest that improvement in SVR rates in subjects who develop anemia compared to those who did not develop anemia during treatment may be related to higher ribavirin exposures.

7.2.3 Special Animal and/or In Vitro Testing

Appropriate preclinical testing was performed. Please refer to Section 4.3 and Dr. Christopher Ellis' review for details of the preclinical program.

7.2.4 Routine Clinical Testing

The routine clinical testing was performed at pre-specified regular intervals during the trials and was adequate. Safety assessments included, but were not limited to, the following; physical examinations, measurement of vital signs, and clinical laboratory tests. Additional testing was performed as indicated during the trials.

7.2.5 Metabolic, Clearance, and Interaction Workup

The metabolic, clearance, and interaction workup was adequate. Please refer to Section 4.4 and to Dr. Ruben Ayala's review for details. As noted in Section 7.5.5, the Applicant plans to conduct a clinical DDI study with another progestin-containing COC.

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

Due to the concern of rash and skin disorders in the clinical development program of telaprevir, another protease inhibitor in the same class, all MedDRA preferred terms containing the words “rash” or “eruption” were reviewed by the Applicant to characterize the occurrence of rash/skin eruption events. The MedDRA preferred terms included under rash/Skin Eruption adverse events are: rash, rash papular, rash maculo-papular, rash erythematous, rash macular, rash pruritic, rash generalized, exfoliative rash, toxic skin eruption.

Table 27: Adverse Events of Rash/Skin Eruption (Pooled Studies P03523, P05216, and P05101)

	Treatment -Naïve P03523/P05216		Treatment-Failure P05101		All Subjects	
	BOC/PR n=1225	PR n=467	BOC/PR n=323	PR n=80	BOC/PR n=1548	PR n=547
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Rash/Skin Eruption	410 (33)	142 (30)	80 (25)	8 (10)	490 (32)	150 (27)
Rash	211 (17)	90 (19)	51 (16)	5 (6)	262 (17)	95 (17)

Source: Integrated Datasets for P03523, P05216, and P05101

Overall, rash/skin eruption AEs were reported at somewhat higher frequency in the boceprevir-containing arms (32%) compared to the control arm (27%). However, rash was reported with similar frequency in both arms (17%). In study P05101, the incidence of rash events was higher in the BOC/PR arms (16%) compared to PR control (5%). This could partly be attributed to the difference in exposure between the two arms. However, as reported by the Applicant exposure-adjusted rates (incidence rate per 100 person years) of rash were also higher in BOC/PR arm (22.6) compared to the PR arm (11.0). Applicant further reports that incidence of rash was lower in the control group compared to historical controls. Discontinuations due to rash/skin eruption AEs were <1%; one subject in PR arm and 5 subjects in BOC/PR arm discontinued; all in treatment-naïve subjects. Six subjects in PR arm and 14 subjects in BOC/PR arm had dose modifications. Exfoliative rash was reported in total 3 subjects; 1 in PR and 2 in BOC/PR and was mild-moderate in severity. There were two cases of toxic skin eruption reported; one each in boceprevir-treated subject and one in control arm.

No cases of Stevens-Johnson syndrome/toxic epidermal necrolysis were reported. There were no life-threatening rash/skin eruption AEs reported. There was one case of serious adverse event reported which is described below.

Subject # 121/002021 (Study P05216)

One serious adverse event of erythematous rash was reported in a 62-year-old white male in the boceprevir-treated subject at approximately TW 24. At the same time the subject also experienced conjunctivitis and pruritis. No dose modification or discontinuation of treatment was needed. The subject received treatment with oral steroids. The rash was resolved approximately after 1 month while the subject continued on full-dose treatment with boceprevir up to TW 48. No recurrence of rash was reported.

7.3 Major Safety Results

7.3.1 Deaths

In the boceprevir clinical development program, there were 8 deaths reported in the completed trials, 4 deaths in the boceprevir-containing arms and 4 deaths in the PR control arm (Table 28).

Table 28: List of all Deaths in Completed boceprevir Trials

Subject ID	Age/Sex	Treatment Group	Cause of Death (MedDra Preferred Term)	Days to Death (Days post-treatment to Death)
Study P03523				
0024-000041	40/M	BOC/PR	Drug Toxicity <i>It was reported that subject died due to life-threatening drug toxicity (cocaine)</i>	127
Study P05101				
0102-012077	53/M	BOC/PR	Completed Suicide Committed suicide during the follow-up phase	463 (128)
Study P05216				
0072-000044	54/M	BOC/PR	Completed Suicide Wife informed that subject committed suicide.	97 (1)
0117-000115	43/M	BOC/PR	Cardiac Arrest Cardiac arrest while driving	480 (144)
0009-002212	54/M	PR	Cardio-Respiratory Arrest <i>Fatal cardiopulmonary arrest and cerebral edema. The exact cause of death unknown.</i>	95 (10)
0036-000290	43/M	PR	Completed Suicide <i>Life-threatening physical assault of housemate noted. Subject's death from a self-inflicted gunshot wound.</i>	57 (2)
0063-002048	67/F	PR	Death (Death by Accident) <i>Found death by her husband in the bath tub.</i>	408 (71)
0181-000276	48/M	PR	Death <i>According to daughter, the cause of death was drug overdose</i>	391 (58)

BOC=boceprevir 800 mg PO TID; PR=peginterferon alfa-2b+ribavirin;

Reviewer's comments:

The total number of deaths in these trials is small and the cause of death in each of these cases is consistent with what might be expected in this trial population receiving interferon therapy. Relapse of drug addiction and drug overdose have been reported in patients receiving interferon therapy. Of the AEs that resulted in death, six were considered by the investigators to be unlikely related to study drugs and two were possibly related to study drug (one suicide each in the PR and RGT arms of Study P05216).

7.3.2 Nonfatal Serious Adverse Events

A total of 164/1548 (11%) subjects in the BOC-containing arms and 43/547 (8%) subjects in the PR control arm had all-causality SAEs reported in the pooled studies. System Organ Classes (SOCs) in which there was numerical increase in SAEs in the boceprevir-containing arms relative to the PR control arm included: blood and lymphatic disorders; gastrointestinal disorders and psychiatric disorders.

Table 29: Serious Adverse Events in ≥ 0.2% of Subjects in Boceprevir/PR arms (Pooled Studies P03523, P05216, and P05101)

MedDRA Preferred Term	Treatment-Naive		Treatment-Failure		All Subjects	
	P03523/P05216		P05101			
	BOC/PR N=1225 n (%)	PR N=467 n (%)	BOC/PR N=323 n (%)	PR N=80 n (%)	BOC/PR N=1548 n (%)	PR N=547 n (%)
Anemia	9 (1)	1 (<1)	5 (2)	0	14 (0.9)	1 (0.2)
Suicidal ideation	7 (1)	2 (<1)	5 (2)	0	12 (0.8)	2 (0.4)
Chest pain	6 (<1)	0	3 (1)	1 (1)	9 (0.6)	1 (0.2)
Depression	4 (<1)	1 (<1)	4 (1)	0	8 (0.5)	1 (0.2)
Pyrexia	6 (<1)	2 (<1)	1 (<1)	0	7 (0.5)	2 (0.4)
Pneumonia	6 (<1)	1 (<1)	1 (<1)	0	7 (0.5)	1 (0.2)
Neutropenia	7 (1)	0	0	0	7 (0.5)	0
Syncope	5 (<1)	0	1 (<1)	0	6 (0.4)	0
Abdominal pain	3 (<1)	1 (<1)	2 (1)	0	5 (0.3)	1 (0.2)
Cellulitis	5 (<1)	1 (<1)	0	0	5 (0.3)	1 (0.2)
Gastroenteritis	5 (<1)	0	0	1 (<1)	5 (0.3)	1 (0.2)
Nausea	4 (<1)	1 (<1)	0	0	4 (0.3)	1 (0.2)
Dyspnea	2 (<1)	0	2 (1)	0	4 (0.3)	0
Homicidal ideation	2 (<1)	0	2 (1)	0	4 (0.3)	0
Intervertebral disc protrusion	2 (<1)	0	2 (1)	0	4 (0.3)	0
Pancreatitis*	4 (<1)	2 (<1)	2 (1)	0	6 (0.4)	2 (0.4)
Vomiting	3 (<1)	2 (<1)	0	0	3 (0.2)	2 (0.4)

Appendicitis	0	1 (<1)	3 (1)	0	3 (0.2)	1 (0.2)
Asthenia	2 (<1)	0	1 (<1)	0	3 (0.2)	0
Dehydration	2 (<1)	0	1 (<1)	0	3 (0.2)	0
Pulmonary embolism	3 (<1)	0	0	0	3 (0.2)	0
Thrombocytopenia	3 (<1)	0	0	0	3 (0.2)	0

* Also includes Preferred Terms of Acute Pancreatitis and Necrotizing Pancreatitis
BOC=boceprevir 800 mg PO TID; PR=peginterferon alfa-2b+ribavirin;
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects
Source: Integrated Datasets for P03523, P05216, and P05101

Some of the serious adverse events of special interest are anemia, neutropenia, thrombocytopenia, suicidal ideations, homicidal ideations, pancreatitis and pulmonary embolism. Selected clinical summaries of non fatal serious adverse events are provided under relevant sections (Section 7.3.4) based on their clinical significance. The clinical descriptions of the other adverse events were consistent with those of the adverse events previously reported in the literature and described in the package inserts for alpha interferons.

As specified in the protocols of the key studies, the modified WHO grading system was to be used for grading the severity of AEs. WHO Grade 4 AEs (excluding laboratory abnormalities without clinical manifestations), were considered life-threatening AEs. These life-threatening AEs were also considered serious AEs. For AEs not covered by the modified WHO grading system, the protocol-specified definition for a life-threatening AE was “one that places the subject, in the view of the initial reporter, at immediate risk of death from the AE as it occurs.”

Life-threatening treatment-emergent AEs were reported in 7 subjects (7/547, 1%) in the PR arms and 22 subjects (22/1548, 1%) in the BOC/PR arms of the key studies. Events reported in more than one subject in either arm were suicidal ideation (3/1548, <1%, BOC/PR) and anemia (3/1548, <1%, BOC/PR).

7.3.3 Dropouts and/or Discontinuations

Discontinuations in the two pivotal trials (P05216 and P05101) were discussed in Section 6.1.3.

Dose modification (reduction or interruption) could be used for the management of AEs. Guidelines for dose modification or discontinuation of treatment for abnormalities in selected hematologic and biochemical parameters were provided in the protocols. The peginterferon alfa-2b (PEG2b) dose was to be modified for neutropenia, leukopenia, thrombocytopenia, and depression. The recommended dose reduction criteria for PEG2b and RBV for selected hematologic and biochemical parameters are shown in Table 30.

Table 30: Recommended Dose Reduction (PEG2b and RBV) for selected Hematologic and Biochemical Parameters (P03523, P05216, and P05101)

Parameter	Dose Reduction	Discontinuation or Interruption ^a of PEG2b/RBV Treatment
Hemoglobin	<10 g/dL (RBV)	<8.5 g/dL (RBV)
White Blood Cell Count	<1.5 x 10 ⁹ /L (PEG2b)	<1.0 x 10 ⁹ /L (PEG2b)
Neutrophil Count	<0.75 x 10 ⁹ /L (PEG2b)	<0.5 x 10 ⁹ /L (PEG2b)
Platelet Count	<50 x 10 ⁹ /L (PEG2b)	<25 x 10 ⁹ /L (PEG2b)
Creatinine	--	>2.0 mg/dL (>176.8 µmol/L)
ALT/AST	--	2 x baseline and >10 x ULN

ULN = Upper limit of normal.

a: Individual study drug regimen interruptions were permissible based on the results of abnormal laboratory parameters. Treatment interruptions were not to exceed 2 consecutive weeks in duration.
Source Data: Applicant's Integrated Summary of Safety

Per the key study protocols, treatment interruptions were not to exceed 2 consecutive weeks in duration. If AEs could not be managed with dose modification, then study drug discontinuation was to occur. In addition, recommended clinical management and dose modification/study drug discontinuation were prospectively defined for subjects who developed depression.

In the pooled analysis there was no difference in the proportion of subjects who experienced AEs resulting in study drug discontinuation; 12% in the PR arm vs. 13% in the BOC/PR arms (Table 31). In Study P05101 there were fewer discontinuations due to AEs in the PR control arm (3%) compared to the BOC/PR arms (10%).

Table 31: Adverse Events leading to Study Drug Discontinuations in ≥1% of Subjects (Pooled Studies P03523, P05216, and P05101)

MedDRA Preferred Term	Treatment-Naive		Treatment-Failure		All Subjects	
	P03523/P05216		P05101			
	BOC/PR N=1225	PR N=467	BOC/PR N=323	PR N=80	BOC/PR N=1548	PR N=547
Any Adverse Event	172 (14)	65 (14)	33 (10)	2 (3)	205 (13)	67 (12)
Anemia	18 (1)	4 (1)	5 (2)	0	23 (1)	4 (1)
Neutropenia	11 (1)	0	0	0	11 (1)	0
Esophageal pain	11 (1)	2 (<1)	3 (1)	0	14 (1)	2 (<1)
Vomiting	8 (1)	0	1 (<1)	0	9 (1)	0
Asthenia	6 (<1)	4 (1)	3 (1)	0	9 (1)	4 (1)
Chills	1 (<1)	3 (1)	0	0	1 (<1)	3 (1)
Fatigue	29 (2)	14 (3)	3 (1)	0	32 (2)	14 (3)

Influenza Like Illness	2 (<1)	3 (1)	1 (<1)	0	3 (<1)	3 (<1)
Irritability	9 (1)	1 (<1)	2 (1)	0	11 (1)	1 (<1)
Decreased Appetite	1 (<1)	1 (<1)	2 (1)	0	3 (<1)	1 (<1)
Disturbance in attention	1 (<1)	0	2 (1)	0	3 (<1)	0
Headache	6 (<1)	6 (1)	0	0	6 (<1)	6 (1)
Anxiety	5 (<1)	4 (1)	1 (<1)	0	6 (<1)	4 (1)
Depression	14 (1)	4 (1)	3 (1)	0	17 (1)	4 (1)
Homicidal Ideation	2 (<1)	0	2 (1)	0	4 (<1)	0
Suicidal Ideation	7 (1)	2 (<1)	3 (1)	0	10 (1)	2 (<1)
Dyspnea	2 (<1)	2 (<1)	2 (1)	0	4 (<1)	4 (1)

Source: Integrated Datasets for P03523, P05216, and P05101 and Applicant's Clinical Summary

The adverse events resulting in discontinuation, including anemia, asthenia, fatigue, nausea, depression, and suicidal ideation are similar to those seen with standard of care therapy with pegylated interferon and ribavirin. Only anemia and fatigue were reported as events that led to discontinuation in >1% of subjects in any arm.

Ten subjects in BOC/PR arms (10/1548, 1%) discontinued due to suicidal ideations compared to two subjects in the PR control arm (2/547, <1%). Four subjects in BOC/PR arms (4/1548, <1%) discontinued due to homicidal ideations compared to none of the subjects in the PR control arm (0%). Nine subjects in BOC/PR arms (9/1548, 1%) discontinued due to vomiting compared to none in the PR control arm (0%).

7.3.4 Significant Adverse Events

All AEs were to be graded by the study sites using the modified WHO grading system for grading the severity of AEs with the exception of laboratory values. A physician may use his/her clinical judgment in assigning severity to abnormal laboratory AEs using clinical criteria. For AEs not covered by this grading system, the following definitions were to be used:

- Mild: awareness of sign, symptom, or event, but easily tolerated;
- Moderate: discomfort enough to cause interference with usual activity and may warrant intervention;
- Severe: incapacitating with inability to do usual activities or significantly affects clinical status, and warrants intervention;
- Life-Threatening: immediate risk of death.

Adverse Events of Special Interest

In addition to the evaluation of adverse events due to concerns/safety signals observed with the use of boceprevir in the clinical development program, other potential toxicities for boceprevir were evaluated based on organ systems for which currently approved products for HCV treatment carry Warnings and Precautions. Adverse events in organ

systems with Warnings and Precautions in current interferon and ribavirin product labels were reported and appeared to be numerically higher in frequency in the boceprevir-containing arms.

Further, events in the Skin and Subcutaneous Structures organ systems were evaluated because of concerns raised in the clinical development program of telaprevir which belongs to the same class.

However, the information pertaining to the safety population other than the pooled trials should be reviewed with caution as majority of these trials used different dosages and durations of study drugs as compared to the proposed dosing regimen and treatment duration.

Bone Marrow Suppression

Interferons suppress bone marrow function and affect white blood cell, platelet and red cell production. As a result subjects treated with interferons can experience pronounced cytopenias. The addition of RBV, which causes hemolytic anemia, can result in profound decreases in hemoglobin levels that can contribute to fatigue and possibly worsening of cardiac status. These decreases in hemoglobin levels, neutrophils count, and platelet levels are exacerbated when combined with boceprevir, likely through its bone marrow suppressive effects.

Overall, there was a higher incidence of Blood and Lymphatic disorders AEs reported in the boceprevir treated subjects than in the PR control arm; this difference was driven mainly by a significantly higher incidence of anemia in the BOC/PR arms. Higher incidences of neutropenia and thrombocytopenia were also seen in the boceprevir treated subjects compared to controls. This section also discusses the hematology laboratory values in two Phase 3 Trials.

Anemia

The most important safety concern during the clinical development of boceprevir has been the decrease in hemoglobin above and beyond that observed with pegylated interferon and ribavirin alone. In the key clinical trials, treatment with boceprevir in combination with pegylated interferon/ribavirin was associated with decline in hemoglobin in proportionally more subjects, and to a greater magnitude than that observed with pegylated interferon/ribavirin alone. The available data suggest that anemia related to boceprevir is not due to a hemolytic process but may be related to bone marrow suppression.

The Applicant notes that use of boceprevir in these trials resulted in a 1 g/dL decrease in hemoglobin over what is generally observed with pegylated interferon and ribavirin alone. However, the exact magnitude of the hemoglobin decrease attributable to

boceprevir cannot be determined from these trials due to confounding by use of erythropoietin and/or ribavirin dose reduction or both. Additionally, use of baseline factors to predict risk for development of anemia in these trials was confounded by the criteria used to define anemia and the recommended management algorithms.

Please refer to Clinical Review by Dr. Charles Cooper specifically addressing the safety concerns related to anemia. Some of the pertinent findings are included here.

The following table (Table 32) shows the FDA analysis of anemia reported as an adverse event in the two Phase 3 trials (P05216 and P05101). These analyses do not include data from the Phase 2 trial (P03523) for reasons described earlier in Section 7.1. Anemia was reported as an adverse event (regardless of causality) in a higher proportion of subjects in the boceprevir-containing arms (52%) than in the PR control arms (30%) overall. Similarly, anemia was reported as serious AE in 1% of boceprevir-treated subjects and none of the PR treated subjects in Phase 3 trials. No deaths were attributed to anemia in these trials. Grade 3 (severe) or grade 4 (life-threatening) anemia was reported in a higher proportion of BOC/PR arms (4%) than in PR controls (2%). Likewise, anemia resulted in more frequent dose reduction or interruption (of ribavirin, boceprevir or pegylated interferon) in boceprevir treatment arms than PR control arms across the Phase 3 trials.

Table 32: Adverse Events: Anemia in Phase 3 trials (P05216 and P05101)

Anemia* Adverse Events	P05216 and P05101 BOC/PR arms N=1057	P05216 and P05101 PR arms N=443
Anemia as AE	548 (52)	131 (30)
Anemia as serious AE	12 (1)	0
Anemia as Grade 3 or 4 AE	45 (4)	7 (2)
Anemia resulting in Study Drug discontinuation	19 (2)	4 (1)
Anemia resulting in dose reduction	264 (25)	58 (13)
Anemia resulting in dose interruption*	31 (3)	9 (2)

*MedDRA Preferred Terms including anemia, decreased hemoglobin, decreased hematocrit, hemolytic anemia

Source: Dr. Charles Cooper's Analyses

The following Table 33 shows the analysis of the number and proportion of subjects who reached hemoglobin nadirs of ≤ 10 g/dL and ≤ 8.5 g/dL in the Phase 3 Trials (P05216, and P05101). Hemoglobin values of < 10 and < 8.5 are those recommended in the approved ribavirin package inserts for ribavirin dose-reduction and discontinuation, respectively. A higher proportion of boceprevir/PR recipients than subjects who received PR alone experienced hemoglobin nadirs of ≤ 10 g/dL and ≤ 8.5 g/dL in the Phase 3 trials. As discussed before, because of confounding and potential bias due to individual investigator's management of anemia, the hemoglobin values

shown below probably do not reflect the magnitude of hemoglobin decline that could potentially occur with boceprevir or pegylated interferon and ribavirin treatment in the absence of such interventions.

Table 33: Hemoglobin Nadir during Phase 3 Trials (P05216 and P5101)

Lowest Hemoglobin Value	All Subjects Boceprevir/PR *N=1048 n/N (%)	All Subjects PR *N=434 n/N (%)
Hgb ≤10 g/dL	547 (52)	141 (32)
Hgb ≤8.5 g/dL	92 (9)	16 (4)

*N was based on number of subjects with post-baseline hemoglobin measurement

Source: Dr. Charles Cooper's Analyses

While adverse events associated with anemia were reported in the boceprevir-containing treatment arms as well as in the pegylated interferon/ribavirin control arms, some AEs were reported in a higher proportion of boceprevir recipients than controls. Of the most common adverse events possibly associated with anemia, dyspnea/exertional dyspnea occurred more often in boceprevir/PR-treated subjects than in PR-treated controls, 443/1548 (29%) vs. 131/547 (24%). Dizziness also occurred in a higher proportion of boceprevir/PR-treated subjects than PR controls, 287/1548 (19%) vs. 86/547 (16%), respectively; and syncope was reported more often in boceprevir/PR-treated subjects, 29/1548 (2%) vs. 5/547 (1%) in PR controls. Other adverse events of interest which may be associated with severe anemia, including myocardial infarction and ischemia were reported too infrequently in these trials to make a meaningful comparison (4 events in boceprevir-treated subjects vs. 2 events in PR-treated subjects).

Please refer to Clinical Review by Dr. Cooper for selected case summaries of adverse events of anemia.

Neutropenia

Neutropenia was more common among subjects receiving boceprevir plus PR than in those receiving PR alone. Neutropenia was reported as an adverse event in 352/1548 (23%) subjects in boceprevir containing arms versus 101/547 (18%) subjects in PR arm, as a serious AE in 7 subjects (0.5%) in boceprevir containing arms compared to none (0%) in control arm, as a severe (Grade 3 and 4) AE in 125 subjects (8%) in boceprevir containing arms compared to 34 subjects (6%) in control arm. Neutropenia resulted in study drug discontinuation in 11/1548 (1%) boceprevir-treated and in 2/547 (<1%) of the PR-treated subjects.

G-CSF use was allowed in the key phase 2 and 3 trials, and was used in 9.3% boceprevir-treated, and 6.2% PR-treated subjects overall in the pooled trial data.

Serious and severe infections (bacterial, viral, or fungal), some fatal, have been reported during treatment with alpha interferons. Overall, the events of AEs in the System Organ Class of Infections and Infestations were reported to be similar in boceprevir-treated subjects (18%) compared to the PR alone (17%). Forty-two (42) subjects in the key studies had any infection within 14 days after Grade 3 or 4 neutropenia.

Two cases of life-threatening neutropenia/decreased neutrophil count were reported, both in boceprevir treated subjects (Study P03523). These cases are described briefly below:

Subject # 22/000057

This subject was hospitalized with neutropenia and multi-organ system failure at TW 10. ANC was $0.78 \times 10^9/L$ nine days prior to hospitalization. Multi-organ system failure was considered to be secondary to sepsis, presented with renal failure, respiratory failure, and partial bowel obstruction. No causative organism was identified. All study drugs were discontinued. The subject was treated empirically with broad-spectrum antibiotics and an antifungal agent for neutropenic fever.

Subject # 38/001666

This subject was hospitalized at TW 2 with a fever of 104.5°F and decreased neutrophils count (ANC= $0.45 \times 10^9/L$). All study drugs were discontinued and subject received treatment with G-CSF. Fever was resolved next day. No infectious source was identified.

It was reported that neutropenia resolved upon discontinuation of all study drugs in both of the above cases.

Three subjects (all in boceprevir containing arms) experienced severe infections (including 1 life-threatening) that occurred within the two weeks of Grades 3 and 4 neutropenia. These adverse events were epiglottitis, upper respiratory infection, and salmonella gastroenteritis/diarrhea. Brief summaries are included below:

Subject # 93/001868 (Study P05216)

The subject was hospitalized with epiglottitis (life-threatening), neutropenia, and acute renal failure at TW 12. ANC was $0.66 \times 10^9/L$ at TW 10. The subject received treatment with dexamethasone, norepinephrine, and piperacillin/tazobactam, followed by moxifloxacin. The subject also required a tracheostomy. All study drugs were discontinued.

Subject # 128/003763 (Study P05216)

This subject developed nausea, vomiting, and diarrhea at TW 10 (ANC=0.57 x10⁹/L at TW 8; ANC= 0.70 x10⁹/L at TW 10) and was diagnosed with severe salmonella gastroenteritis. Study drug was temporarily interrupted and was subject received treatment with ciprofloxacin and metronidazole as outpatient.

Subject # 90/001941 (Study P05216)

Fever and a severe upper respiratory tract infection was reported in this subject at TW 10 (ANC=0.31 x10⁹/L at TW 8). All study drugs were discontinued; subject was hospitalized and received treatment first with vancomycin and cefepime, then meropenem, followed by amoxicillin/clavulanic acid.

The following table (Table 34) shows the lowest absolute neutrophil count (ANC) reported during the treatment in the Phase 3 trials. A higher proportion of boceprevir recipients experienced Grade 3 and 4 decrease in neutrophil counts than subjects who received PR alone.

Table 34: Lowest Absolute Neutrophil Count (ANC) on Treatment in Phase 3 Trials (P05216 and P05101)

Lowest ANC on Treatment	Boceprevir–PR (P05216 and P05101) N=1050* n(%)	PR (P05216 and P05101) N=438 n(%)
<0.5 to <0.75 x 10 ⁹ /L (Grade 3)	239 (23%)	57 (13%)
<0.5 x 10 ⁹ /L (Grade 4)	71 (7%)	19 (4%)

*N was based on number of subjects with post-baseline neutrophil value measurement.

Source: Integrated Datasets for P05216, and P05101

Thrombocytopenia

Thrombocytopenia was more common among subjects receiving boceprevir plus PR than in those receiving PR alone. Thrombocytopenia was reported as an adverse event in 68/1548 (4%) subjects in boceprevir containing arms versus 10/547 (2%) subjects in PR arm, as a serious AE in 3 subjects (0.2%) in boceprevir containing arms compared to none (0%) in PR arm, as a severe (Grade 3 and 4) AE in 18 subjects (1%) in boceprevir containing arms compared to 3 subjects (1%) in PR arm. Thrombocytopenia resulted in study drug discontinuation in 5/1548 (<1%) boceprevir-treated and in none of the PR-treated subjects.

Subject# 021/002043 (Study P05216)

An SAE of thrombocytopenia was reported in a 52-year-old white female with no documented relevant medical history who was randomized into study Arm 3

(BOC/PR48). Baseline hemoglobin (Hgb), neutrophils, and platelets (PLT) were 14.2 g/dL, $2.98 \times 10^9/L$, and $238 \times 10^9/L$, respectively. After 10 days, the subject developed mild fatigue. Boceprevir was added to the regimen at treatment week TW 4; Hgb was 8.5 g/dL and erythropoietin was initiated. At TW 8 neutropenia was noted (neutrophil = $0.95 \times 10^9/L$) and granulocyte colony stimulating factor (G-CSF) was initiated. After a week, the anemia worsened (Hgb = 8.0 g/dL) and thrombocytopenia was noted (PLT = $41 \times 10^9/L$); PEG2b dose was reduced while RBV dose was interrupted then reduced upon restarting. Once Hgb was 10.7 g/dL and EPO was discontinued; neutrophils = $7.98 \times 10^9/L$ and PLT remained at $41 \times 10^9/L$. The subject showed temporary improvement in Hgb value (11.0 g/dL) and neutrophil count ($1.12 \times 10^9/L$) on (b) (6). Hgb again reduced to 9.0 g/dL and EPO was restarted. She was discontinued from the study due to fatigue. Within the same week, anemia and thrombocytopenia worsened (Hgb = 6.3 g/dL, PLT = $9 \times 10^9/L$) that resulted in hospitalization; EPO and G-CSF were discontinued. She was transfused with four units of packed red blood cells and ten units of platelets. After 2 weeks, she received additional six units of platelets during which the subject developed fever ($103^\circ F$) and was diagnosed with transfusion reaction and was hospitalized. The subject completed the follow-up period and events were considered resolved. The last reported Hgb (12.6 g/dL), neutrophil ($1.71 \times 10^9/L$), and PLT ($139 \times 10^9/L$) values were at FW 24. The Investigator assessed the events of fatigue, pancytopenia, thrombocytopenia and anemia as probably related to study drugs. The Investigator assessed the event of transfusion reaction as unlikely related to study drugs.

Subject # 76/5007 (Study P03523)

This subject with Grade 3 thrombocytopenia and pre-existing portal hypertension and portal gastropathy had significant bleeding (hematemesis) during Follow-up Week 4 (FW 4).

Three subjects in boceprevir-containing arms had Grade 4 thrombocytopenia (platelet values $< 25 \times 10^9/L$) compared with none of the subjects in the PR control arms. All three subjects experienced epistaxis which was considered mild and did not require intervention.

As shown in the following table 35, a higher proportion of subjects in boceprevir-containing arms than the PR arms experienced Grade 3 or 4 decrease in platelet counts in the two Phase 3 trials.

Table 35: Lowest Absolute Platelet Count on Treatment in Phase 3 Trials (P05216 and P05101)

Lowest absolute Platelet count on Treatment	Boceprevir–PR (P05216 and P05101) N=1050 n(%)	PR (P05216 and P05101) N=438 n(%)
25 to <50 x 10 ⁹ /L (Grade 3)	38 (4%)	5 (1%)
<25 x 10 ⁹ /L (Grade 4)	2 (<1%)	0 (0%)

*N was based on number of subjects with post-baseline platelet value measurement
Source: Integrated Datasets for P05216, and P05101

Pancytopenia

Based on WHO grades, there was one subject with Grade 3 anemia, Grade 3 neutropenia and Grade 3 thrombocytopenia and one subject with Grade 4 anemia, Grade 4 neutropenia and Grade 4 thrombocytopenia in the pooled data (P03523, P05216 and P05101). Both subjects were in BOC/PR arm. One subject discontinued due to pancytopenia.

The number of subjects with pancytopenia using the hemoglobin cut-off value of 8.5 to <10 g/dL and <8.5 g/dL for worst hemoglobin grades and WHO Grade 3 and 4 for neutrophils and platelet values are shown in the Table 36.

Table 36: Incidence of Pancytopenia using worst Hemoglobin values and WHO Grades (3 and 4) for Neutrophil count and Platelet values

Worst Grade	BOC/PR N=1548 n (%)	PR N=547 n (%)
Hgb 8.5 to <10 g/dL + Grade 3 Neut + Grade 3 Plt	7 (<1)	1 (<1)
Hgb 8.5 to <10 g/dL + Grade 4 Neut + Grade 3 Plt	8 (1)	0
Hgb 8.5 to <10 g/dL + Grade 3 Neut + Grade 4 Plt	0	0
Hgb 8.5 to <10 g/dL + Grade 4 Neut + Grade 4 Plt	0	0
Hgb <8.5 + Grade 3 Neut + Grade 3 Plt	3 (<1)	0
Hgb <8.5 + Grade 4 Neut + Grade 3 Plt	5 (<1)	0
Hgb <8.5 + Grade 3 Neut + Grade 4 Plt	1 (<1)	0

Hgb <8.5 + Grade 4 Neut + Grade 4 Plt	1 (<1)	0
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Hgb – Hemoglobin; Neut – Neutrophil count; Plt – Platelet count

Source: Applicant's submission dated March 17, 2011 in response to FDA Information Request

Overall, the number of subjects with severe pancytopenia was low and most of the subjects were in boceprevir containing arms.

Neuropsychiatric Events

The alpha interferons are known to cause life-threatening or fatal neuropsychiatric events, including suicide, suicidal and homicidal ideation, depression, relapse of drug addiction/overdose, aggressive behavior sometimes directed towards others, psychoses, hallucinations, bipolar disorders, and mania. Additionally, treatment with interferon can lead to depression and other psychiatric symptoms.

The overall frequency of treatment-emergent psychiatric events was comparable across treatment groups in the pooled data analyzed for safety, ranging from 54% in boceprevir treated subjects to 52% in PR controls. Discontinuation of study drugs due to psychiatric AEs was similar in boceprevir-treated subjects compared to controls. Adverse events such as anxiety (13% vs. 12%), depression (20% vs. 21%) and insomnia (33% vs. 33%) were noted in similar proportion of boceprevir-treated subjects compared to subjects treated with PR alone, respectively.

A total of 24 (2%) subjects in the boceprevir-containing arms reported serious psychiatric AEs compared to five subjects (1%) in the PR control arm. Three subjects (1 in PR arm and 2 in the BOC/PR arm) completed suicide. An small but increased number of subjects reported psychiatric symptoms of suicidal and homicidal ideation in boceprevir-containing arms as compared to control. Suicidal ideations were reported in 12/1548 (1%) boceprevir-treated subjects compared to 2/547 (<1%) subjects in control arm; homicidal ideations were reported in 4/1548 boceprevir-treated subjects compared to none of the subjects in control arm. This is of concern due to its potential life-threatening implications.

A total of 657 boceprevir-treated subjects and 219 PR-treated subjects were reported to be on antidepressant therapy during treatment in the pooled studies. Subjects receiving antidepressants had a higher incidence of psychiatric events in both the boceprevir containing arms and PR control arms compared with those who were not on antidepressants; however, no difference in AEs was observed between the boceprevir containing arms and PR control arms in these two group of subjects, suggesting that the use of antidepressant therapy may not have an effect on the adverse event profile associated with boceprevir use. Psychiatric events with at least 5% difference in incidence between the boceprevir/PR arm with antidepressant therapy use and no antidepressant therapy use are shown below in Table 37.

Table 37: Psychiatric Adverse Events in Subjects with Antidepressant therapy compared to No Antidepressant therapy with at least >5% difference (Pooled Studies P03523, P05216, and P05101)

MedDRA Preferred Term	Boceprevir/PR Arms (P03523, P05216, and P05101)		PR Control Arms (P03523, P05216, and P05101)	
	Antidepressant Therapy Use N=657 n(%)	No Antidepressant Therapy Use N=891 n(%)	Antidepressant Therapy Use N=219 n(%)	No Antidepressant Therapy Use N=328 n(%)
Anxiety	144 (22)	60 (7)	46 (21)	20 (6)
Depression	247 (38)	60 (7)	87 (40)	26 (8)
Insomnia	286 (44)	226 (25)	88 (40)	89 (27)

Boceprevir 800 mg PO TID; PR=peginterferon alfa-2b+ribavirin;
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects
Source: Applicant's Integrated Summary of Safety 8.6.2.2.19

Proportion of subjects who were not on any psychiatric medication at baseline but started psychiatric medication after initiation of boceprevir were similar; 21%-23% in boceprevir-treated subjects compared to 24% in PR control arm (Table 38). Similarly, there were no differences noted in proportion of subjects who had psychiatric medication added to baseline psychiatric medication after initiation of boceprevir.

Table 38: Summary of Baseline and Concomitant Use of Psychiatric Medication (P03523, P05216, P05101)

	RGT BOC/PR 28/48 36/48 wk n=740	BOC/PR 48 wk * n=749	PR † n=547
Subjects with Psych Med at Baseline	131 (18)	122 (16)	77 (14)
Subjects with Psych Med added to Baseline Psych Med after Initiation of Boceprevir	18 (2)	12 (2)	15 (3)
Subjects switching from Baseline Psych Med to different psych Med after Initiation of Boceprevir	10 (1)	14 (2)	5 (1)
Subjects without Psych Med at baseline started psych Med after Initiation of Boceprevir	154 (21)	169 (23)	129 (24)

Medications starting during PR Lead-in in BOC/PR group are not considered.

* P05101/P05216 Arm 2 and P03523 Arms 2 and 3 are included in this group.

† P05101/P05216 Arm 3 and P03523 Arms 4, 5 and 6 are included in this group. P03523 Arm 7 is not included in this table.

BOC=boceprevir 800 mg PO TID; PR=peginterferon alfa-2b+ribavirin;

Source: Applicant's submission dated March 21, 2011 in response to FDA Information Request

In Study P05101 in previous treatment-failure subjects, the proportion of subjects with psychiatric AEs, serious psychiatric AEs, and events leading to study drug discontinuations was higher in the BOC/PR arms compared with the control arm. However, this could partly be due to the difference in exposure between the two arms.

Reviewer's comment:

Life-threatening or fatal neuropsychiatric events, including suicide, suicidal and homicidal ideation, and depression have been reported in patients with and without a previous psychiatric disorder with PegIntron therapy. No novel psychiatric events were reported. Additionally, these data are confounded to some degree due to the shorter duration of therapy in the PR control arm than in the boceprevir treatment arms in Study P05101, as subjects were discontinued at Week 12 for futility. Based on the currently available data, it is difficult to make any meaningful clinical conclusions from this observation. However, these events should be monitored post-marketing to assess for any emerging safety signal.

Cardiovascular Adverse Events

Cardiovascular events including angina pectoris, and myocardial infarction have been observed in patients treated with interferons. No increase in the frequency of deaths, life-threatening AEs, study drug discontinuations, or dose modifications due to cardiac/vascular AEs was noted in boceprevir- containing arms. Cardiac/vascular SAEs were reported in more BOC/PR-treated subjects (25/1548, 2%) than in PR control subjects (2/547, <1%). After excluding those events that occurred in lead-in or started after ≥30 days of follow up, 18 subjects receiving BOC/PR experienced a total of 20 cardiac/vascular SAEs in the key studies. Of these events, four were disturbances of rhythm (supraventricular tachycardia, atrial fibrillation, atrial flutter), eight were thromboembolic (including deep venous thrombosis, arterial thrombosis, pulmonary embolism), six represented coronary artery disease (myocardial infarction, angina), and two were myopericarditis.

Ischemic cardiovascular AEs were reported in nine subjects (2/547 in PR arm and 7/1548 in BOC/PR arm). Two of the boceprevir-treated subjects had the events during the PR lead-in period. There were two events of myocardial ischemia (1 in PR arm, 1 in BOC/PR48), three events of myocardial infarction (1 in PR arm, 2 in RGT arm), three events of chest pain or angina (1 RGT, 2 BOC/PR), and three cases of coronary artery disease (2 in RGT, 1 in BOC/PR48).

Reviewer's comment:

In most of the cases, the subject had a prior history of cardiovascular disease or cardiovascular risk factors and no clustering of events was noted.

Gastrointestinal Disorders

Dysgeusia (alteration of taste) was a common adverse event reported at an increased frequency in boceprevir-treated subjects as compared to control (37% in boceprevir-containing arms versus 16% in control arm); however, the majority of dysgeusia events were mild-moderate in intensity and were not treatment-limiting. Only two subjects discontinued to the adverse event of dysgeusia and four subjects had dose modification. Gastrointestinal symptoms such as nausea, diarrhea, and vomiting (4%-6% difference compared to controls) also occurred at a somewhat increased frequency in boceprevir-treated subjects.

Decreased appetite which might be potentially due to dysgeusia was more common in the BOC/PR arm than the control arm of Study P05101, but was reported with similar frequency in treatment-naïve subjects in both arms. Most events of dysgeusia, nausea or vomiting were reported to be mild to moderate in severity. One subject in PR arm and 3 boceprevir treated subjects experienced SAEs of vomiting. One boceprevir-treated subject experienced gastrointestinal bleeding due to possible Mallory-Weiss tear.

Subject: # 056/007468 (Study P05216)

Serious Adverse Event(s): Hematemesis, Gastrointestinal Hemorrhage, Mallory-Weiss Syndrome, Syncope

A case of possible Mallory-weiss tear was reported in a 73-year old black male with history of thrombocytopenia, gingival bleeding, dyspepsia, and uncontrolled hypertension, a day after starting boceprevir. Subject received blood transfusion. The event was considered resolved. The Investigator considered the events unlikely related to study drugs.

Reviewer's comment:

Adverse events of dysgeusia may impair subject's adherence to therapy and may be a cause for non-compliance leading to potential compromise of the efficacy.

Pancreatitis

Fatal and nonfatal pancreatitis have been observed in patients treated with alpha interferon. Elevated triglyceride levels have been observed in patients treated with interferon alpha; and hypertriglyceridemia may result in pancreatitis. In the pooled data, there were eight SAEs of pancreatitis reported, including one case each of acute pancreatitis and necrotizing pancreatitis, both in boceprevir-treated subjects. Six subjects in the boceprevir-containing arms (6/1548, <1%) and 2 subjects (2/547, <1%) in the control arm had SAEs of pancreatitis. One case occurred during follow-up period;

one case was temporally associated with alcohol use; and two cases were associated with gallstones. The following cases are described below.

Subject # 77/001623 (Study P03523; Arm 5 with PR lead-in)

A SAE of pancreatitis reported in a 58 year-old-black female subject; blood amylase increased to >700 U/L, and lipase increased to >1500 U/L. Occurred at Day 44 of BOC/PR treatment. No prior history of gallstones or alcohol abuse. Events resolved over the course of 3 days. The investigator considered the pancreatitis to be possibly related and the blood amylase increased and lipase increased to be probably related to study drugs. Study drugs were discontinued.

Subject No. 32/011076 (Study P05101 BOC/PR 48)

A 55-year-old white male subject diagnosed with necrotizing pancreatitis approximately 5 months after starting boceprevir. Lipase value was 1585 U/L. Study drugs were discontinued. Later hyperglycemia and pancreatic insufficiency were reported. The investigator considered the necrotizing pancreatitis as possibly related to the PR and boceprevir.

Subject No. 27/001887 (Study P05216; BOC/PR 48)

A 46 year-old-white female diagnosed with acute pancreatitis at approximately TW 36. Amylase value was 541 U/L and lipase was 1088 U/L. Computed tomography of the abdomen and endoscopic ultrasound revealed findings consistent with acute pancreatitis.

As reported by the applicant, there were increases in nonfasting triglycerides in both treatment groups, however, of a greater magnitude in the boceprevir-treated subjects compared with PR control. The largest median increase from baseline in triglycerides in the boceprevir-treated group was at TW 8 (from a median of 106 mg/dL to 162 mg/L; 60% increase) compared with the largest median increase in the PR control group at TW 36 (from a median of 107 mg/dL to 146 mg/dL; 42% increase). A similar proportion of subjects in the PR and boceprevir treated groups experienced WHO Grade 1, 2, or 3 abnormalities in triglycerides during treatment; less than 1% of PR-treated subjects and 1% of BOC/PR-treated subjects had on-treatment Grade 3 abnormalities in triglycerides.

There was increase in amylase values over the course of treatment. The largest median change from baseline in amylase in the PR group was at TW 4 (75.0 U/L to 83.0 U/L; 11.8% increase), and in the BOC/PR group was at TW 6 (from 75.0 U/L to 92.5 U/L; 22.2% increase). These findings are unlikely to have clinical significance as the applicant reports that the lipase values were stable in both treatment arms over the treatment period. The amylase and lipase values during the treatment phase by modified WHO grade are shown in Table 39.

Table 39: Amylase and Lipase Values during the Treatment Phase, by Modified WHO Grade (Pooled Studies P03523, P05216, and P05101)

	WHO Grade	PR N=547	BOC/PR N=1548
		Number (%) of Subjects	
Amylase (U/L)			
Number of Subjects Included		n=540	n=1527
>1 to <1.5 x ULN	1	124 (23)	385 (25)
1.5 to 2.0 x ULN	2	32 (6)	98 (6)
2.1 to 5.0 x ULN	3	6 (1)	26 (2)
≥5.1 x ULN	4	1 (<1)	1 (<1)
Lipase (U/L)			
Number of Subjects Included		n=540	n=1527
>1 to 1.5 x ULN	1	25 (5)	67 (4)
>1.5 to 2.0 x ULN	2	9 (2)	19 (1)
>2.0 to 5.0 x ULN	3	2 (<1)	12 (1)
>5.0 x ULN	4	0 (0)	3 (<1)

The table summarizes the worst category observed within the period per subject per laboratory test. Only subjects with at least one treatment value for a given laboratory test are included. BOC=boceprevir 800 mg PO TID; PR=peginterferon alfa-2b+ribavirin; ULN=upper limit of normal; LLN=lower limit of normal; WHO=World Health Organization.

Source: Applicant's Submission dated April 11, 2011.

Reviewer's Comment:

Based on the current data, it is difficult to make any meaningful clinical conclusions from this observation and adverse events of pancreatitis will need to be monitored closely during the post-marketing phase.

Thromboembolic Events

Cases of pulmonary embolism, deep vein thrombosis, retinal ischemia and arterial thrombosis were reported in the pooled data and have been described in next Section 7.3.5.

Ischemic and hemorrhagic cerebrovascular events have also been observed in patients treated with interferon alfa-based therapies. One case of cerebral ischemia was

reported in boceprevir containing treatment arm. This subject also received erythropoietin.

Subject # 1/000052 (RGT arm, Study P05216)

A 45-year-old white male with a history of right bundle branch block, experienced severe alteration of the visual field and was diagnosed with cerebral ischemia at TW 24. The subject had received erythropoietin (30,000 units/week) for anemia, which was discontinued as a result of the event. The subject's hemoglobin values around the event were 12 g/dL. The event led to the study drug discontinuation and was considered probably related to boceprevir, PEG2b, and erythropoietin by the investigator, and unlikely related to RBV.

Ophthalmologic Disorders

The currently approved interferon products carry Warnings relative to potential for decreased or loss of vision, retinopathy including macular edema, retinal artery or vein thrombosis, retinal hemorrhages and cotton wool spots, optic neuritis, papilledema, and serous retinal detachment.

There were two SAEs of retinal ischemia reported in Study P03523, in boceprevir-treated subjects.

Subject # 16/000004

A 45-year old white male was found to have mild hypertension and mild retinal ischemia with moderate cotton wool spots at approximately TW 6 (TW 2 of BOC/PR). The investigator considered the event to be probably related to study medication.

Subject # 53/000302

A 53-year old female, reported a scotoma in her left visual field after approximately TW 8. Ophthalmologic examination revealed cotton wool spots and scotoma of the visual field, findings consistent with retinal ischemia. No loss of visual acuity was reported. The investigator considered the event to be probably related to PEG2b and unlikely related to boceprevir or RBV.

Endocrine and Metabolic Disorders

There was no increased frequency of hypothyroidism or hyperthyroidism reported in the BOC/PR arm (3% and 1%, respectively) compared to the PR control arm (4% and 1%, respectively).

Adverse events of gout was reported in 9/1548 (1%) of BOC/PR-treated subjects compared to 0/547 (0%) of PR-treated subjects. There were somewhat greater increases in uric acid values over the treatment period in the BOC/PR group (19-20%

median change from baseline between TW 8 and TW 16) compared with the PR group (12-14% change from baseline between TW 8 and TW 16). In addition, a higher proportion of subjects in the BOC/PR group (29%) had WHO Grade 1 abnormalities of uric acid compared with the PR group (23%).

7.3.5 Submission Specific Primary Safety Concerns

The most important safety concern during the clinical development of boceprevir has been the decrease in hemoglobin above and beyond that observed with pegylated interferon and ribavirin alone. The anemia appears to be part of an overall bone marrow suppressive effect of boceprevir as evidenced by the increased frequency of neutropenia and thrombocytopenia in boceprevir-treated subjects compared to PR-treated controls. The Applicant notes that use of boceprevir in these trials resulted in a 1 g/dL decrease in hemoglobin over what is generally observed with pegylated interferon and ribavirin alone. However, the exact magnitude of the hemoglobin decrease attributable to boceprevir cannot be determined from these trials due to presence of confounding factors such as use of erythropoietin and/or ribavirin dose reduction or both. Additionally, use of baseline factors to predict risk for development of anemia in these trials was confounded by the criteria used to define anemia and the recommended management algorithms.

The protocols for the key studies provided guidelines for the use of EPO and/or ribavirin dose reduction to treat anemia. Please note that although ribavirin package inserts include recommendations for ribavirin dose reduction; erythropoietin and other erythropoiesis-stimulating agents (ESAs) are not FDA-approved for treatment of anemia in patients with chronic hepatitis C. Erythropoietin was provided at no cost to subjects by the Applicant in these trials. However, the management decisions for individual patients (including the decision whether to use EPO) were at the discretion of the investigator. The use of EPO or ribavirin dose reduction was recommended at hemoglobin concentrations < 10 g/dL.

The protocols for the trials provided specific guidelines for the use of EPO based on the subject's hemoglobin values. EPO use was not recommended if serum hemoglobin ≥ 12 g/dL. Despite recommendations to initiate EPO therapy for hemoglobin < 10 g/dL, overall 3 subjects treated with BOC/PR and 3 subjects treated with PR had EPO treatment initiated when their hemoglobin levels were >12 g/dL. In these studies 4% (26/667) of subjects treated with BOC/PR compared to 9% (12/131) subjects treated with PR had treatment initiated with EPO when their hemoglobin was > 11 g/dL; and 26% (173/667) of subjects treated with BOC/PR compared to 34% (45/131) treated with PR had EPO treatment initiated when their hemoglobin was >10 g/dL. There were 51% (340/667) of subjects treated with BOC/PR and 56% (74/131) of subjects treated with PR who received EPO and had a hemoglobin level >12 g/dL response at any time during the study. There were 6% (40/667) of subjects treated with BOC/PR and 11%

(15/131) of patients treated with PR who received EPO and had a hemoglobin >14 g/dL response at any time during the study. There were a total of 10% (82/798) patients treated with BOC/PR or PR who had at least 2 hemoglobin values \geq 13 g/dL after treatment with EPO during the studies.

Hematology Reviewer's comment (rephrased):

The decision to add EPO to the treatment regimens of BOC/PR or PR in order to manage anemia was at the discretion of the investigator. Despite recommendations regarding the use of EPO, i.e., to initiate treatment at hemoglobin < 10 g/dL in the key safety trials, overall 27% (218/798) of subjects treated with BOC/PR or PR had EPO treatment initiated when their hemoglobin was >10 g/dL. There were overall, 7% (55/798) of subjects treated with BOC/PR or PR who had a hemoglobin > 14g/dL response after treatment with EPO at any time during the studies. There were a total of 10% (82/798) subjects treated with BOC/PR or PR who had at least 2 hemoglobin values \geq 13 g/dL after treatment with EPO during the studies. These results suggest (b) (4) clinicians may feel that treatment with EPO is necessary, which may increase the chances to improve the SVR but may also increase the patient's exposure to risks associated with EPO.

Reviewer's comment:

As noted by the hematology consultant, the continued use or initiation of EPO in patients with higher hemoglobin values may unnecessarily pose an additional potential risk of adverse events associated with EPO use in these patients.

Adverse Events Associated with ESA Use

Erythropoietin use was permitted, at the investigator's discretion, with or without ribavirin dose reduction in the boceprevir clinical trials as a supportive therapy for the management of anemia. Medically important AEs associated with the use of erythropoietin including cardiovascular events, thrombotic or thromboembolic events such as stroke, deep vein thrombosis, or pulmonary embolism, and progression of cancer tumors have been described in epoetin alfa product labeling. In addition, cases of pure red cell aplasia with or without other cytopenias, associated with neutralizing antibodies to EPO have been reported in patients treated with Procrit. In the key boceprevir trials analyzed for safety, a number of adverse events, including serious or severe/life-threatening adverse events associated with ESA use, were reported during the treatment phase in subjects who received erythropoietin. These include pulmonary embolism (n=2), arterial thrombosis (n=1), deep vein thrombosis (n=4), cerebral ischemia (n=1), and myocardial infarction (n=1). One case of pure red cell aplasia was reported during the follow-up period. However, each of these cases was confounded by underlying disease and by concomitant use of pegylated interferon, which has also been associated with these events. Some of these adverse events such as pulmonary

embolism (n=1), deep vein thrombosis (n=2) and myocardial infarction (n=1) were also reported in subjects who did not receive erythropoietin. Additionally, because subjects were not randomized to ESA use and ESA use was open-label in boceprevir trials, no conclusions can be drawn about safety of ESA use in this population.

There was one case of pure red cell aplasia (PRCA) reported in the follow-up of study P05216 and the narrative is summarized below:

Subject # 080-002163

A case of PRCA was reported in a 56-year-old white female with no other significant past medical history. The subject's baseline hemoglobin was 13.9 g/dL. The subject was randomized to the BOC/PR48 arm of the study and began treatment with PR. Approximately one month later boceprevir was added to the treatment regimen. Approximately 2 weeks later the subject had a decrease in hemoglobin to 9.0 g/dL and she received EPO 40,000 units three times a week for approximately the next seven weeks. The subject had adjustment in her EPO to twice a week and then once weekly over the next eight weeks. The subject's hemoglobin remained above 14 g/dl and her EPO dose was interrupted. Approximately 4 weeks later, the subject had a decrease in hemoglobin down to 9.5 g/dL and she was restarted on EPO 40,000 units three times a week for approximately the next eight weeks. The subject's hemoglobin increased to 12.8 g/dL. The subject's EPO dose was decreased to once weekly for the next four weeks. The subject complained of asthenia and discomfort and saw her primary care physician. The subject had hemoglobin of 6.0 g/dL, Platelets= $38 \times 10^9/L$ and neutrophils= $0.57 \times 10^9/L$. All study drugs and EPO treatment were discontinued. She received two transfusions with packed red blood cells and her hemoglobin remained low but stabilized for the next few weeks. However, her hemoglobin decreased again to 8.3 g/dL and she was started on darbepoetin alfa. Her hemoglobin continued to decrease to 6.6 g/dL. The subject was admitted to hospital and a bone marrow biopsy at the time was consistent with PRCA; considered probably related to long-acting EPO use. Antibody testing was also positive for anti-EPO antibodies. The subject was treated with packed red blood cell transfusions. The sponsor reports that the PRCA is ongoing. The investigator considered the events of anemia and thrombocytopenia to be possibly related to boceprevir and probably to PR therapy and the PRCA event unlikely related to boceprevir and ribavirin therapy but probably related to PEG2b.

Reviewer's Comment:

PRCA has also been reported as a rare event with the alpha interferon therapy.

EPO use in the management of anemia that occurred in subjects during these studies was not systematically studied and was administered at the discretion of the investigator in a nonrandomized, open-label fashion.

As noted by the hematology consult, the approval and dosing for EPO is based on use of EPO to avoid the requirement for red blood cell transfusions. Accordingly, the proper management of EPO for the labeled indications should target this clinical endpoint. Managing EPO to target hemoglobin levels of >10 to <12 g/dL exceeds levels needed to avoid transfusions and likely confers increased risk for cardiovascular adverse events.

Reviewer's comment:

Following are the RBC transfusion guidelines published by "Clinical practice guideline: Red blood cell transfusion in adult trauma and critical care".⁴

- *A "restrictive" strategy of RBC transfusion (transfuse when Hb <7 g/dL) is as effective as a "liberal" transfusion strategy (transfusion when Hb < 10 g/dL) in critically ill patients with hemodynamically stable anemia, except possibly in patients with acute myocardial ischemia. (Level 1)*
- *The use of only Hb level as a "trigger" for transfusion should be avoided. Decision for RBC transfusion should be based on an individual patient's intravascular volume status, evidence of shock, duration and extent of anemia, and cardiopulmonary physiologic parameters. (Level 2)*

(Level I: Evidence obtained from at least one properly randomized controlled trial.

Level II: Evidence obtained from well-designed controlled trials without randomization, cohort or case-control analytic studies, preferably from more than one center, or research or evidence obtained from comparisons between times or places with or without the intervention).

A case of arterial thrombosis was reported in a subject who received EPO and is summarized below because of its clinical significance.

Subject # 49/007492 (Study P05216)

A case of arterial thrombosis was reported in a 56-year-old black female with hypertension (baseline BP=162/92 mm Hg) receiving anti-hypertensive medications and on estrogen therapy after total hysterectomy was randomized in BOC/PR 48 arm. Baseline hemoglobin (Hgb) and hematocrit (Hct) were 12.0 g/dL and 0.44, respectively. Boceprevir was added at TW 4. Two weeks later, Hgb and Hct had decreased to 9.6 g/dL and 0.33, respectively. Hgb further decreased to 9.2 g/dL after a week. Subject experienced mild dyspnea, and erythropoietin was initiated (40,000 units/week). Her Hgb remained below normal, ranging from 9.2 to 11.7 g/dL during the duration of study treatment. Approximately after 2 months, Hgb was 11.7 g/dL and Hct was 0.48; EPO was

⁴ **Clinical practice guideline: Red blood cell transfusion in adult trauma and critical care***

Lena M. Napolitano, MD et al. for the American College of Critical Care Medicine of the Society of Critical Care Medicine and the Eastern Association for the Surgery of Trauma Practice Management Workgroup

discontinued. Four to five days later, the subject was hospitalized for evaluation of pain and numbness in her left leg. Work-up included venous duplex, X-rays, CT scan of brain and abdominal ultrasound. Work-up was unremarkable and subject was diagnosed with mononeuritis multiplex. An angiogram was not performed. She experienced increasing pain and discoloration of the lower extremity and returned to the hospital approximately 2 weeks later. She was diagnosed with acute arterial insufficiency of the left lower extremity with thrombosis involving the left common and external iliac segments, with no flow below the mid popliteal artery. Study drugs were discontinued. Imaging tests showed atherosclerotic disease of the aorta. Hypercoagulable workup was done: low protein S = 41 (normal range 65-140), Protein C and antithrombin activity within normal limits (WNL); C3 was elevated at 159 (normal ranges 90-120), C4 WNL. A few days later, she underwent a left below-the-knee amputation (10 cm below the knee).

The investigator assessed the event of arterial thrombosis to be possibly related to erythropoietin. The investigator assessed the events as unlikely related to all three study drugs.

Reviewer's Comment:

The Applicant considers that atherosclerotic disease and Protein S deficiency are also major contributing factors to the events and the outcome of the event (below-the-knee amputation was mostly due to a delayed diagnosis of the arterial thrombosis. This reviewer agrees that no definitive conclusions regarding causality assessments can be made due to the presence of confounding factors.

The final results of the study protocol P06086 may inform the safety of EPO in the proposed patient population particularly with regard to potential serious adverse events such as arterial thrombosis and pure red cell aplasia.

Testicular Function

Male reproductive changes consistent with testicular degeneration were observed in nonclinical studies in rats receiving boceprevir. These findings were not detected in mice or monkeys; however, to further investigate any potential boceprevir effect on male fertility in humans, inhibin B (a surrogate marker of testicular function) and semen samples were monitored in early clinical development (Phase 1 P03516, P04487) and in the Phase 2 clinical trials P03523 and P03659.

- P03516: Results of the semen analysis showed no clinically significant changes between treatment and baseline values.

- P04487: Serum inhibin B and semen samples were obtained from men during the trial and through the maintenance protocol (P04531) to monitor for potential testicular AEs after prolonged boceprevir exposure. Sperm counts and motility evaluation in 19 male HCV infected subjects treated with boceprevir monotherapy (up to 400 mg TID) for 14 days showed no clinically significant changes between treatment and baseline values. Although high and low values for inhibin B and FSH serum levels were observed, no pattern was evident and no clinically significant change from baseline in any individual was noted for either parameter.
- P03523: An analysis of approximately 1600 inhibin B samples collected from 355 men treated with boceprevir 800 mg TID plus PEG/RBV for a mean duration of 32 weeks showed no shift to low inhibin B values compared with the PR control arm.
- P03659: In this Phase 2 trial, 216 men received boceprevir at doses ranging 100 mg to 800 mg TID for a mean duration of 25 weeks. There were no clinically significant inhibin B decreases over time to suggest a decrease in testicular function during treatment or follow-up. At the last assessment during the treatment or follow-up period, no subjects with a normal or high inhibin B value at Baseline had a clinically relevant decrease in inhibin B to below the normal range.

These results show no evidence for boceprevir-related testicular toxicity in man, and therefore, inhibin B was not further studied in the later boceprevir clinical development program.

7.4 Supportive Safety Results

Phase 1 Trials

Healthy Volunteers

A total of 191 healthy volunteers experienced at least one treatment-emergent AE, including 169 boceprevir-treated subjects (45%). The most common AEs among boceprevir-treated healthy subjects were: dysgeusia (15%), headache (14%), nausea (8%), diarrhea (4%), abdominal pain (3%), and constipation (3%). Treatment-related AE analyses were similar. Dysgeusia demonstrated a dose-dependent effect with <10% occurrence in subjects treated with all boceprevir QD doses and 200-400 mg TID doses, and >25% occurrence with boceprevir 800-1200 mg TID doses. Nausea, diarrhea and abdominal pain were also more common at the higher boceprevir TID doses. Most AEs were mild. One SAE of renal colic occurred Day 6 after receiving a single 200 mg boceprevir dose in Protocol 2727. This subject experienced a similar episode eight months prior to enrollment, requiring lithotripsy.

AEs leading to study discontinuation in boceprevir-treated subjects included: vomiting (N=4), liver function test abnormalities (N=4), gastroenteritis, diarrhea, pregnancy and axillary dermatitis. Of note, vomiting occurred in three subjects in Protocol P03588 after administration of 800 mg ¹⁴C boceprevir as an oral suspension formulation.

Hepatitis C-infected Subjects

A total of 149 HCV infected subjects experienced at least one treatment-emergent AE, including 123 boceprevir-treated subjects. The most common AEs among boceprevir-treated HCV infected subjects were: headache (26%), myalgia (19%), fatigue (15%) and dysgeusia (10%). Treatment-related AE analyses were similar. Dysgeusia demonstrated a dose-dependent effect similar to the healthy volunteer trials. Most AEs were mild. Moderate severity AEs occurring in $\geq 2\%$ boceprevir-treated subjects included headache (8%), myalgia (4%), influenza-like illness (4%), fatigue (3%) and neutropenia (3%). Five boceprevir-treated subjects experienced severe AEs: fatigue (N=1), influenza-like illness (N=2), electrocardiogram QT prolonged (N=1), neutropenia/ALT increased (N=1). The subject who experienced QTc prolongation was a 64 year old man who experienced nine AEs of QTc prolongation, one of which was severe, throughout a three-period crossover trial (P03527). One of these events occurred pre-dosing with PEG, one seven days post the single administration of PEG (both Period 1), and one pre-dosing with boceprevir (Period 2). The other six events occurred at various timepoints during Period 2 (boceprevir alone 400 mg TID) and Period 3 (boceprevir 400 mg TID with PEG). All QTc prolongations were judged unlikely to be related to study drug, and except for the one event considered to be severe, the other QTc prolongations were judged to be moderate in severity. No action was taken, and the subject completed the trial.

One SAE of complex partial seizures occurred in Protocol P03527:

Subject 104 50 year old woman with HCV and a history of fainting episodes for several years (considered due to hypoglycemia), received a single boceprevir 200 mg dose and PEG-Intron. Approximately seven hours later, the subject experienced abdominal pain, nausea, decreased vision, and fainting. She transiently lost consciousness and had a brief tonic-clonic seizure associated with hypertension followed by hypotension. Serum glucose and ECG were reportedly normal. She was treated with oxygen, intravenous NaCl, KCl, glucose and steroids. Following this event, the subject experienced one vomiting episode, confusion and asthenia. By the next day the subject fully recovered. Neurologic consultation diagnosed hypertonic crisis that could be partial complex seizure, with possible epilepsy. The investigator considered the event unlikely related to study drug, and noted similar events have occurred in the past in this subject. Boceprevir and PEG-Intron were discontinued.

One additional boceprevir-treated subject discontinued due to an AE of neutropenia:

Subject 204 52 year old man assigned to the 400 mg boceprevir dose group in Period 1, and PEG-intron monotherapy in Period 2 discontinued treatment due to decreased neutrophil count (Grade 4) in Period 2. The investigator assessed this AE as probably related. Follow up neutrophil count was < Grade 1. Of note, this subject experienced Grade 2 neutropenia during boceprevir monotherapy dosing; however this value improved to < Grade 1 prior to PEG-intron dosing.

Phase 2 Trials

P03659

No deaths occurred in P03659, the Phase 2 trial conducted in HCV GT 1 previous treatment-failure subjects. A total of 26 subjects experienced nonfatal SAEs on treatment or within 30 days of discontinuation: 24 boceprevir-treated subjects (8%) and 2 placebo-treated subjects (4%). The majority of subjects experienced SAEs prior to Amendment 2 (65%). Frequent SAEs regardless of causality reported in at least two boceprevir-treated subjects included chest pain (N=3), diarrhea (N=2), hepatocellular carcinoma (N=2), syncope (N=2) and vomiting (N=2). Notable SAEs in boceprevir-treated subjects include:

- **Anemia**

Subject 70 60 year old man randomized to PR developed anemia Day 29 resulting in erythropoietin treatment. On Day 113 boceprevir 800 mg TID was added and on Day 130 he experienced Grade 3 anemia along with Grade 1 neutropenia and Grade 2 thrombocytopenia. Study treatment was discontinued Day 132, the subject received a blood transfusion Day 133 and subsequently recovered.

- **Syncope**

Subject 82 56 year old man with a history of diabetes on an insulin pump, hypertension, and convulsions attributed to hypoglycemia, was randomized to boceprevir 200 mg TID/PEG. Day 73 the subject experienced witnessed seizure activity with loss of consciousness. Blood glucose was lower than the subject's normal range (value=78, range 95-130) and the investigator did not consider this event related to study treatment. The subject recovered and continued study treatment without subsequent events.

Subject 272 60 year old woman was randomized to boceprevir 400 mg TID/PEG/RBV for 24 weeks and increased boceprevir to 800 mg TID (post-Amendment 2) on Day 110. On Day 160 the subject experienced syncope associated with nausea and decreased oral intake and orthostatic hypotension. Treatment with intravenous fluids was initiated and the subject recovered after 1 day and was able to continue study treatment. The investigator considered this event related to study therapy.

- Thromboembolic Events

Subject 537 33 year old man with history of hypertriglyceridemia and hypertension was randomized to boceprevir 800 mg TID/PEG and added RBV Day 50. On Day 153 he was diagnosed with pneumonia. On Day 168 he experienced a pulmonary embolism. Notably this subject was not receiving erythropoietin. Study treatment was discontinued and the event was considered related to study therapy.

- Pancreatitis

Subject 263 54 year old man with a history of alcohol abuse, pancreatitis was randomized to boceprevir 400 mg TID/PEG for 24 weeks and experienced recurrent alcoholic pancreatitis Day 83. The investigator did not consider this event related to study therapy, and the subject continued study treatment without subsequent events.

- Hepatocellular Carcinoma

Subject 250 52 year old man with Baseline MRI detecting a wedge shaped liver lesion and no cirrhosis was randomized to PEG/RBV and added boceprevir 400 mg TID Day 112. On Day 129 boceprevir was increased to 800 mg TID (post-Amendment 2). An MRI on Day 280 detected a 5cm liver lesion, and a biopsy Day 308 was positive for hepatocellular carcinoma. In the interim, study therapy was discontinued (Day 297), and the subject underwent an orthotopic liver transplant Day 410.

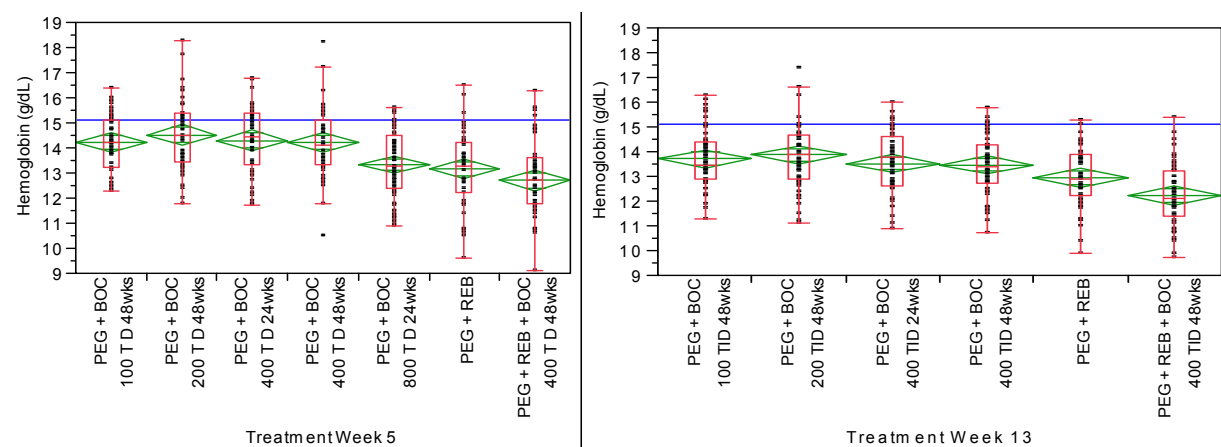
Subject 90 59 year old man with elevated Baseline alfa-fetoprotein (AFP) was randomized to PEG/RBV and added boceprevir 400 mg TID Day 116. On Day 211 boceprevir was increased to 800 mg TID. An ultrasound Day 255 detected a liver nodule confirmed by subsequent MRI. Day 283 biopsy was positive for hepatocellular carcinoma. The subject discontinued study therapy.

Discontinuations due to AE occurred in 30 subjects: 10 occurred prior to Amendment 2, including 8 in BOC-treated subjects, and 20 occurred after Amendment 2. Hematologic and gastrointestinal AEs were the most common AEs leading to discontinuation.

The most common AEs occurring in $\geq 10\%$ boceprevir-treated subjects were headache, fatigue, myalgia, chills, pyrexia, nausea, arthralgia, diarrhea, dysgeusia, insomnia, influenza-like illness, injection site erythema, alopecia, depression, asthenia, back pain, neutropenia, irritability, vomiting, upper abdominal pain, cough, injection site reaction, dyspnea and dizziness. Dysgeusia was boceprevir dose-dependent, occurring in $<10\%$ in ≤ 200 mg BOC-treated subjects, 21-27% in 400 mg BOC-treated subjects, and 48% in 800 mg BOC-treated subjects. All dysgeusia events were either mild or moderate in severity and did not result in discontinuation. No reports of Stevens-Johnson syndrome, toxic epidermal necrolysis, rash SAEs or discontinuations due to rash occurred.

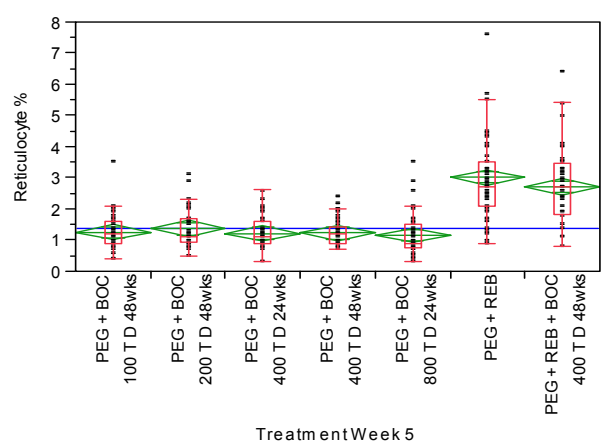
Pre-Amendment 2 hematologic laboratory analyses demonstrate a BOC dose-dependent effect (Figures 13, 14). Median pre-treatment Hgb was 15.3 g/dL, represented in the blue reference line. At Week 5, the RBV-containing arms and the 800 mg BOC arm had overall lower Hgb values (median 12.7-13.3 g/dL) compared to the non RBV-containing arm with BOC \leq 400 mg TID doses (median 14.1-14.5 g/dL). By Week 13, the BOC 400 mg TID plus PEG/RBV arm had a median lower Hgb -0.8 g/dL (median 12.1 g/dL) than the PEG/RBV arm (median 12.9 g/dL). Note the BOC 800 mg TID arm is no longer included since all eligible subjects added RBV by Week 13. Erythropoietin use was 4% prior to Amendment 2: 6% in the PR control arm, <1% in all boceprevir arms without RBV, and 20% in the boceprevir 400 mg TID plus PR arm. This observed Hgb decrease was accompanied by a compensatory increased reticulocyte count in the RBV-containing arms only (Fig. 14).

Figure 13: Protocol P03659: Hemoglobin by Treatment Arm



*Source: (b) (4) dataset for Protocol P03659

Figure 14: Protocol P03659: Reticulocyte Counts by Treatment Arm



*Source: (b) (4) dataset for Protocol P03659

These analyses demonstrate a boceprevir dose-dependent hemoglobin effect at boceprevir doses ≥ 400 mg TID, with the 400 mg TID dose causing additional decreased hemoglobin in combination with RBV. This finding supports boceprevir-related bone marrow suppression as the likely mechanism for anemia.

7.4.1 Common Adverse Events

The AE tables in this section are derived from FDA analyses of the pooled Phase 2b trial (P03523) and Phase 3 pivotal trial (P05216) in treatment-naïve subjects and Phase 3 pivotal trial (P05101) in treatment-failure subjects. The AEs represented in the tables are without regard to drug causality, which in this reviewer's opinion is an appropriate way to present AE data for this application, as frequently reported adverse events are those noted with pegylated interferon and ribavirin therapy.

Clinical AEs were common in study subjects, occurring in >98% of all subjects receiving either boceprevir/PR or PR alone. The most common AEs occurring in > 30% of subjects and which were observed with similar frequency in each treatment arm were fatigue, nausea, headache, insomnia, chills, and pyrexia. Common AEs reported in boceprevir-treated subjects with greater frequency over control arm include anemia (49% versus 30%), and dysgeusia (37% versus 16%). Neutropenia was also observed with greater frequency in BOC-treated subjects (23% versus 18%). Gastrointestinal symptoms such as nausea, vomiting, and diarrhea also occurred at a somewhat increased frequency in BOC-containing arms (Table 40).

Table 40: Common Adverse Events (≥ 20% of Subjects in any treatment arm) in the Decreasing Frequency by MedDRA Preferred Term (Pooled Studies P03523, P05216, and P05101)

MedDRA Preferred Term	Treatment-Naive		Treatment-Failure		All Subjects	
	P03523/P05216		P05101			
	BOC/PR N=1225 n (%)	PR N=467 n (%)	BOC/PR N=323 n (%)	PR N=80 n (%)	BOC/PR N=1548 n (%)	PR N=547 n (%)
Fatigue	715 (58)	277 (59)	179 (55)	40 (50)	894 (58)	317 (58)
Anemia	612 (50)	148 (32)	145 (45)	16 (20)	757 (49)	164 (30)
Headache	568 (46)	199 (43)	133 (41)	39 (49)	701 (45)	238 (44)
Nausea	566 (46)	199 (43)	140 (43)	30 (38)	706 (46)	229 (42)
Dysgeusia	429 (35)	80 (17)	142 (44)	9 (11)	571 (37)	89 (16)
Chills	416 (34)	137 (29)	106 (33)	24 (30)	522 (34)	161 (29)
Insomnia	415 (34)	161 (34)	97 (30)	19 (24)	512 (33)	180 (33)
Pyrexia	405 (33)	156 (33)	93 (29)	20 (25)	498 (32)	176 (32)
Alopecia	334 (27)	127 (27)	71 (22)	13 (16)	405 (26)	140 (26)
Diarrhea	308 (25)	104 (22)	79 (24)	13 (16)	387 (25)	117 (21)
Decreased Appetite	306 (25)	113 (24)	83 (26)	13 (16)	389 (25)	126 (23)
Neutropenia	306 (25)	93 (20)	46 (14)	8 (10)	352 (23)	101 (18)
Myalgia	284 (23)	112 (24)	81 (25)	19 (24)	365 (24)	131 (24)
Pruritus	273 (22)	117 (25)	62 (19)	14 (18)	335 (22)	131 (24)
Influenza Like Illness	270 (22)	118 (25)	79 (24)	20 (25)	349 (23)	138 (25)
Irritability	267 (22)	109 (23)	67 (21)	10 (13)	334 (22)	119 (22)
Depression	259 (21)	103 (22)	48 (15)	12 (15)	307 (20)	115 (21)
Vomiting	246 (20)	63 (13)	47 (15)	6 (8)	293 (19)	69 (13)
Dizziness	235 (19)	78 (17)	52 (16)	8 (10)	287 (19)	86 (16)
Dyspnea	233 (19)	76 (16)	69 (21)	14 (18)	302 (20)	90 (16)
Arthralgia	232 (19)	88 (19)	74 (23)	13 (16)	306 (20)	101 (18)
Dry Skin	224 (18)	85 (18)	72 (22)	7 (9)	296 (19)	92 (17)
Cough	216 (18)	97 (21)	70 (22)	14 (18)	286 (18)	111 (20)
Rash	211 (17)	92 (20)	51 (16)	5 (6)	262 (17)	97 (18)
Asthenia	183 (15)	85 (18)	69 (21)	13 (16)	252 (16)	98 (18)

BOC=boceprevir 800 mg PO TID; PR=peginterferon alfa-2b+ribavirin;

MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects

Source: Integrated Datasets for P03523, P05216, and P05101

7.4.2 Laboratory Findings

In the Phase 2 and 3 studies, clinical laboratory evaluations included assessment of hematologic, blood chemistry, thyroid function tests, and liver function parameters.

The laboratory values of decreased hemoglobin, decreased neutrophil counts, and decreased platelet counts were discussed in previous Section 7.3.4.

The laboratory values of nonfasting triglycerides, amylase and lipase have also been discussed in Section 7.3.4 under the subsection on pancreatitis.

Prothrombin time (PT) and aPTT were monitored because of a dose-dependent increase in aPTT observed in preclinical studies in monkeys. No differences in the mean aPTT and change from baseline in the BOC/PR arms compared with the PR control arms were reported.

Inhibin B monitoring was performed in male subjects in two Phase 2 studies, P03523 and P03659, to assess testicular function based on preclinical findings in male rats exposed to boceprevir and discussed in Section 7.3.5.

Liver Enzymes:

Grade 3 and 4 changes (WHO grade values) in liver enzymes aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin concentrations during the treatment phase occurred in <1% of the subjects and were similar across the PR and BOC/PR arms. The highest value for each liver enzyme observed during the treatment phase in the key studies is summarized in Table 41.

Table 41: Highest Value for Selected Liver-Related Laboratory Parameters during the Treatment Phase, by Modified WHO category (Pooled Studies P03523, P05216, and P05101)

	Treatment-Naive P03523/P05216		Treatment-Failure P05101		All Subjects	
	BOC/PR N=1225	PR N=467	BOC/PR N=323	PR N=80	BOC/PR N=1548	PR N=547
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of Subjects	1215	461	322	80	1537	541
ALT*						
Grade 3 (5.10 -10.0 x Baseline)	1 (<1)	3 (1)	0	0	1 (<1)	3 (1)
Grade 4 (>10.0 x Baseline)	0	0	0	0	0	0
AST*						
Grade 3 (5.10 -10.0 x Baseline)	0	3 (1)	0	0	0	3 (1)
Grade 4 (>10.0 x Baseline)	1 (<1)	0	0	0	1 (<1)	0

Only subjects with at least one treatment value for a given laboratory test are included

* Worst category observed per subject per laboratory test

Source: Applicant's Integrated Summary of Safety 8.4.1.6

The number of subjects with Grade 3 and 4 elevations in liver enzymes (ALT and AST) was low and there were no subjects with Grade 3 and Grade 4 total bilirubin values in the pooled studies.

In the pooled data, 6 out of 2095 subjects met laboratory criteria of AST or ALT ≥ 3 x ULN, concurrent with total bilirubin ≥ 2 x ULN and alkaline phosphatase ≤ 2 x ULN: 2/547 subjects in the PR arms, and 4/1548 subjects in BOC/PR arms. In all subjects improvement in laboratory values from baseline was seen as HCV viral load decreased; laboratory values returned to near baseline in subjects who were nonresponders. Subjects who met the laboratory criteria AST or ALT ≥ 3 x ULN, concurrent with total bilirubin ≥ 2 x ULN and alkaline phosphatase ≤ 2 x ULN were those with advanced liver disease and the findings were consistent with the progression of the liver disease.

7.4.3 Vital Signs

Vital signs (blood pressure, pulse, and temperature) were measured at all visits, and weight was measured at scheduled intervals in the key studies. Clinically significant changes from baseline (Screening visit) were recorded as AEs. There were no significant effects noted on vital sign measurements in subjects treated with boceprevir. The most common adverse events reported were weight loss and pyrexia which are known effects associated with peginterferon and ribavirin therapy.

7.4.4 Electrocardiograms (ECGs)

The potential risk of boceprevir to cause delayed ventricular repolarization in humans was investigated in several nonclinical studies. The studies included *in vivo* evaluation of cardiovascular function, including blood pressure and ECG intervals (PR, QRS, QT) and morphology, in dogs and monkeys, and *in vitro* evaluation of the effects on human ether-a-go-go-related gene (hERG) current and on dog cardiac Purkinje fibers. Overall, the nonclinical results suggested the risk for QT interval prolongation in humans at therapeutic concentrations is likely to be very low.

In the Phase 1 program, an HCV-infected subject enrolled in Protocol P03527 experienced several episodes of QT interval prolongation as described in Section 5.3. These episodes included one predose event, and were not treatment-limiting. A formal ECG study (thorough QT study, TQT) was performed in healthy volunteers (Protocol P04489) and was reviewed by the FDA Interdisciplinary Review Team (IRT) for QT Studies. The Review Team concluded the following:

The effect of Boceprevir 800 mg and 1200 mg on QTc interval was evaluated in a randomized, multiple-dose, placebo-, and active-controlled (moxifloxacin 400 mg) 4-way crossover thorough QT study in 36 healthy subjects. In the study with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on individual correction method (QTci) was below 10 ms, the threshold for regulatory concern (see Table 42). The dose of 1200 mg yields about 15% increase in the maximum exposure, which is insufficient to cover the exposure increase due to coadministration of a strong CYP3A4 inhibitor (42%). The marginal difference in exposure (from 15% to 40% increase) does not appear to lead to concerns of the QT effect under high exposure scenario, because no apparent concentration-QT relationship was identified.

Table 42: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Boceprevir (800 mg and 1200 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	$\Delta\Delta QTcI$ (ms)	90% CI (ms)
Boceprevir 800 mg	4	1.9	(-0.9, 4.6)
Boceprevir 1200 mg	4	4.4	(1.8, 7.1)
Moxifloxacin 400 mg*	2	13.9	(11.5, 16.3)

- Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 10.6 ms after 5 days of moxifloxacin administration. The predicted largest lower bound after a single dose is 7.97 ms.

Source: IRT review

Reviewer's Comment:

Another possible high exposure scenario is in patients with severe hepatic impairment (an estimated 60% increase in maximum boceprevir exposure).

In the pivotal Phase 3 trials, ECGs were obtained at screening visit and were only done during the treatment phase when clinically indicated.

7.4.5 Special Safety Studies/Clinical Trials

Trials to evaluate Anemia

Protocol 05351: Assessment of the Effects of Boceprevir on Red Blood Cells in Healthy Male Volunteers

This non-IND randomized, placebo-controlled, blinded protocol was conducted in the Netherlands and designed to determine the effect of BOC on red blood cell (RBC) survival. A total of 16 men were randomized 1:1 to receive BOC 800mg TID or placebo for 57 days. The primary study endpoint was RBC survival half-life. Secondary endpoints included RBC volume, RBC sequestration and RBC fragility. One subject discontinued for unknown reasons and 15 subjects completed the trial. All subjects were white men with a mean age of 38 years. Labeled ^{51}C Chromium RBC was used to determine RBC survival and volume. Mean RBC survival half-life was similar between the two groups: 27 days in the BOC group and 28.9 days in the placebo group with a difference of -1.9 days and an upper limit of the 90% one-sided confidence interval of 2.0 days. Mean RBC volume was also similar between the two groups. RBC sequestration throughout the body was determined using gamma-camera imaging. No evidence of a different sequestration pattern was noted between treatment groups. Overall, RBC deformability remained within the physiological range. Markers associated

with RBC differentiation and proliferation (cell surface CD markers: CD34, CD34/CD45, CD47, CD55, CD59; IL-6; IL-1; TNF- α), haptoglobin, ferritin and iron did not support an explanation for BOC-associated anemia. Erythropoietin concentrations remained within normal range. No deaths, SAEs, severe or life-threatening AEs, or discontinuations due to AEs were reported in this trial.

Median Day 1 Hgb was 15.9 g/dL (13.5-16.4 g/dL) and 15.1 g/dL (14.2-16.1 g/dL) in the BOC and placebo groups, respectively. Median Hgb changes from Day 1 in the BOC group were -0.4g/dL (Day 14), -0.4 g/dL (Day 28), -1.0 g/dL (Day 42) and -1.0 g/dL (Day 57). Median Hgb changes in the placebo group were -0.3 g/dL (Day 14), -0.3 g/dL (Day 28), -0.6 g/dL (Day 42) and -0.6 g/dL (Day 57).

One boceprevir-treated subject had Hgb change (Δ) Day 1-14 and Δ Day 1-21 of -2.3 g/dL and -2.4 g/dL, respectively. In addition, platelet Δ Day 1-14 and Δ Day 1-28 counts were $-67 \times 10^9/L$ and $-112 \times 10^9/L$, respectively. White blood cell and neutrophil counts remained within the normal range. This subject's hematologic parameters returned to baseline following trial completion.

These data indicate the mechanism of BOC-associated anemia is not due to RBC hemolysis. In addition, BOC does not appear to interfere with RBC differentiation, proliferation or clearance from the systemic circulation. Therefore, the mechanism of BOC-associated anemia is thought to result from a bone marrow suppressive effect.

Protocol P06086

Protocol P06086 is an ongoing Phase 3 open-label trial in treatment-naïve HCV subjects receiving boceprevir and pegylated interferon/RBV, comparing erythropoietin (EPO) use versus RBV dose reduction for the management of anemia. P06086 is open label for boceprevir and PEG/RBV; the Sponsor is blinded to the anemia management strategy (EPO use versus RBV dose reduction). Anemia is defined as Hgb ≤ 10 g/dL. The primary objective is to compare SVR between the EPO versus the RBV dose reduction groups in HCV GT1 infected subjects who become anemic while receiving 800 mg TID BOC/PEG/RBV treatment. Subjects must have screening Hgb ≤ 15 g/dL. The original protocol specified a 48 week treatment duration (PEG/RBV for a 4 week lead-in, followed by boceprevir 800 mg TID plus PEG/RBV for 44 weeks); however a protocol amendment (September 2010) introduced a response-guided therapy strategy, in which subjects were assigned to either a 28-week or 48-week treatment duration based on TW 8 HCV RNA (after 4 weeks of boceprevir). The trial design includes a TW 12 futility rule: subjects with TW 12 detectable HCV RNA and a HCV RNA $< 2 \log_{10}$ decline are considered treatment failures and are to discontinue treatment. In addition, subjects with TW 24 HCV RNA $\geq LLQ$ are considered treatment failures and are to discontinue treatment. Eligible subjects will continue in the Pending Randomization Arm if their Hgb remains > 10 g/dL throughout the 48-week treatment period. Subjects who become anemic within the 48-week treatment period are randomized in a 1:1 ratio (at

the time they become anemic) to Arm 1 (RBV dose reduction) or Arm 2 (EPO, initial dose 40,000 units SC QW) for management of the anemia. The EPO dose should be adjusted for each subject to achieve and maintain Hgb levels between approximately 10 g/dL and 12 g/dL. Subjects developing a sudden loss of EPO response, accompanied by severe anemia and low reticulocyte count, the possibility of pure red cell aplasia (PRCA) and severe anemia, with or without other cytopenias, should be ruled out. The total treatment duration is 48 weeks. Subjects with Hgb \leq 8.5 g/dL will be declared anemia management strategy failures; however, these subjects may remain in the trial per investigator discretion. If the Hgb continues to decrease to \leq 7.5 g/dL, the subject must be discontinued. The Applicant planned for approximately 660 subjects to be enrolled with 60% subjects anticipated to become anemic, resulting in 400 subjects eligible for randomization to one of the two anemia management arms.

As of the SUR database cutoff date (02 DEC 2010), the trial is fully enrolled and 687 subjects have received at least one PEG/RBV dose and 653 subjects have reached TW 4 and received at least boceprevir dose. One of the P06086 enrollment criteria was Hgb \leq 15 g/dL; therefore, more women (63%) than men (37%) were enrolled. Most subjects (77%) were white; 19% subjects were black. The mean age was 49 years. Approximately 54% of subjects had HCV GT 1a, and 81% had a baseline viral load $>$ 800,000 IU/mL. Median treatment duration was 199 days. A total of 44 subjects (6%) completed the treatment phase and 187 (27%) discontinued treatment. The main reason for treatment discontinuation was discontinuation due to AEs. In addition, 56 (8%) subjects discontinued study drugs due to treatment failure, including subjects with breakthrough and incomplete virologic response, as defined in the protocol. The treatment phase is ongoing for 456 (66%) subjects, and the follow-up phase is ongoing for 172 (89%) of the 193 subjects who entered follow-up. No subjects have died, 8% experienced SAEs and 11% discontinued due to an AE. The P06086 AEs are similar to the AEs in completed Phase 2 and 3 trials. Notable AEs include:

- Anemia: Six subjects (1%) have experienced an SAE of anemia, eight subjects have discontinued due to anemia (1%), and 13 subjects have received a blood transfusion (2%), including one subject with diabetes and hypertension who experienced a myocardial infarction in the setting of Grade 2 decreased hemoglobin. Grade 3/4 hemoglobin was reported in 5% of subjects.
- Neutropenia: Two subjects have experienced an SAE of neutropenia ($<$ 1%) and three subjects have discontinued due to neutropenia ($<$ 1%). Grade 3/4 neutrophil counts were reported in 35% of subjects.
- Psychiatric AEs: Four subjects reported psychiatric SAEs (1%): depression (4), suicidal ideation (3), suicidal behavior (1). Nineteen subjects discontinued due to psychiatric AEs (3%): depression (7), suicidal ideation (6), anxiety (3), aggression (2), insomnia (2), affect lability, paranoia.
- Pancreatitis: Two pancreatic AEs leading to study discontinuation were reported: pancreatitis Day 198 associated with a pancreatic cyst, and pancreatitis Day 87 ultimately diagnosed as pancreatic carcinoma.

Ongoing Trials

Safety data from several additional ongoing boceprevir trials are included with this NDA submission: P05411, P05063, and P05514. The completed protocol, P05685, is reviewed in Section 7.5.

Protocol P05411 is a Phase 2b, safety and efficacy trial of boceprevir in HCV GT1 treatment-naïve subjects coinfecting with HIV. The primary efficacy endpoint is SVR. Eligible subjects should have HIV-1 RNA < 50 copies/mL, CD4 count \geq 200 cells/ μ L, and be on an optimized antiretroviral regimen for at least six months that does not contain zidovudine, didanosine, stavudine, efavirenz, etravirine or nevirapine. Protocol-specified inclusion hemoglobin is 1 g/dL lower than in other boceprevir trials: \geq 11 g/dL for women and \geq 12 g/dL for men. Eligible subjects are randomized 2:1 to BOC (800 mg TID)/PEG/RBV or PEG/RBV for 48 weeks, following a PEG/RBV lead-in. The trial design includes a TW 12 futility rule whereby subjects with TW 12 detectable HCV RNA and HCV RNA <2 log₁₀ decline are considered treatment failures and are to discontinue treatment. In addition, subjects with TW 24 HCV RNA \geq LLQ are considered treatment failures and are to discontinue treatment. Subjects in the PEG/RBV control arm with TW 24 HCV RNA \geq LLQ are eligible to receive open label boceprevir and PEG/RBV. Anemia is managed by investigator discretion. As of the SUR data cutoff date (01 DEC 2010), the trial is fully enrolled and remains blinded. A total of 93 subjects have received at least one dose of PR, and 88 subjects reached TW 4 and received at least one dose of boceprevir/placebo. Median treatment duration was 141 days; no subject has completed the treatment phase. Eighteen (19%) subjects have discontinued treatment including 8 (9%) subjects who discontinued due to AEs and 8 (9%) subjects who discontinued due to treatment failure. The treatment phase was ongoing for 75 (81%) of the 93 treated subjects, and the follow-up phase was ongoing for 13 of the 16 subjects who had entered follow-up.

Most subjects were male (72%) and white (83%), with a mean age of 43 years. A total of 13% of subjects were black. Approximately 65% of the subjects had HCV subtype 1a and 25% had subtype 1b. Most subjects (87%) had a baseline HCV viral load >800,000 IU/mL. Cirrhosis was reported in 5% of subjects. At baseline, most (96%) subjects had an HIV viral load of <50 copies/mL and only one subject had a CD4+ cell count of <200 cells/ μ L. Most subjects (83%) used an HIV ritonavir-boosted protease inhibitor in their baseline optimized antiretroviral treatment regimen.

As of the SUR, there have been no deaths. SAEs and discontinuations due to AEs occurred in 11% and 9% of blinded subjects, respectively. These events are similar to AEs described in the completed Phase 2 and 3 trials. A total of 23% subjects initiated EPO, and 4% subjects received a blood transfusion.

Protocol P05514 (PROVIDE) is an open label trial providing BOC 800 mg TID/PEG/RBV to subjects without response to PEG/RBV alone in previous boceprevir

trial control arms. Subjects from P05101, P05216, and P05685 may be enrolled if they received at least 12 weeks of PEG/RBV treatment and discontinued treatment during the referring trial due to the futility rule (as defined in the previous protocol), had virologic breakthrough, or relapsed. For the P05514 protocol-specified futility rule, subjects with TW 12 detectable HCV RNA are considered treatment failures and are to be discontinued from treatment. The protocol provided guidelines for the use of erythropoietin, but anemia management decisions, including the decision whether to use erythropoietin or reduce the ribavirin dose, were made per investigator's discretion. As of the SUR database cutoff date (06 DEC 2010), 148 subjects had been enrolled and had received at least one dose of study medication. The median treatment duration, including the 4-week PR pretreatment, was 216 days. Thirty-seven (25%) subjects had completed the treatment phase; 47 (32%) had discontinued treatment. Seven (5%) subjects discontinued treatment due to AEs. In addition, 29 (20%) subjects discontinued study drugs due to treatment failure. The treatment phase was ongoing for 64 (43%) subjects, and the follow-up phase was ongoing for 48 (59%) of the 81 subjects who had entered follow-up.

The majority of the 148 treated subjects were men (69%) and white (82%), with a mean age of 52 years (range, 25 to 73 years). A total of 14% subjects were black. Fifty percent of the subjects were HCV GT 1a, and 39% were HCV GT 1b. Most subjects (78%) had a baseline viral load >800,000 IU/mL. Upon entry into the referring trials, most subjects had nonbridging fibrosis (51% were stage F1 and 24% were F2). Cirrhosis was reported in 11% of subjects.

As of the SUR cutoff date, no subject had died, 6% had SAEs and 5% discontinued study drugs because of AEs. These AEs included neutropenia, optic neuropathy, hepatic cirrhosis, diarrhea, fatigue, depression, chest pain, muscular weakness, sarcoidosis, appendicitis, joint injury, dehydration, hyponatremia, and arterial occlusive disease. The subject with arterial occlusive disease of the upper limb was not receiving EPO; this event was attributed to ergotamine induced arterial vasospasm. EPO use occurred in 38% of the subjects. A single subject received a blood transfusion.

Protocol P05063 is a long-term follow-up study of subjects previously enrolled in Phase 1, 2 or 3 boceprevir trials in either treatment or control arms; and no treatment is administered. Subjects are followed for 3.5 years after the previous trial's end of treatment. Of the 2828 subjects who received study medication in a previous Phase 1, 2, or 3 boceprevir clinical trial, 1064 (38%) have been enrolled into P05063 as of the SUR cutoff date (23 NOV 2010) with 17% completing long-term follow-up, 9% discontinuing, and 73% ongoing. Deaths in P05063 include metastatic pancreatic carcinoma (P03659), hepatic adenocarcinoma (P03523) and progression of hepatic cirrhosis (P03523).

7.4.6 Immunogenicity

Boceprevir is a small molecule, not a peptide; therefore, development of immunogenicity directed against boceprevir was not specifically evaluated.

7.5 Other Safety Explorations

P05685: A Phase 3 Safety and Efficacy Study of Boceprevir in Combination with Peginterferon Alfa-2a and Ribavirin in Subjects with Chronic Hepatitis C Genotype 1 Who Failed Prior Treatment With Peginterferon/Ribavirin

The SUR contains summary data from the recently completed Phase 3 trial P05685. The full study report and datasets have not been submitted to this NDA because the trial was recently completed. This double blinded 48 week trial compared boceprevir or placebo, each in combination with open-label peginterferon alfa-2a plus ribavirin (PEG2a/RBV). Weight-based RBV dosing at 1000 or 1200 mg was used. Eligible subjects demonstrated prior PEG/RBV treatment interferon responsiveness but failed to achieve SVR. Eligible subjects were randomized 2:1 to either the boceprevir 800 mg TID plus PEG2a/RBV arm or the PEG2a/RBV control arm. Subjects were stratified by prior treatment responsiveness (HCV RNA became undetectable versus HCV RNA did not become undetectable) and by HCV genotype (subtype 1a versus 1b). Both arms used a 4-week PEG2a/RBV lead-in prior to adding blinded boceprevir or placebo. The response guided therapy approach was not used in this trial. A TW 12 futility rule stated: subjects who failed to achieve TW 12 undetectable HCV RNA were discontinued no later than TW 16. The protocol recommended ribavirin dose reduction if the hemoglobin decreased to <10 g/dL; ribavirin was to be interrupted or PEG2a/RBV was to be discontinued if hemoglobin decreased to <8.5 g/dL. The protocol provided erythropoietin use guidelines, but anemia management decisions, including the decision whether to use erythropoietin or reduce the ribavirin dose, were made at the investigator's discretion.

A total of 134 subjects enrolled in the BOC/PEG2a/RBV arm, and 67 subjects enrolled in the PEG2a/RBV comparator arm. The majority of subjects were white (88%) men (70%) with a mean age of 52.5 years (29-70 years). Black subjects represented 10% of the trial population. Approximately 45% of subjects had HCV GT 1a, and 47% had HCV GT 1b. Most (77%) subjects had a baseline viral load >800,000 IU/mL. Cirrhosis was reported in 16% of subjects, and 23% had baseline Metavir fibrosis score >F2. The majority of subjects were prior PEG/RBV treatment relapsers (approximately 70%).

The TW 12 futility rule led to a lower TW 20 subject proportion remaining on treatment in the PEG2a/RBV control arm (31%), compared with the boceprevir-containing arm (72%). Median treatment duration was 105 days in the control arm and 334 days in the boceprevir-containing arm. The most frequent reasons for overall study drug discontinuation during the treatment phase were treatment failure (32%) and AEs (13%). The boceprevir-containing arm had more discontinuations for AEs (17%)

compared with the control arm (3%). Fatigue and asthenia were the most frequent AEs leading to study drug discontinuation in the boceprevir-containing arm.

Efficacy:

Based on the Applicant's analyses, a significant improvement in SVR rates (Δ SVR, 43%; $p < .0001$) was observed in the boceprevir arm versus the control arm. Addition of boceprevir to PEG2a/RBV increased the SVR rate compared with PEG2a/RBV therapy alone (64% boceprevir arm versus 21% control arm). Lower relapse rates occurred in the boceprevir arm compared with the control arm (12% versus 33%, respectively). Prior PEG/RBV treatment relapsers had increased SVR rates: 70% boceprevir arm versus 28% control arm.

Similar to the pivotal Phase 3 trials, the following subgroups were associated with lower SVR rates: blacks, high baseline HCV RNA, cirrhosis, GT 1a. Boceprevir-treated subjects previously treated with PEG2a had higher overall SVR rates (68%) compared with subjects previously treated with PEG2b (59%).

Safety:

SAEs were reported with similar frequencies in the boceprevir-containing and control arms (13% versus 10%, respectively); dose modifications (43% versus 22%) and study drug discontinuations (17% versus 4%) were reported more frequently in the boceprevir-containing arm.

Two deaths occurred in this trial, both in boceprevir-treated subjects.

- **Subject 603** 48 year old man with a history of diabetes experienced a skin laceration approximately Day 84 and subsequently developed staphylococcus bronchopneumonia Day 89 followed by neutropenia (nadir Grade 4, ANC = $0.01 \times 10^9/L$, on Day 93) which was treated with G-CSF. Hemoglobin values at the time of the event are not provided; however the narrative states erythropoietin was given. Platelet count decreased from Grade 1 prior to the pneumonia to a nadir of Grade 4 ($18 \times 10^9/L$) on Day 96 and was treated with blood products starting Day 98. Study medications were discontinued Day 91 and the subject died due to multiorgan failure following staphylococcus bronchopneumonia on Day 106.
- **Subject 17** 47 year old man died Day 170 of cardiac failure during sexual activity after taking sildenafil. Hemoglobin was 10.0 g/dL eight days before event and this subject is listed as being on erythropoietin (although this detail was not mentioned in narrative summary).

SAEs were reported in 13% of boceprevir-treated subjects. These SAEs include: neutropenia, thrombocytopenia, cardiac failure, coronary artery disease, diarrhea, upper gastrointestinal hemorrhage secondary to bleeding esophageal varices, asthenia,

multiorgan failure, pyrexia, bronchitis, cellulitis, pneumonia, staphylococcus infection/bacteremia/pneumonia, hyponatremia, syncope, subarachnoid hemorrhage following a fall in an intoxicated subject, gunshot wound, lethargy, deep venous thrombosis, suicidal ideation, and mental status changes.

Increased infection-related SAEs were reported in the boceprevir-containing arm (N=7) compared with none in the control arm; however, two subjects experienced their events during the lead-in phase. The remaining five boceprevir-treated subjects with infection-related SAEs include three *Staphylococcus aureus*-related infections (pneumonia, cellulitis, bacteremia), and two pneumonias (*Chlamydia pneumoniae* and possible *Haemophilus influenzae*). Two of these subjects experienced Grade 4 neutropenia at the time of their infections (fatal staphylococcal pneumonia, Chlamydia pneumonia).

Treatment-emergent treatment-related AEs (as reported by the investigator) reported more frequently in the boceprevir-containing arm than in the control arm included anemia (50% vs 33%), neutropenia (31% vs 18%), and leukopenia (15% vs 3%); rash (22% vs 7%); myalgia (19% vs 7%); alopecia (16% vs 7%); and gastrointestinal disorders, including dysgeusia (39% vs 15%), nausea (38% vs 27%), diarrhea (22% vs 7%), and vomiting (10% vs 0%).

Dose modification due to anemia occurred in 32% boceprevir-treated subjects compared with 13% control subjects. None of the anemia events were SAEs and only one subject discontinued due to anemia:

- **Subject 13** 55 year old woman developed symptomatic anemia Day 43 (shortness of breath, Hgb=9.2 g/dL). Two days later erythropoietin was started. Nadir Hgb occurred Day 71 (7.8 g/dL) prompting interrupting RBV dosing. Day 111 RBV was restarted at a reduced dose when Hgb improved to 12.8 g/dL. Hgb levels fluctuated between 9.1-12.1 g/dL until Day 311 when Hgb=7.9 g/dL. At this point all study drugs were discontinued and the subject recovered.

No discontinuations due to rash-related AE occurred; rash with mucosal involvement was not reported. The most common psychiatric AEs were anxiety, insomnia, and depression, and sleep disorder, which occurred with similar frequencies in the control and boceprevir-containing arms with the exception of depression (14% boceprevir arm vs 9% control arm). One suicidal ideation SAE occurred in a boceprevir-treated subject:

- **Subject 409** 58 year old man without a psychiatric history developed irritability Day 68, treated with bupropion. Day 89 he developed insomnia, followed by suicidal ideations Day 94. The subject was hospitalized and all study medications discontinued. He was subsequently diagnosed with moderate depression and medically treated with ultimate symptom resolution.

Boceprevir-treated subjects experienced more Grade 3 and 4 hemoglobin, neutrophil, platelet and white blood cell decreases than control subjects.

A total of 37% boceprevir-treated subjects met hemoglobin guidelines (Hgb <10 g/dL) for dose reduction (versus 22% of control subjects), and 13% boceprevir-treated subjects met hemoglobin guidelines (Hgb <8.5 g/dL) for study drug discontinuation or interruption (versus 4% of control subjects). Five boceprevir-treated subjects (2%) received a transfusion for the management of anemia; all five subjects also received erythropoietin, and four of these subjects had cirrhosis.

Erythropoietin use was more common in the boceprevir arm (47%) compared with the control arm (30%). Notable SAEs in boceprevir-treated subjects receiving erythropoietin include: fatal staphylococcal pneumonia, fatal cardiac failure in the setting of sildenafil use, staphylococcal bacteremia/thrombocytopenia, neutropenia, deep vein thrombosis. Granulocyte colony-stimulating factor (G-CSF) use was permitted during the study. One (1%) subject in the boceprevir-containing arm used G-CSF; no subjects in the control arm used G-CSF.

In summary, this recently completed Phase 3 trial comparing boceprevir versus placebo, each in combination with PEG2a/RBV in treatment-experienced HCV GT1 infected subjects, demonstrated a similar safety and efficacy profile to that seen in the pivotal Phase 3 boceprevir trials using PEG2b. Further analyses will be performed when the final study report is submitted to the Agency.

7.5.1 Dose Dependency for Adverse Events

Please refer to Section 7.4 for discussion of Phase 1 and Phase 2 (P03659) dose dependent adverse events. Only the boceprevir 800 mg TID dose was used in the Phase 2 HCV treatment-naïve trial (P03523), and in the Phase 3 trials (P05216 and P05101).

7.5.2 Time Dependency for Adverse Events

Assessment of Safety in regards to Response Guided Therapy (P05216 and P05101)

In both Phase 3 trials, subjects in the RGT arms who were early virologic responders (*undetectable* HCV RNA at TW 8) were eligible to complete treatment early; after 28-weeks of treatment in Study P05216 and after 36-weeks of treatment in Study P05101 respectively. This offers a shorter duration of therapy for a proportion of subjects who achieve undetectable HCV RNA at week 8 (early virologic responders).

Table 43: Comparison of Adverse Events in RGT Arm versus Boceprevir/PR 48 Arm in Phase 3 Trials (P05216 and P05101)

	P05216		P05101	
Safety Parameter	Arm 2 RGT (24 weeks BOC) N=368 n (%)	Arm 3 BOC/PR48 (44 weeks BOC) N=366 n (%)	Arm 2 RGT (36 weeks BOC) N=162 n (%)	Arm 3 BOC/PR48 (44 weeks BOC) N=161 n (%)
Any AE	365 (99)	364 (99)	160 (99)	161 (100)
SAEs	42 (11)	45 (12)	16 (10)	23 (14)
Discontinuations due to AEs	45 (12)	60 (16)	13 (8)	20 (12)
Grade 3 or 4 AEs	120 (33)	123 (34)	44 (27)	59 (37)
Anemia	182 (49)	180 (49)	70 (43)	75 (47)

BOC=boceprevir 800 mg PO TID; PR=peginterferon alfa-2b+ribavirin; RGT=response-guided therapy
For Study P05216, Arm 2 (RGT) = PR lead-in for 4 weeks, then BOC/PR for 24 weeks (if undetectable HCV-RNA at TW 8) or BOC/PR for 24 weeks followed by placebo/PR for 20 weeks (if detectable HCV-RNA at TW 8).

For Study P05101, Arm 2 (RGT) = PR lead-in for 4 weeks, then BOC/PR for 32 weeks (if undetectable HCV-RNA at TW 8) or BOC/PR for 32 weeks followed by placebo/PR for 12 weeks (if detectable HCV-RNA at TW 8).

Arm 3 (BOC/PR48) = PR lead-in for 4 weeks, then BOC/PR for 44 weeks.

Source: Adapted from Applicant's Integrated Summary of Safety

In treatment-naïve trial (P05216), study drug discontinuations due to AE were less frequent in the RGT arm (12%) compared with the BOC/PR 48-week arm (16%); SAEs were reported by a similar proportion of subjects in the RGT and BOC/PR 48-week arms (11% and 12%, respectively). However, it must be noted that subjects in RGT arms who were late responders received an extra 20 weeks of PR therapy alone beyond 24 weeks of triple therapy (BOC+PR).

In previous treatment failure trial (P05101), the proportion of subjects with SAEs (10%) and study drug discontinuations due to AE (8%) was lower in the RGT arm compared with the 48-week BOC/PR arm (14% and 12%, respectively). However, these were more frequently reported in the boceprevir-containing arms than in the PR control arm (in controls, 5% SAEs and 3% discontinuations). This difference may be due to the decreased exposure in the control arm. In this trial, subjects in RGT arms who were late responders received an extra 12 weeks of PR therapy alone beyond 32 weeks of triple therapy.

Reviewer's Comment

It should be noted that the length of exposure was different in the control arm versus boceprevir-containing arms, particularly in the study of previous treatment failure study

(P05101), in which many control subjects discontinued early due to treatment failure (futility rule at TW 12), leading to a 2.5-fold increase in duration of therapy in the boceprevir-containing arms compared to control. Overall drug exposure was also decreased in the RGT arms, compared to the BOC/PR48 regimen, leading to decrease in SAEs and discontinuations.

Sponsor further reported that subjects in the shorter RGT arms of both studies also experienced fewer SAEs and discontinuations due to AE than subjects assigned to the longer RGT arms. This could be attributed to additional PR therapy in longer RGT arms. Thus, there may be a potential benefit in terms of safety for shorter vs. longer duration of treatment with boceprevir in combination with pegylated interferon/ribavirin for patients in whom efficacy is predicted to be similar with shorter vs. longer durations of triple therapy.

The sponsor also reported the results of an analysis of AEs according to the time to onset (before and after 28 weeks of treatment). Most subjects reported at least one AE within the first 28 weeks of treatment. After TW 28, 67% of PR-treated subjects and 70% of BOC-PR-treated subjects experienced a new onset of at least one AE. The frequently reported adverse events with new onset after TW 28 were mainly anemia and neutropenia.

Adverse Events during and after Lead-in Phase

A 4-week lead-in period of PR prior to the initiation of boceprevir was utilized in the two Phase 3 pivotal trials P05216 and P05101. In treatment-naïve Phase 2 study P03523, 3 out of the 7 arms included a PR lead-in phase.

The most frequent AEs reported during the PR lead-in phase are consistent with those reported with standard of care therapy and include influenza-like symptoms (including pyrexia, arthralgia, myalgia and chills).

After the PR lead-in phase, the most frequently reported AEs are anemia, dysgeusia, fatigue, nausea and neutropenia. Anemia occurs with PR therapy and addition of boceprevir is associated with an additional drop in hemoglobin and neutrophil count. Dizziness (13%) and dyspnea (14%) were reported more frequently in the BOC/PR arm after the lead-in compared to during lead-in (6% and 7%, respectively). These could be partly due to additional decrease in hemoglobin values seen after the addition of boceprevir. Rash was reported more often in both the PR control arm (13%) and BOC/PR arm (16%) after lead-in than during lead-in (5%).

Adverse Events during Follow-up Phase

Since some of the adverse events associated with pegylated interferon and ribavirin therapy may take longer time to resolve after the completion of treatment, AEs in the follow-up phase were also evaluated by the applicant.

Treatment-related AEs (as determined by the investigator) that were ongoing at the follow-up visit were reported in 76% of subjects in the PR control arm compared to 81% in the boceprevir-containing arms. Most of the reported AEs were observed in similar frequency in both boceprevir treated subjects and controls. However, the frequency of anemia was higher in the boceprevir-containing arms (13%) compared to PR arm (7%).

Overall, subjects with ongoing AEs through follow-up week 24, i.e., AEs that were still ongoing after 6 months of follow-up, were similar in PR control arm (50%) and boceprevir-containing arms (52%). Events that occurred in $\geq 10\%$ of subjects in any treatment arm included fatigue and insomnia.

7.5.3 Drug-Demographic Interactions

Applicant reports that there did not appear to be a sex-related difference in the effects of BOC/PR treatment on white blood cell count, neutrophils, or platelets. The proportion of females and males with severe anemia in the BOC/PR arms was similar. The lower hemoglobin values in females in both the PR and BOC/PR arms during treatment were due to lower baseline hemoglobin values in females compared with males.

In the small group of subjects ≥ 65 years of age ($n=38$), there was an increased frequency of anemia reported by the investigators in subjects receiving boceprevir; 31/38 (82%) compared to 55% of those 50-64 years of age. In the PR group anemia was reported in 48% of those ≥ 65 years of age compared to 35% of those 50-64 years of age.

7.5.4 Drug-Disease Interactions

Phase 1 Hepatic/Renal Impairment Trials

One AE occurred in the hepatic impairment trial, P03747: mild vomiting on Day 3 in a woman with severe hepatic impairment. No clinically significant decreases in hemoglobin were observed; lab data were collected through Day 4.

Three unrelated AEs occurred in two end stage renal disease subjects in the renal impairment trial, P05579: catheter thrombosis in one subject and moderate flatulence and transient ventricular extrasystoles in another subject. In this trial, hemoglobin values declined from baseline to Day 6 with a median change of 0.75 g/dL (range 0.2-3.1 g/dL). Of note, five out of eight subjects with ESRD received concomitant erythropoietin as part of their pretrial medications that continued throughout P05579.

Subjects with Cirrhosis

A total of 143 subjects with cirrhosis participated in the key safety studies. In the pooled safety data, cirrhotic subjects treated with boceprevir had higher rates of SAEs than noncirrhotics (16% vs. 10%, respectively); in comparison, 10% of cirrhotic subjects experienced SAEs vs. 8% of non-cirrhotic subjects in the control arm. Sponsor reports that there did not appear to be any boceprevir-defining toxicity leading to treatment discontinuation in cirrhotic subjects.

In subjects with cirrhosis, all three hematopoietic cell lines were lower in subjects treated with BOC/PR compared with PR controls. There was no apparent difference noted in the effects of boceprevir treatment when given in combination with PR on hemoglobin, white blood cell count, or neutrophils in subjects with or without cirrhosis. However, there was a trend towards lower platelet counts in boceprevir/PR treated subjects who had cirrhosis compared to boceprevir/PR treated subjects without cirrhosis. A total of 14% of subjects with cirrhosis experienced WHO Grade 3 thrombocytopenia on treatment compared to 2% of subjects without cirrhosis; compared to 7% and 1% of PR-treated subjects with and without cirrhosis respectively. No boceprevir-treated subject with cirrhosis experienced Grade 4 thrombocytopenia, compared to three (3/1386, <1%) subjects without cirrhosis. No subject developed Grade 4 thrombocytopenia in PR arm.

Reviewer's comment:

The number of subjects with cirrhosis and advanced fibrosis (F3/F4) in each arm of the two phase 3 studies was small to allow any clinically meaningful conclusions about the safety of boceprevir in RGT arm versus BOC/PR48 arm.

7.5.5 Drug-Drug Interactions

Please refer to Clinical Pharmacology Review of the Phase 1 drug-drug interaction trials. Some issues regarding insufficient available data have been discussed earlier in Section 4.4.3.

The safety and efficacy of combined oral contraceptive (COC) use during boceprevir coadministration have not been sufficiently characterized. A consult was requested from the Division of Reproductive and Urologic Products (DRUP) relating to drug-drug interaction (DDI) studies already performed for boceprevir against combination oral contraceptives and possible recommendations concerning additional DDI studies. Some of the findings of their review are noted here. The completed DDI study conducted with Yaz® (ethinyl estradiol/drospirenone) showed a 24% decrease in ethinyl estradiol (EE) exposure and a 100% increase in drospirenone (DRSP) exposure during boceprevir administration. The magnitude of increase in DRSP exposure may potentially increase the risk of adverse events, including hyperkalemia and thromboembolism. It is unknown

whether the doubling of exposure would necessarily occur with other progestational components (e.g. norgestimate or norethindrone). The 25% decrease in EE exposure may result in breakthrough bleeding and may theoretically impact COC efficacy, though there is limited information on which to draw a conclusion. Further, because of deficiencies in the design of the completed DDI study, reliability of the PK results and interpretation of the findings are in question. Because it may be challenging for women of child-bearing potential to rely on two barrier methods while on concomitant treatment with ribavirin, the safety and efficacy implications of boceprevir coadministration with COCs should be further characterized. The Applicant has acknowledged these concerns and plans to conduct a clinical DDI study with another progestin-containing COC.

A total of 96 subjects used concomitant oral contraceptives in the BOC/PR arm compared to 31 subjects in the PR arm in the pooled studies. There was an increased frequency of anemia in boceprevir-treated subjects who used oral contraceptives (67%, 64/96) than in those who did not (48%, 693/1452), and a higher incidence in both groups compared with PR. The frequency of anemia was similar in PR-treated subjects who used oral contraceptive compared with those who did not (26% vs. 29%). There was also an increased frequency of gastroesophageal reflux disease in boceprevir-treated subjects who used oral contraceptives (11%, 11/96) than in those who did not (6%, 82/1452), compared to 0% (0/31) and 3% (13/516) of PR-treated subjects who used or did not use oral contraceptives, respectively. The applicant concluded that the clinical significance of these findings is unknown.

Another outstanding issue is that a DDI study was not conducted to assess the effect of boceprevir on antidepressant exposure. Unanticipated decreases in the exposure of selective serotonin reuptake inhibitors (SSRIs), including paroxetine, sertraline and escitalopram, have been observed in DDI studies conducted with other HCV and HIV protease inhibitors. Because the mechanism of these observed decreases have not been characterized, and given the importance of these agents in HCV patient care, an in vivo study is considered important to rule-out a potentially significant interaction.

Patients receiving opioid-agonist substitution therapy were allowed to participate in the studies P05216 and P05101 but were not allowed, by protocol, in Study P03523. A total of one PR-treated subject and 16-boceprevir-treated subjects were using methadone as opioid-agonist substitution therapy in studies P05216 and P05101; 12 men and 5 women. Of these 17 subjects, 11 completed therapy. None required dose reduction for psychiatric events, and none reported recurrence of intravenous drug use. Eight of these subjects reported psychiatric AEs, the most common being insomnia and anxiety. No psychiatric SAEs were reported.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The maximum study duration of boceprevir trials (approximately 72 weeks) limits the assessment for oncologic events. Most of the reported malignancies are those consistent with the patient population and no clustering of any particular events was noted. A long-term follow-up study (P05063) is ongoing which may provide additional information.

7.6.2 Human Reproduction and Pregnancy Data

No reproductive studies in humans have been done for boceprevir at this time. Because ribavirin is genotoxic and teratogenic, pregnancy was an exclusion criterion during the clinical development program of boceprevir. Males with pregnant partners were not to be enrolled. In addition, urine pregnancy testing was performed at regular intervals during study as defined in each protocol.

The available information on pregnancy outcomes in subjects and female partners of subjects was collected by the sponsor. Pregnancies were reported in 4 female subjects and 8 female partners of male subjects. Two pregnancies in female subjects occurred during follow-up period (after 6 months) and one prior to start of treatment. Outcome was unknown in two and one baby's status was reported a good. An unintended pregnancy in a 29-year old female occurred on an unknown date; an elective termination occurred without complications and no embryo abnormalities were reported.

Based on the available data, the effects of *in utero* exposure to boceprevir are unknown.

7.6.3 Pediatrics and Assessment of Effects on Growth

The Applicant has requested a waiver of pediatric studies in children < 3 years of age and a deferral for submission of pediatric data in children aged 3 to 18 years. This was discussed at the FDA Pediatric Review Committee meeting held on February 9, 2011 and the request has been accepted. A pediatric development plan was submitted by the applicant, the review of which is ongoing at this time.

Boceprevir has only been administered in adults, and therefore no clinical assessment of effects on growth has been performed.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The data on human overdose with boceprevir is very limited. Two cases of potential boceprevir overdose were reported as of June 01, 2010. Per protocol, an overdose of boceprevir was defined as a total daily dose above 3600 mg. The exact number of extra capsules taken per day is not known.

Subject # 78/011095 (Study P05101)

A 51-year-old male was unintentionally dispensed two kits of blinded study medication instead of one kit for one week. The subject consumed 92 capsules of boceprevir (200 mg boceprevir per capsule). No AEs were reported by the subject.

Subject # 19/001902 (Study P05514)

A pill count at TW 18 visit in a 60-year-old male revealed that he took 12 extra ribavirin pills and 43 extra boceprevir pills over 5-6 weeks period (the subject had stopped using a pill box and was taking the pills out of the bottle). No AEs were reported.

The abuse potential of boceprevir is anticipated to be low based on the pharmacologic class of the drug. As per the applicant, there is no information to indicate that withdrawal and rebound occur with boceprevir. Viral resistance to boceprevir may develop in subjects who fail on treatment with boceprevir-containing regimens. This was discussed in Section 4.

7.7 Additional Submissions / Safety Issues

The Applicant submitted the Safety Update Report in February 2011 and the data have been integrated into the appropriate sections of this review.

In addition, the Applicant provided responses to FDA requests for information throughout the review. Pertinent information provided through these responses is incorporated into this review.

8 Postmarket Experience

This product has not yet been approved for marketing in any country and therefore there is no postmarketing experience at this time.

9 Appendices

9.1 Literature Review/References

1. Clinical Review by Dr. Charles Cooper focusing on the specific safety concern of anemia.
2. Consult from the Division Of Hematology Products
3. Consult from the Division of Reproductive and Urologic Products

Literature citations are provided as footnotes in the relevant sections of this document.

9.2 Labeling Recommendations

The proposed package insert (PI or label) is being reviewed by all disciplines involved in the review of this application. The following important revisions are being considered:

- **Dosage and Administration section:** Add information about discontinuation of therapy for fertility or virologic breakthrough.
- **Contraindications Section:** Information regarding coadministration with potent CYP3A4/5 inducers, where significantly reduced boceprevir plasma concentrations may be associated with reduced efficacy.
- **Warnings and Precautions Section:** To add information about neutropenia and (b) (4). To add descriptive information about erythropoietin use during the trials and the potential risk associated with erythropoietin use.
- **Adverse Reactions Section:** Include clinically significant adverse events under “*Less Common Adverse Reactions*”
- **Clinical Studies Section:** The efficacy tables are being revised based on the analyses conducted by FDA Statistical Reviewer. (b) (4)

Discussions regarding the labeling recommendations are ongoing at this time and have not been finalized with the Applicant. The final agreed upon PI will be available at the time of approval.

9.3 Advisory Committee Meeting

The Antiviral Drugs Advisory Committee meeting is being convened by the Division on April 27, 2011 to solicit the committee's comments and recommendations regarding this application. Specific preliminary questions/issues which will be addressed and discussed are listed below. Please also refer to the FDA background package dated April 04, 2011 which address these issues in depth. Detailed information on the AC discussions and recommendations will be accessible in the transcripts after the committee meeting.

Issue 1: Please comment on the increased frequency and severity of anemia, and also the increased risk for neutropenia and thrombocytopenia when boceprevir is added to pegylated interferon and ribavirin.

Issue 2: Considering potential risk and benefits do the available data support approval of boceprevir for treatment of patients with chronic hepatitis C genotype 1 in combination with pegylated interferon and ribavirin?

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

Issue 3: Please comment on the strength of the evidence for use of boceprevir in combination with pegylated interferon/ribavirin in prior null responders (patients with < 2 log₁₀ decrease in HCV RNA at 12 weeks), who were not included in the treatment-experienced population in the Phase 3 trial, P5101.

Issue 4: Please comment on the strength of the evidence for use of response-guided therapy with boceprevir in combination with pegylated interferon and ribavirin for the following groups of patients:

- a. Treatment-naïve patients:
 - I. Should treatment-naïve patients with detectable HCV RNA at Week 8 and undetectable at Week 24 (i.e., late responders not meeting futility rule) receive longer durations of boceprevir plus PR?
 - II. Black patients
 - III. Patients with more advanced fibrosis stage or cirrhosis (Metavir scores F3 or F4)
- b. Patients who have previously failed treatment with pegylated interferon/ribavirin, including relapsers, partial responders, and null responders

Issue 5: In addition to pediatric studies, are there any other postmarketing studies you would like to see for boceprevir? What postmarketing trials are needed to further define risks or optimal use of boceprevir?

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/s/

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Clinical Review
Charles Cooper, M.D.

Background

It is well recognized that treatment of chronic hepatitis C infection with pegylated interferon and ribavirin is associated with development of anemia and significant declines in hemoglobin (Hgb) concentration. Ribavirin has been shown to cause a dose-related hemolysis which is exacerbated by interferon-related bone marrow suppression resulting in blunted reticulocytosis. Typical hemoglobin concentration declines of approximately 3 grams/dL may interfere with treatment by requiring ribavirin dose reduction.

In phase 1 monotherapy clinical trials, boceprevir was not shown to result in anemia. However, as with other ketoamides, the addition of boceprevir to pegylated interferon/ribavirin (PR) has been associated with an incremental decrease in hemoglobin concentration beyond that typically seen with PR.

A randomized, placebo-controlled, third-party/evaluator blind study of boceprevir in healthy male volunteers was conducted (Assessment of the Effects of Boceprevir (SCH 503034) on Red Blood Cells in Healthy Male Volunteers (Protocol No. P05351). The data from this study suggest that anemia related to boceprevir is not due to a hemolytic process but may be related to bone marrow suppression.

The two pivotal phase 3 trials were conducted in a way to allow for investigator discretion with regard to anemia management, in that investigators were allowed to manage subjects with declining Hgb levels using a variety of approaches including erythropoietin (epo), ribavirin dose reduction, transfusion, observation, or any combination of these. At the same time, protocol-defined recommendations instructed investigators to pursue some form of intervention when hemoglobin levels dropped below 10g/dL.

This review includes assessment of anemia in the two phase 3 pivotal trials submitted in support of NDA 202258, Study P05101, and study P05216. All analyses include both studies unless otherwise indicated.

Summary/Overview

Boceprevir was associated with increased rates of anemia-related adverse events, Grade 3 and 4 anemia-related adverse events, anemia-specific interventions, and greater magnitude of absolute hemoglobin decline from baseline in comparison to pegylated interferon/ribavirin alone. Occurrence of serious anemia-related serious adverse events, mostly associated with hospitalization and transfusion, were higher in boceprevir-treated subjects; however, these events were still uncommon.

There isn't a clear definition of anemia that can be used in the analysis of the phase 3 data to fully characterize the magnitude of toxicity conferred by boceprevir. Use of investigator-reported anemia is not directly indicative of the degree of boceprevir-induced toxicity, due to confounding that resulted from the study design and also due to misclassification bias.

The design of the two phase 3 trials included an anemia management strategy in which investigators were advised to intervene when hemoglobin concentrations fell to 10g/dL or lower. Because the definition of an adverse event included any laboratory value resulting in an intervention, anemia adverse event reporting in these studies was linked to the occurrence of an intervention prompted by of hemoglobin concentrations at or below the threshold of 10g/dL. In fact, subjects who developed a hemoglobin ≤ 10 g/dL, but who didn't receive an intervention (transfusion, ribavirin or boceprevir dose reduction and/or use of erythropoietin), were unlikely to be reported as having experienced an anemia adverse event. This was the case for 25/122 (21%) subjects who had developed a hemoglobin ≤ 10 g/dL in the phase 3 trials.

Because investigators weren't required to intervene upon development of a hemoglobin ≤ 10 g/dL, there was some degree of variability with regard to how anemia was managed leading to differences in anemia adverse event reporting and inherent misclassification.

This resulted in two findings:

1. Subjects with hemoglobin ≤ 10 were not always reported as having had an anemia adverse event 108/688 (16%)
2. Subjects with hemoglobin ≤ 10 did not always have an intervention 122/688 (18%).

Additionally complicating the assessment of boceprevir-associated toxicity is the fact that using hemoglobin level of ≤ 10 g/dL as a protocol-specified intervention trigger added additional bias by increasing the likelihood that patients, particularly females, who had lower baseline hemoglobin levels, would receive an intervention, and thus be reported as having had an anemia event. As a result, the reporting of an anemia adverse event was closely tied to lower baseline hemoglobin measurements, leading to subsequent interventions with less regard for overall magnitude of hemoglobin decline. This caused a significant overlap in absolute magnitude of hemoglobin decline for subjects with no intervention or reported anemia adverse events and those with an intervention and/or reported anemia adverse event.

Paradoxically, those subjects who had lower baseline hemoglobin, who thus experienced a higher rate of interventions and anemia adverse event reports, actually experienced a smaller absolute decline in hemoglobin concentration. Meanwhile, subjects with higher baseline hemoglobin levels (such as males), despite having a lower rate of reported anemia-related adverse events and interventions, experienced a greater magnitude of absolute hemoglobin decline when compared to female subjects. This finding may be due to the fact that subjects with lower baseline hemoglobin concentrations, such as females, were not only more likely to experience an intervention, but also to

experience that intervention earlier in the time course of their therapy, thus preventing the opportunity for a larger absolute decline. For these patients, it is not known whether the magnitude of their decline, in the absence of an intervention would truly have been different than subjects whose baseline hemoglobin levels were higher in the normal range. Conversely, for male subjects, there were fewer interventions and, when interventions occurred, they did so later in the course of treatment, thus providing more opportunity for greater magnitude of hemoglobin declines.

The combination of these confounders and biases makes it difficult to do a detailed characterization of boceprevir-related anemia in the phase 3 trials. Even basic subgroup assessment by baseline demographic characteristics is not interpretable because of post-baseline variations in adverse event reporting and anemia management, as well as varying baseline hemoglobin levels across each subgroup. As a result, characterization of boceprevir-related anemia based on phase 3 clinical trial data is limited to simple descriptive analyses of overall measures of anemia according to laboratory values by treatment arm as well as the proportions of interventions, and assessment of adverse events, serious adverse events, and discontinuations.

The applicant notes that use of boceprevir in these trials resulted in a 1 g/dL decrease in hemoglobin over what is generally observed with pegylated interferon and ribavirin alone. However, it is important to note that the magnitude of the hemoglobin decrease attributable to boceprevir cannot be determined from these trials due to confounding by use of erythropoietin and/or ribavirin dose reduction. Additionally, use of baseline factors to predict development of anemia in these studies was confounded by the criteria used to define anemia and the recommended management algorithms.

Assessment of Possible Confounding and Bias

Adverse Events

In order to understand analyses of adverse events for the two phase 3 studies, it is important to review the study design which, for the endpoint of anemia, has a significant impact.

AE definition:

Per the protocols for Studies P05101 and P05216, an adverse event (AE) is any untoward medical occurrence in a subject administered a pharmaceutical product, biologic (at any dose), whether or not considered related to the use of that product.

In addition, clinically significant laboratory abnormalities that meet one or several of the following criteria are considered to be adverse events:

- Requires intervention/additional therapy
- Requires a dose modification
- Associated with a clinical manifestation

The protocols also advise investigators that if the serum hemoglobin is ≤ 10 g/dL, corrective action should occur and should include either reduction of ribavirin, or initiation of erythropoietin therapy or combination of both may be used.

Therefore, because the protocol directed investigators to institute corrective action/intervention when the Hgb was ≤ 10 g/dL, the protocol indirectly increased the likelihood that investigators reported Hgb ≤ 10 g/dL as an AE, particularly in those cases when a hemoglobin concentration of 10g/dL or lower was associated with an intervention.

Table 1. shows that the proportions of patients that were reported as having had an anemia adverse event in relation to whether or not an intervention occurred. This analysis shows that the likelihood that a patient was reported as having had an anemia adverse event was higher if their nadir Hgb of ≤ 10 g/dL was accompanied by an intervention.

Table 1. Likelihood of Anemia Adverse Event Reporting by Intervention and Nadir Hemoglobin Concentration

	Intervention Occurred		No Intervention	
	Nadir Hgb \leq 10g/dL N=566	Nadir Hgb>10g/dL N=114	Nadir Hgb \leq 10g/dL N=122	Nadir Hgb>10g/dL N=698
Anemia adverse event reported	555 (98%)	64 (56%)	25 (21%)	22 (3%)

Table 2 shows the numbers of subjects according to whether an anemia adverse event was reported, an anemia intervention occurred, and a nadir Hgb \leq 10g/dL was recorded.

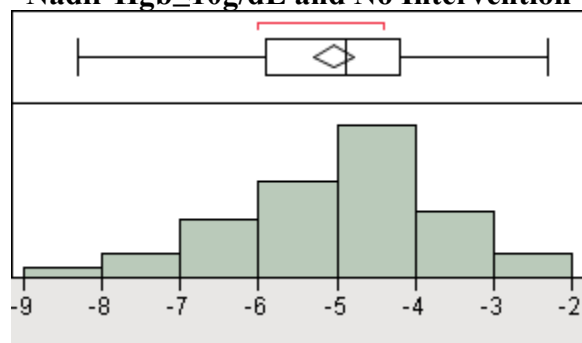
Table 2. Number of Subjects by Nadir Hgb, Anemia Event and Anemia Intervention*

Nadir Hgb \leq 10g/dL	Anemia AE reported	Anemia Intervention	No. of Subjects
None			676
Yes	Yes	Yes	555
Yes	No	No	97
No	Yes	Yes	64
No	No	Yes	50
Yes	Yes	No	25
No	Yes	No	22
Yes	No	Yes	11

*Each Subject is represented once.

There were 97 subjects who developed a nadir hemoglobin concentration of \leq 10g/dL and yet did not have an adverse event reported or intervention. **Figure 1.** shows the distribution of absolute hemoglobin decline for these subjects. This graph shows that this subset of patients experienced significant declines in hemoglobin concentration, despite not having had an adverse event reported.

Figure 1. Distribution of Absolute Hgb Decline for Subjects with Nadir Hgb \leq 10g/dL and No Intervention*



*x-axis is magnitude of hemoglobin decline in g/dL

The lower quartile, median, upper quartile, and mean of maximum hemoglobin concentration change for this group of subjects in g/dL was: -4.2, -4.9, -5.9, and -5.0.

Due to either lack of intervention and/or inconsistent adverse event reporting, 108/688 (16%) who developed a nadir Hgb ≤ 10 g/dL had no anemia adverse event reported. The proportions of these subjects who had a nadir Hgb ≤ 10 g/dL and with no anemia adverse event reported ranged from 12-25% across the treatment groups (Arm 1: 35/141 (25%) , Arm 2 (28wk): 26/192 (14%), Arm 2 (36wk): 15/81 (19%), Arm 3 32/274 (12%). Arm 1 appears to have had a higher overall percentage of subjects with a nadir Hgb ≤ 10 but without a reported anemia adverse event.

Although the study protocols directed investigators to intervene upon development of Hgb ≤ 10 , this was not required. As a result, differences in anemia management occurred. This resulted in 122/688 (18%) of subjects with a nadir Hgb of ≤ 10 receiving no intervention.

Tables 3 and 4 show the difficulty that this creates when trying to understand the relationship between reported anemia adverse events and the severity of toxicity. **Table 3** shows the number of subjects with and without anemia adverse events reported according to absolute change in hemoglobin concentration from baseline. There is a significant overlap in the numbers of subjects who were reported as having had an anemia adverse event at varying levels of hemoglobin decline. **Table 4** shows that differences in reporting appear to be related to development of a Hgb nadir ≤ 10 g/dL and/or an intervention. At all levels of absolute hemoglobin decline, subjects with a nadir Hgb ≤ 10 and/or intervention were much more likely to have had an anemia adverse event reported. This makes it difficult to use adverse event reporting as a measure of the severity of toxicity, because the magnitudes of hemoglobin decline does not correlate well with likelihood of anemia adverse event reporting.

Table 3. Adverse Event Reporting by Absolute Hemoglobin Change from Baseline

	No Anemia Adverse Event	Yes Anemia Adverse Event
Absolute Change Hgb g/dL	n	n
≥ 6	58	181
≥ 5	192	382
≥ 4	400	545
≥ 3	640	636

n= number of subjects

Table 4. Differences in Anemia-related Adverse Event Reporting by Nadir Hemoglobin, Intervention, and Absolute Change

	NO Anemia Adverse Event Plus Nadir Hgb ≤ 10 and/or Intervention (n/N)*	YES Anemia Adverse Event Plus Nadir Hgb ≤ 10 and/or Intervention (n/N)†
Absolute Change Hgb g/dL		
≥ 6	29/58	180/181
≥ 5	68/192	373/382
≥ 4	113/400	530/545
≥ 3	143/640	616/636

*n= number of subjects with no anemia adverse event reported and a nadir hgb ≤ 10 and/or intervention

*N=total number of subjects with no anemia adverse event by absolute hgb change

†n= number of subjects who did have an anemia event reported and a nadir hgb ≤ 10 and/or intervention

†N=total number of subjects who did have an anemia adverse event by absolute hgb change

Distribution of Absolute Hgb decline for patients with Nadir Hgb Above and Below 10 by Reported Anemia Event

Table 5 shows that for subjects with a nadir Hgb ≤ 10 , the magnitude of hemoglobin concentration decline was similar regardless of whether an adverse event was reported.

Table 5 Measures of Central Tendency for Maximum Hemoglobin Concentration Decline for Subjects with Nadir Hgb Concentration of Less than 10g/dL by AE Reporting Status

Measure	Hgb ≤ 10 g/dL and No AE reported	Hgb ≤ 10 g/dL and AE reported
Median	-4.9	-5.3
Mean	-5.0	-5.2
25 percentile	-5.9	-6.2
75 th percentile	-4.2	-4.4

Effect of Baseline Hemoglobin Concentration on Adverse Event Reporting

Because anemia adverse event reporting was associated with occurrence of an intervention, often prompted by a drop in Hgb concentrations to 10g/dL or lower, baseline hemoglobin levels for subjects with and without a reported anemia adverse event were explored. A trend towards lower baseline hemoglobin levels was seen in subjects who were reported as having had an anemia adverse event. Additional analyses were done that showed lower baselines for subjects whose nadir Hgb concentrations were 10 g/dL or lower. Subjects with lower baseline hemoglobin required less of an absolute decline to reach a level of 10 or lower.

Table 6 shows median and mean baseline measures by treatment arm for subjects according to whether they developed a nadir hemoglobin concentration of ≤ 10 g/dL. This table shows that for each arm, baseline hemoglobin measures were lower on average for subjects who developed a nadir hemoglobin concentration of ≤ 10 g/dL. This finding is consistent with the conclusion that subjects with a lower baseline hemoglobin were more likely to develop a nadir hemoglobin of ≤ 10 g/dL.

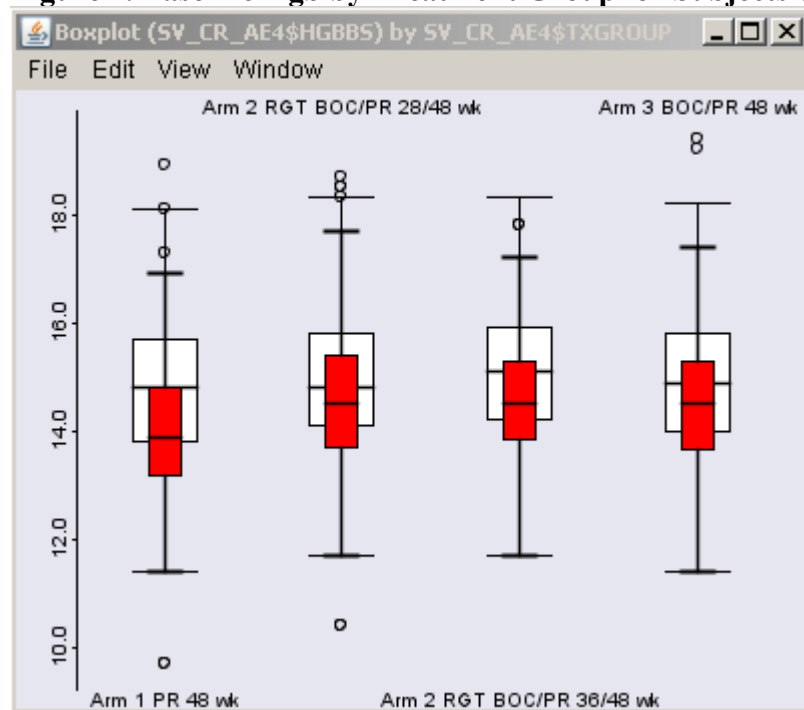
Table 6. Average Baseline Hemoglobin for Subjects by Nadir Hgb

	Baseline for subjects with Nadir Hgb ≤ 10 g/dL		Baseline for Subjects with Nadir Hgb ≥ 10 g/dL	
	Median	Mean	Median	Mean
Arm 1	13.9	14.0	15.2	15.1
Arm 2	14.5	14.5	15.4	15.3
Arm 3	14.5	14.5	15.4	15.4
Total	14.4	14.4	15.3	15.3

Arm 1= peg/ribavirin, Arm 2 = boceprevir/peg/ribavirin response guided therapy, Arm 3= boceprevir/peg/ribavirin

Figure 2 shows a box plot of baseline hemoglobin by treatment arm. This box plot shows that subjects who developed a hemoglobin concentration of 10g/dL or less tended to have lower baseline hemoglobin concentrations.

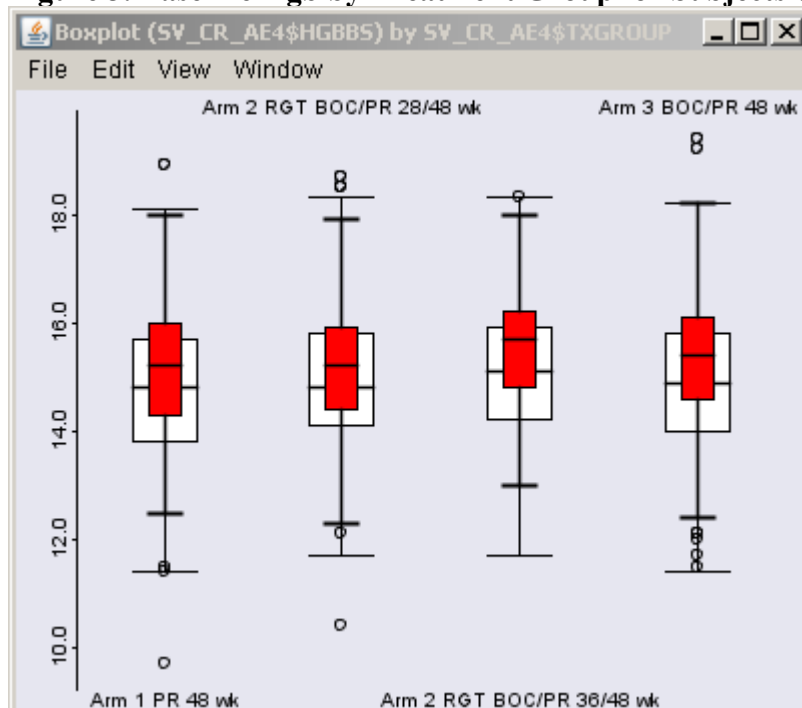
Figure 2. Baseline Hgb by Treatment Group for Subjects with Nadir Hgb of 10 or less



Clear boxes: all subjects in each arm; Red shaded boxes: subjects with nadir Hgb ≤ 10 g/dL; Y-axis: baseline hemoglobin in g/dL. Boxes: middle line represents median, bottom of box represents 25th percentile, top of box represents 75th percentile, lower whisker is 2nd percentile, upper whisker is 98th percentile.

Figure 3 shows a box plot by treatment arm that shows that subjects with a nadir hemoglobin concentration of greater than 10 tended to have higher baseline hemoglobin concentrations.

Figure 3. Baseline Hgb by Treatment Group for Subjects with Nadir Hgb of Greater than 10



Clear boxes: all subjects in each arm; Red shaded boxes: subjects with nadir Hgb ≥ 10 g/dL; Y-axis: baseline hemoglobin in g/dL. Boxes: middle line represents median, bottom of box represents 25th percentile, top of box represents 75th percentile, lower whisker is 2nd percentile, upper whisker is 98th percentile.

These box plots demonstrate that subjects who had higher baseline hemoglobin concentrations were less likely to cross the intervention trigger threshold of 10g/dL and those with lower baseline hemoglobin concentrations were more likely to reach a Hgb of ≤ 10 g/dL.

Table 7 shows the rates of anemia AE reporting, nadir hemoglobin decline to ≤ 10 g/dL, and intervention by baseline hemoglobin concentration of ≤ 14 vs. ≥ 16 . This table shows that anemia adverse event reporting, hemoglobin decline to 10g/dL or lower, and interventions occurred more often in subjects with lower baseline hemoglobin concentrations.

Table 7. Rates of Anemia AEs, Hgb ≤ 10 g/dL, and Interventions by Baseline Hgb

	n/N	%
Baseline Hgb ≤ 14 g/dL		
Anemia AE	246/393	63
Nadir Hgb ≤ 10	265/393	67
Intervention	243/393	62
Baseline Hgb ≥ 16 g/dL		
Anemia AE	76/298	26
Nadir Hgb ≤ 10	76/298	26
Intervention	56/298	19

Misclassification

Although the study protocols directed investigators to intervene upon development of Hgb ≤ 10 , this was not required. As a result, differences in anemia management occurred amongst the 688 subjects who developed a post-baseline nadir hemoglobin of 10g/dL or less. This resulted in the following inconsistencies.

- 108/688 (16%) who developed a nadir Hgb ≤ 10 g/dL had no anemia adverse event reported.
- 122/688 (18%) subjects developed a hemoglobin ≤ 10 g/dL without any intervention
- 97/688 (14%) of subjects with a nadir Hgb of ≤ 10 received no intervention and no anemia adverse event reported.

Also, there were subjects who experienced quite significant declines in hemoglobin concentrations but were not reported as having had an anemia adverse event. **Tables 2 and 4** above show that magnitude of absolute hemoglobin decline was not a good predictor of which subjects were reported as having an anemia adverse event. In subjects who experienced a hemoglobin decline of 4 g/dL or greater, 400/945 (42%) had no anemia adverse event reported and in subjects with a decline of 5g/dL or greater, 192/574 (33%) had no anemia adverse event reported. Even in subjects who had the largest declines in hemoglobin concentrations (7 to 10 g/dL), 15/84 (18%) were not reported as having had an anemia adverse event.

Effects of Confounding on Subgroup Analysis of Anemia

Because of the identified confounders related to baseline hemoglobin levels and adverse event reporting, it is very difficult to interpret the results of any sub-group analysis. As previously shown in **Table 7**, subjects with lower baseline levels were at increased risk for reaching the intervention trigger point and thus experiencing an intervention and reported anemia-related adverse event. In addition, variability in anemia management and subsequent adverse event reporting resulted in a meaningful proportion of subjects who were not managed in the same way as other similar subjects. This adds additional challenges to interpreting the results of sub-group analyses.

Additionally, subsets of subjects appear to have received an intervention earlier in the course of treatment and experienced a smaller absolute hemoglobin decline from baseline. Since the likelihood of adverse event reporting was linked to the occurrence of an intervention, assessment of adverse events as a measure of boceprevir toxicity is also affected.

So, for any sub-group, there is variation across the treatment arms in factors shown to impact measures of anemia assessment. Since the numbers of subjects in these subgroups is relatively small, these factors are not distributed evenly across the treatment arms.

A good example of the difficulties encountered in trying to assess anemia toxicity within subgroups can be seen with attempting to assess differences in toxicity by sex. These same issues pertain to other subgroup analyses.

Table 8 shows anemia-related adverse event occurrence by treatment arm for females vs. males. This analysis appears to indicate that females are at significantly greater risk for anemia-related adverse events than males.

Table 8. Anemia-related Adverse Events by Arm and Sex

	Females n/N (%)	Males n/N (%)
Arm 1	77/179 (43)	53/264 (20)
Arm 2	128/203 (63)	139/327 (43)
Arm 3	132/194 (68)	139/333 (42)
Total	337/576 (59)	331/924 (36)

Arm 1= peg/ribavirin, Arm 2 = boceprevir/peg/ribavirin response guided therapy, Arm 3= boceprevir/peg/ribavirin

However, a different picture emerges if an attempt is made to control for differences in baseline hemoglobin concentration. The analysis shown in **Table 7** demonstrates that lower baseline measures, as typically found with females, were associated with increased anemia interventions and adverse event reporting. In **Table 9**, an analysis of anemia-related adverse events by sex is presented, however, for this analysis, only subjects (male and female) with baseline hemoglobin measurements of $\geq 14\text{g/dL}$ and $\leq 15\text{g/dL}$ are included. This assessment reduces possible confounding that may occur as a result of differences in baseline hemoglobin, because all subjects in this analysis share similar baseline hemoglobin concentrations. The analysis shown in **Table 9** does not support the finding of an association of female sex with anemia events.

Table 9. Anemia-related Adverse Events by Arm and Sex for Subjects with Baseline Hgb of $\geq 14\text{g/dL}$ and $\leq 15\text{g/dL}$

	Females n/N (%)	Males n/N (%)
Arm 1	20/58 (34)	14/64 (22)
Arm 2	49/91 (54)	47/84 (56)
Arm 3	42/74 (57)	52/90 (58)
total	111/223 (50)	113/238 (48)

Arm 1= peg/ribavirin, Arm 2 = boceprevir/peg/ribavirin response guided therapy, Arm 3= boceprevir/peg/ribavirin

Further analyses were conducted (**Tables 10, 11**) to assess the proportion of subjects with interventions as well as the median and mean hemoglobin concentration changes for males vs. females who shared similar baseline hemoglobin measurements ($\geq 14\text{g/dL}$ and $\leq 15\text{g/dL}$). **Table 10** does not show differences in median and mean absolute hemoglobin change from baseline for males and females with similar baseline hemoglobin concentrations.

Table 10. Median and Mean Absolute Hemoglobin Change by Arm for Males and Females with Baseline Hemoglobin Concentration of $\geq 14\text{g/dL}$ and $\leq 15\text{g/dL}$

	Females		Males	
	Median (g/dL)	Mean (g/dL)	Median (g/dL)	Mean (g/dL)
Arm 1	-3.8	-3.7	-3.4	-3.7
Arm 2	-4.6	-4.4	-4.7	-4.6
Arm 3	-4.8	-4.7	-4.9	-4.7
Total	-4.4	-4.3	-4.5	-4.4

Arm 1= peg/ribavirin, Arm 2 = boceprevir/peg/ribavirin response guided therapy, Arm 3= boceprevir/peg/ribavirin

Table 11 shows the proportion of female and male subjects with similar baseline hemoglobin concentrations who experienced an anemia intervention. The number of subjects is relatively small in each category which increases variability; however, no discernable consistent pattern of difference is seen.

Table 11. Proportion of Anemia Interventions for Males and Females with Similar Baseline Hgb Concentrations ($\geq 14\text{g/dL}$ and $\leq 15\text{g/dL}$)

	Females n/N (%)	Males n/N (%)
Arm 1	22/58 (38)	17/64 (27)
Arm 2	46/91 (51)	48/83 (58)
Arm3	41/74 (55)	55/90 (61)
Total	109/223 (49)	120/237 (51)

Arm 1= peg/ribavirin, Arm 2 = boceprevir/peg/ribavirin response guided therapy, Arm 3= boceprevir/peg/ribavirin

These analyses support the conclusion that confounding by baseline hemoglobin concentration may be responsible for sex-related differences in anemia adverse event reporting, anemia interventions, and absolute hemoglobin change from baseline. There are additional sources of bias that these analyses do not take into account, including: differential anemia adverse event reporting and interventions (males were more likely than females to experience a nadir hemoglobin concentration of $\leq 10\text{g/dL}$ without having an intervention or adverse event reported). Attempts to increase the baseline hemoglobin window for inclusion would result in larger proportion of subjects at the lower end of the range being female, thus, adversely affecting the analysis results.

Because potential subgroups of interest are relatively small, differences in baseline Hgb exist across treatment arms within the subgroup. In order to perform subgroup analyses, one would have to control for: baseline hemoglobin measurement, differences in anemia interventions, and differences in adverse event reporting. However, this would not address the effect that post-baseline interventions, inconsistently applied across the study population, have on the magnitude of absolute hemoglobin decline. **Table 12** shows that a larger percentage of females, were treated with erythropoiesis stimulating agents (ESAs) or had their ribavirin dose decreased earlier (by study day 75) in the course of study therapy. This likely would result in less opportunity for females to experience further declines in hemoglobin concentration. Meanwhile, males, with larger baseline hemoglobin concentrations and later interventions, had more opportunity to experience larger declines prior to reaching the intervention trigger point of Hgb of 10g/dL .

Table 12. ESA or RBV Dose Reduction by Day 75 by Treatment Arm and Sex

Arm	Sex	n/N (%)
Arm 1	F	48/179 (27)
	M	35/264 (13)
Arm 2	F	80/203 (39)
	M	78/327 (24)
Arm 3	F	96/194 (50)
	M	73/333 (22)

Arm 1= peg/ribavirin, Arm 2 = boceprevir/peg/ribavirin response guided therapy, Arm 3= boceprevir/peg/ribavirin

n= number of subjects with intervention prior to study day 75

N=total number of subjects by sex in the treatment group

These issues demonstrate the uncertainty that exists when attempting to interpret the results of subgroup analyses of anemia for these studies. A more thorough assessment of risk characteristics for boceprevir-related anemia toxicity would require the conduct of a larger study or a study that accounted for differences in baseline hemoglobin measures for subgroups of interest and in which post-baseline interventions were applied evenly across the study population.

Assessment of Anemia by Hemoglobin Concentration

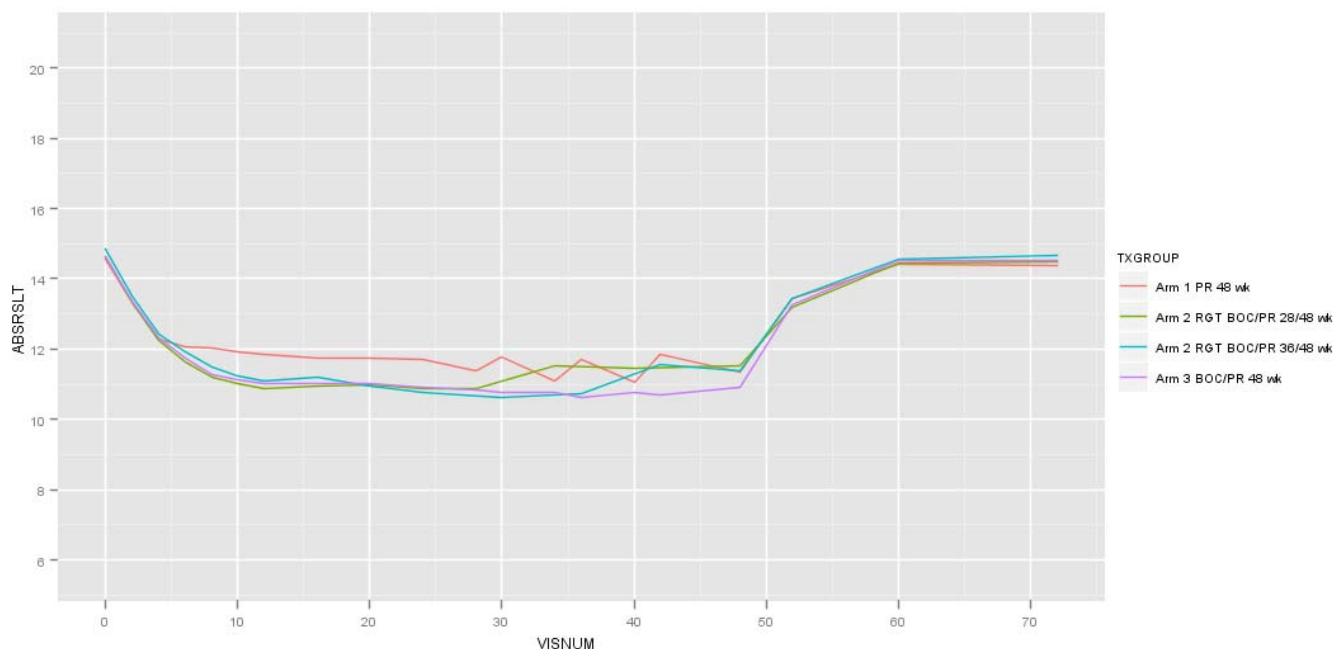
Hemoglobin Concentration Decline During Therapy

Overall Hemoglobin Decline by Visit

Figure 4 shows a plot of mean hemoglobin measures by visit and by treatment group. This graph shows a steep initial decline in mean hemoglobin levels over the first 4-5 weeks, following which there is a stabilization of hemoglobin declines for subjects in the control arm (PR). For the boceprevir arms, however, mean hemoglobin levels continue to decline for another 4-5 weeks, ultimately resulting in an additional approximately 1 g/dL decline. This analysis includes a large percentage of subjects who received interventions specifically aimed at reducing further hemoglobin declines. It is unclear if this observed average additional magnitude of decline could be expected for patients who do not receive interventions similar to those of these studies' anemia management strategy. Because these studies employed a management strategy in which post-baseline interventions were applied in a non-randomized fashion, sub-group analysis of mean hemoglobin measure is confounded.

Figure 4 also shows a pattern of hemoglobin concentration recovery for both studies' arm 2 response guided therapy, occurring soon after cessation of boceprevir (week 28 for study 5216, and week 36 for study 5101).

Figure 4. Mean Hemoglobin Concentration by Visit, Studies 5216 and 5101



X-axis is the week number of study visit. Y-axis is mean absolute Hgb

Table 13 shows the number of subjects from PR and boceprevir treated arms from each phase 3 trial that experienced a decline in hemoglobin to ≤ 10 and 8.5g/dL . For both studies combined, boceprevir-treated patients experienced larger proportions of subjects with nadir hemoglobin concentrations ≤ 10 and $\leq 8.5\text{g/dL}$.

Table 13. Hemoglobin Nadir during Phase 3 Trials (P05216 and P5101)

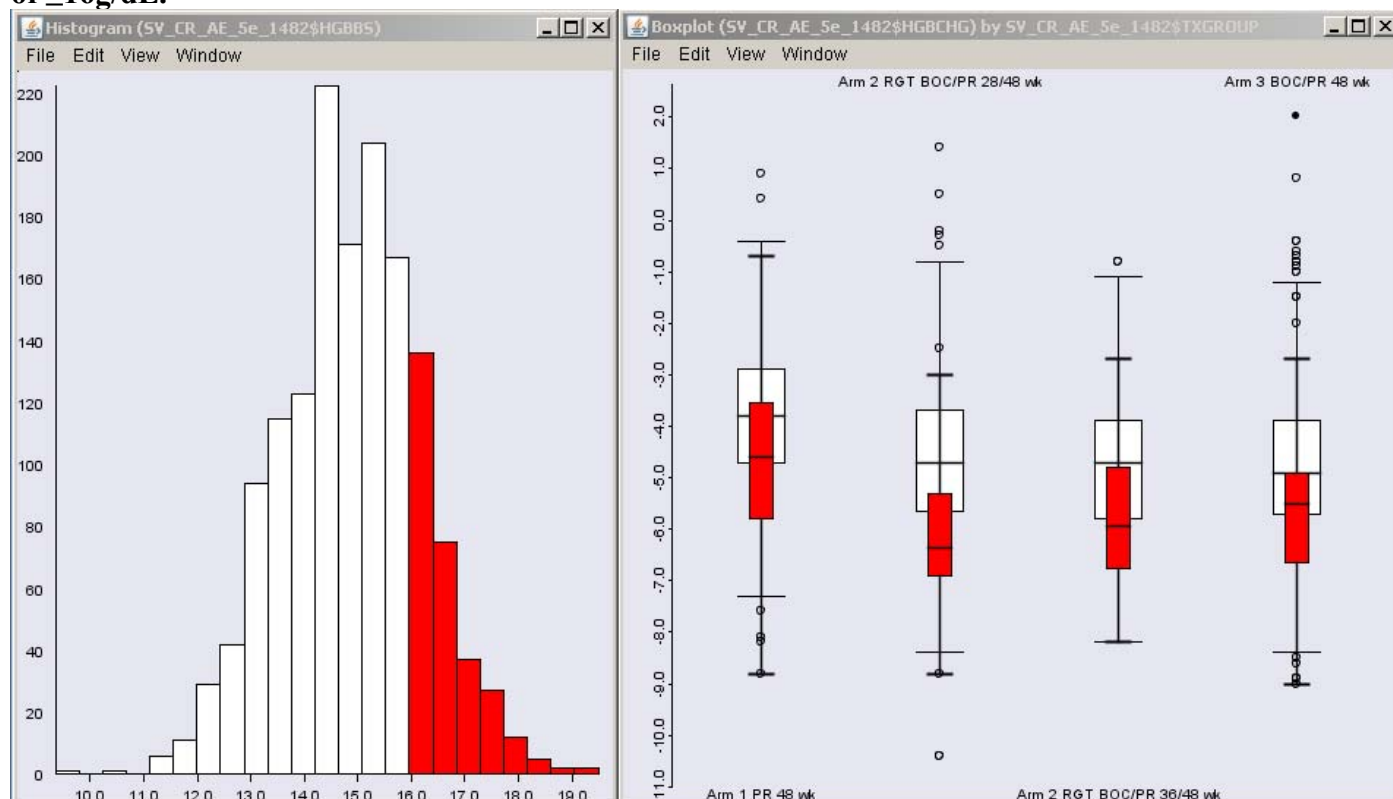
Lowest Hemoglobin Value	P05216 Boceprevir/PR *N=726 n/N (%)	P05216 PR *N=354 n/N (%)	P05101 Boceprevir/PR *N=322 n/N (%)	P05101 PR *N=80 n/N (%)	All Subjects Boceprevir/PR *N=1048 n/N (%)	All Subjects PR *N=434 n/N (%)
Hgb ≤ 10 g/dL	383 (53)	120 (34)	164 (51)	21/80 (26)	547 (52)	141 (32)
Hgb ≤ 8.5 g/dL	58 (8)	15 (4)	34 (11)	1/80 (1)	92 (9)	16 (4)

*N was based on number of subjects with post-baseline hemoglobin measurement

Change in Hemoglobin Concentration by Treatment Group and Baseline Hemoglobin

Differences in hemoglobin decline by baseline hemoglobin were explored. **Figure 5** shows a histogram showing distribution of baseline hemoglobin (left), and a box plot (right) of absolute hemoglobin decline for subjects with a baseline hemoglobin of $\geq 16\text{g/dL}$. This box plot shows that subjects in all arms who had higher baseline hemoglobin measurements experienced greater overall magnitude of absolute declines in hemoglobin concentration.

Figure 5. Hemoglobin Concentration Change by Treatment Group and Baseline Hemoglobin of ≥ 16 g/dL.

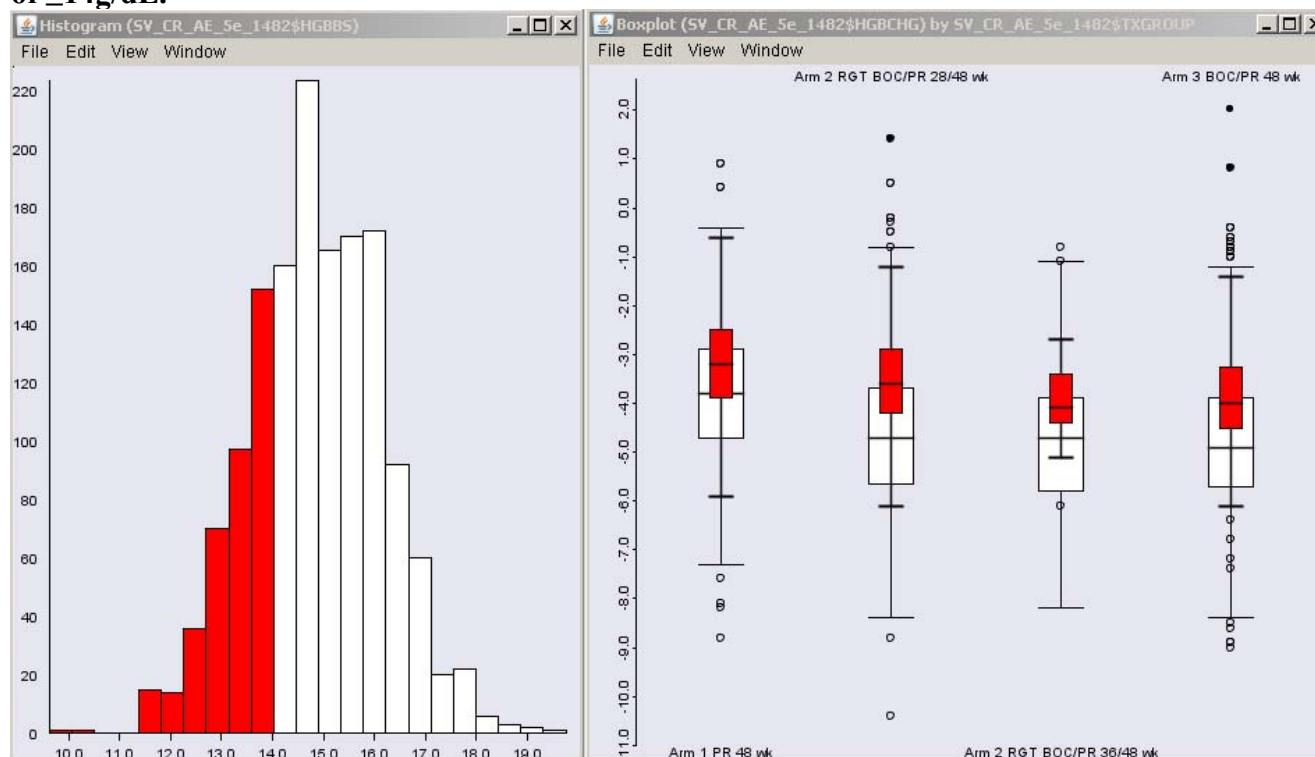


Histogram show distribution of baseline hemoglobin concentration with x-axis as baseline Hgb in g/dL and y-axis as absolute subject count. Subjects with baseline of ≥ 16 g/dL are highlighted/shaded in red.

Box plot: Clear boxes: all subjects in each arm; Red shaded boxes are subjects with baseline Hgb ≥ 16 g/dL; Y-axis: absolute hemoglobin change in g/dL. Boxes: middle line represents median, bottom of box represents 25th percentile, top of box represents 75th percentile, lower whisker is 2nd percentile, and upper whisker is 98th percentile.

Figure 6 shows that subjects in all arms with lower baseline hemoglobin measurements experienced lower overall declines in hemoglobin concentration.

Figure 6. Hemoglobin Concentration Change by Treatment Group and Baseline Hemoglobin of ≤ 14 g/dL.



Histogram: distribution of baseline hemoglobin concentration with x-axis has baseline Hgb in g/dL and y-axis as absolute subject count. Subjects with baseline of ≤ 14 g/dL highlighted/shaded in red.

Box plot: Clear boxes: all subjects in each arm; Red shaded boxes: subjects with baseline Hgb ≤ 14 g/dL; Y-axis: absolute hemoglobin change in g/dL. Boxes: middle line represents median, bottom of box represents 25th percentile, top of box represents 75th percentile, lower whisker is 2nd percentile, and upper whisker is 98th percentile.

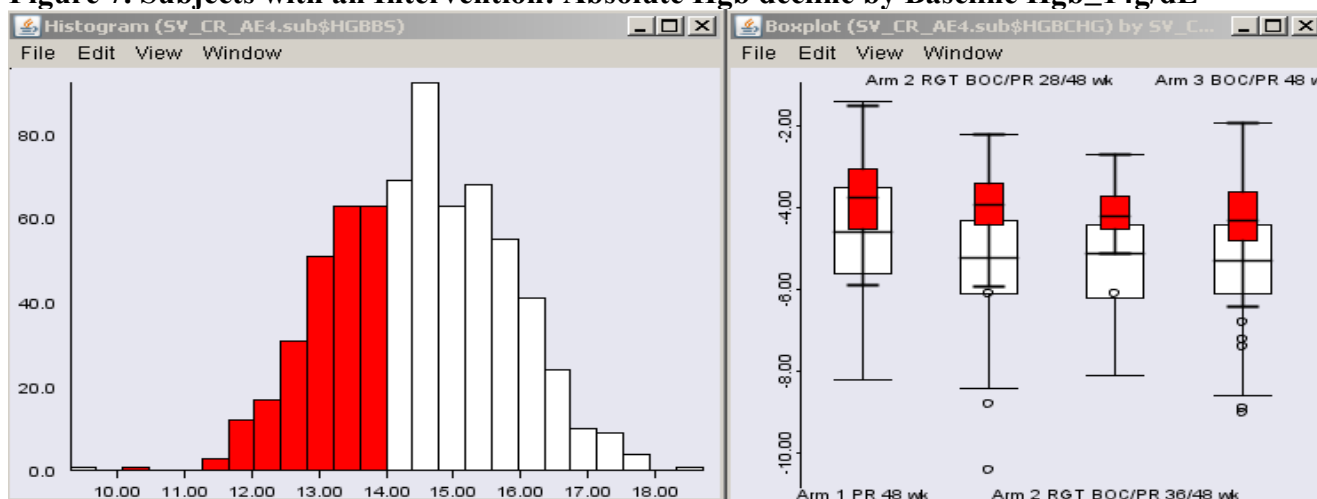
Table 14 Shows the rates of anemia AE reporting, nadir hemoglobin decline to less than 10g/dL, and intervention by baseline hemoglobin concentration of ≤ 14 vs. ≥ 16 . This table shows that anemia adverse event reporting, hemoglobin decline to 10g/dL or lower, and interventions occurred more often in subjects with lower baseline hemoglobin concentrations.

Table 14. Rates of Anemia, Hgb ≤ 10 g/dL, and Interventions by Baseline Hgb

	n/N	%
Baseline Hgb ≤ 14 g/dL		
Anemia AE	246/393	63%
Nadir Hgb ≤ 10	265/393	67%
Intervention	243/393	62%
Baseline Hgb ≥ 16		
Anemia AE	76/298	26%
Nadir Hgb ≤ 10	76/298	26%
Intervention	56/298	19%

This finding is even more pronounced when assessing only those subjects who experienced an intervention (ribavirin dose reduction, ESA use, boceprevir dose reduction, transfusion) as seen in **Figures 7 and 8**.

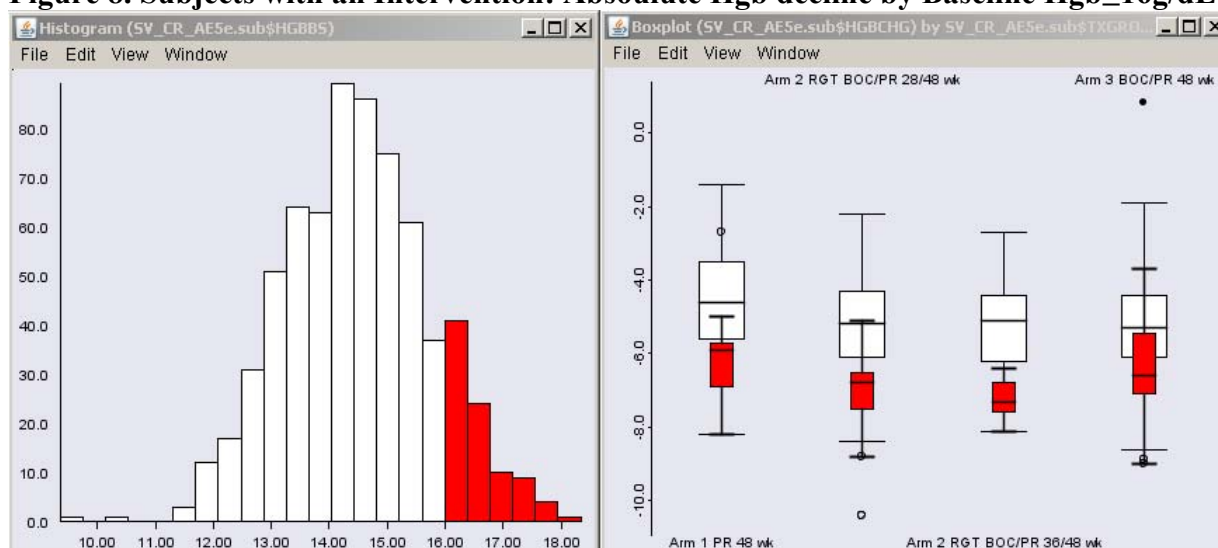
Figure 7. Subjects with an Intervention: Absolute Hgb decline by Baseline Hgb \leq 14g/dL



Histogram: distribution of baseline hemoglobin concentration with x-axis has baseline Hgb in g/dL and y-axis as absolute subject count. Subjects with baseline of ≤ 14 g/dL highlighted/shaded in red.

Box plot: Clear boxes: all subjects in each arm; Red shaded boxes: subjects with baseline Hgb ≤ 14 g/dL; Y-axis: absolute hemoglobin change in g/dL. Boxes: middle line represents median, bottom of box represents 25th percentile, top of box represents 75th percentile, lower whisker is 2nd percentile, and upper whisker is 98th percentile.

Figure 8. Subjects with an Intervention: Absolute Hgb decline by Baseline Hgb \geq 16g/dL



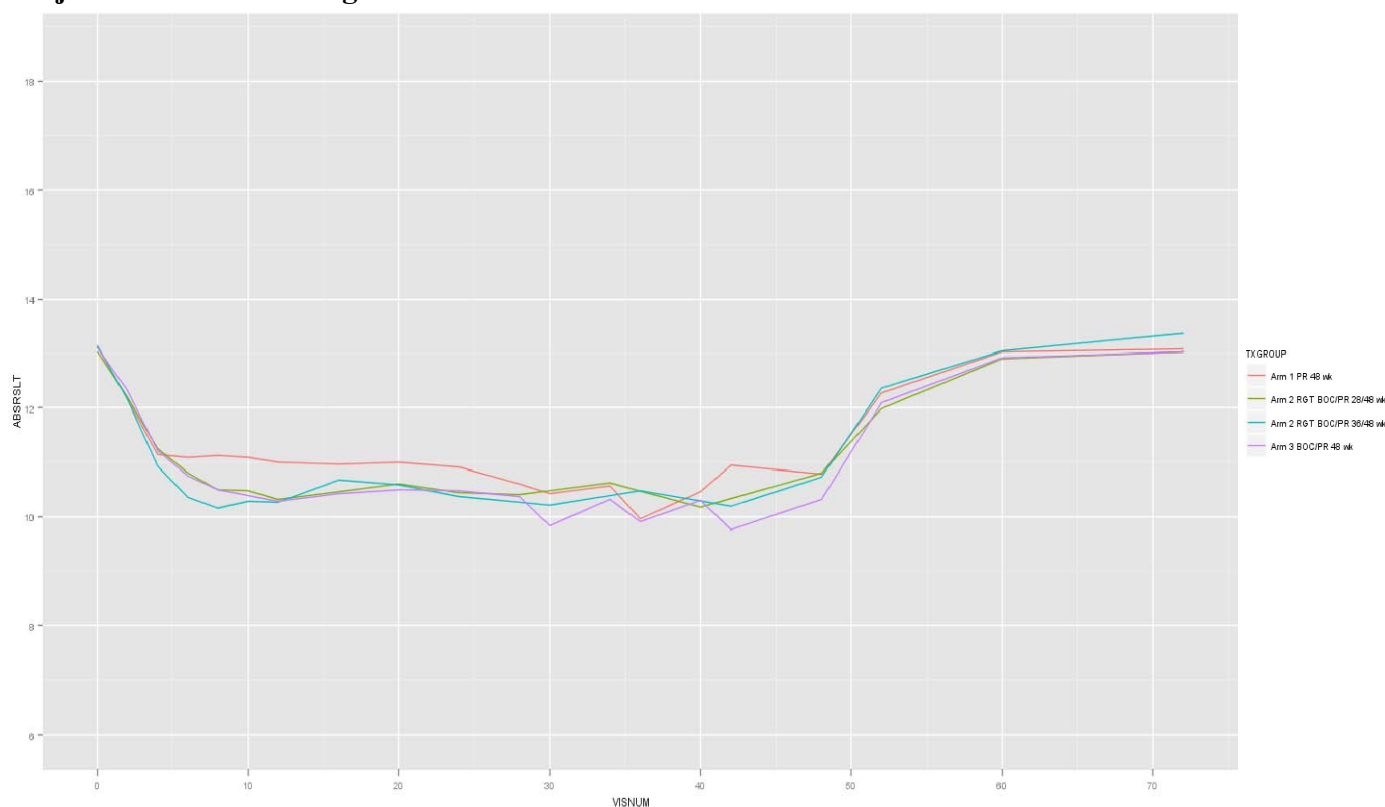
Histogram show distribution of baseline hemoglobin concentration with x-axis as baseline Hgb in g/dL and y-axis as absolute subject count. Subjects with baseline of ≥ 16 g/dL are highlighted/shaded in red.

Box plot: Clear boxes: all subjects in each arm; Red shaded boxes are subjects with baseline Hgb ≥ 16 g/dL; Y-axis: absolute hemoglobin change in g/dL. Boxes: middle line represents median, bottom of box represents 25th percentile, top of box represents 75th percentile, lower whisker is 2nd percentile, and upper whisker is 98th percentile.

Together, these analyses reveal a counter-intuitive finding that subjects with lower baseline hemoglobin measures, despite having higher rates of anemia adverse event reporting and interventions, actually experienced smaller absolute hemoglobin declines. One possible explanation for this finding is that these subjects who started with lower baseline hemoglobin measures were more likely to reach the intervention trigger point of 10g/dL resulting in an intervention which prevented further hemoglobin declines. They also were more likely to experience the intervention earlier in the course of treatment, thus also preventing further hemoglobin declines.

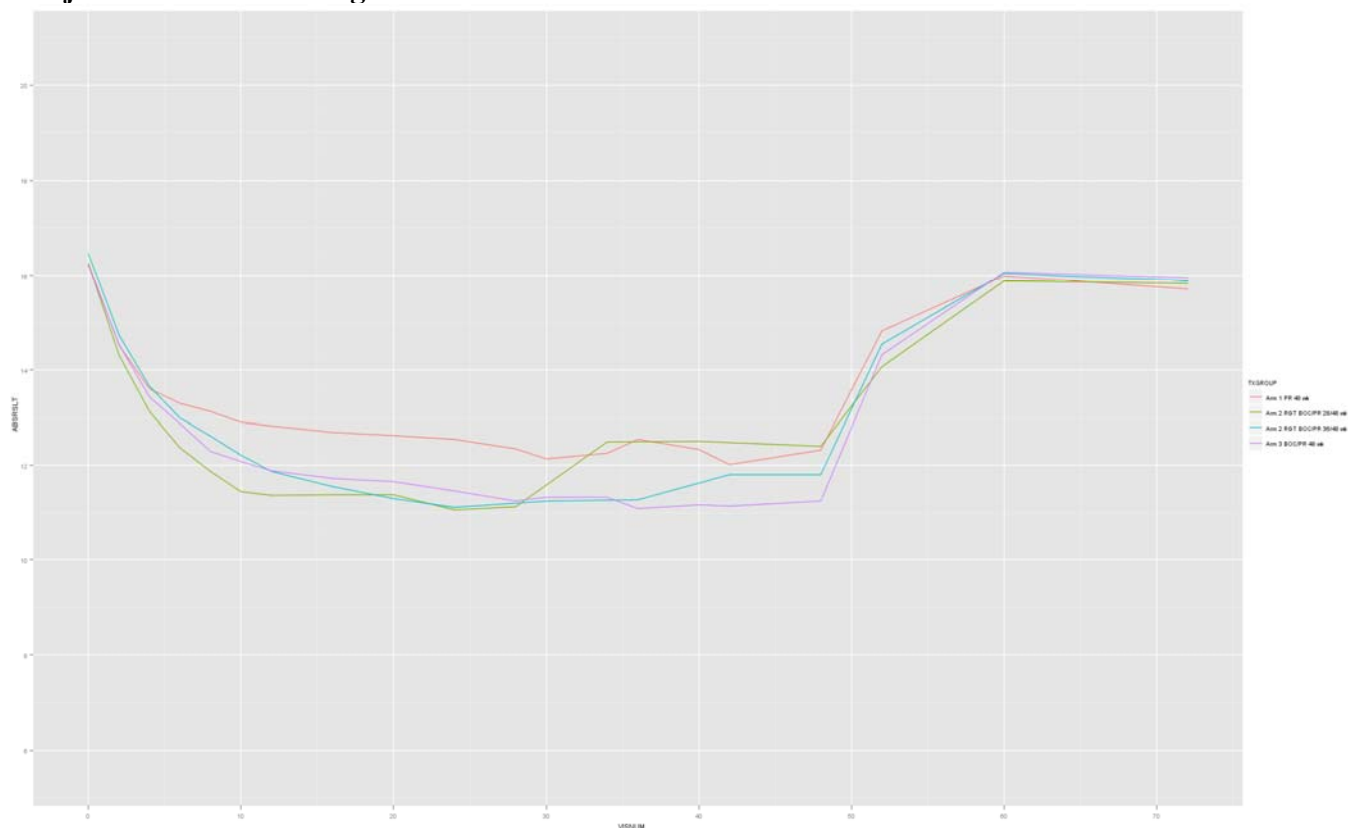
Figure 9 shows the change over time in mean hemoglobin concentrations for subjects with baseline hemoglobin concentrations ≤ 14 g/dL. This graph shows that magnitude of difference in mean hemoglobin concentrations between boceprevir-treated subjects and control subjects is smaller than is seen in **Figure 10**, which includes only subjects with baseline hemoglobin concentrations ≥ 16 g/dL. In addition, the downward slope in mean hemoglobin concentration, although halted by week 10 in subjects with a baseline Hgb of ≤ 14 g/dL, continues beyond week 20 for subjects with a baseline Hgb of ≥ 16 g/dL. This difference in slope is possibly related to the fact that those with lower baselines reached the intervention trigger point of 10g/dL sooner and experienced more interventions which also occurred earlier.

Figure 9. Mean Hemoglobin Concentration Decline by Visit, Studies 5216 and 5101 for Subjects with Baseline Hgb ≤ 14



X-axis is the week number of study visit. Y-axis is mean absolute Hgb

Figure 10. Mean Hemoglobin Concentration Decline by Visit, Studies 5216 and 5101 for Subjects with Baseline Hgb≤16



X-axis is the week number of study visit. Y-axis is mean absolute Hgb

Table 15 shows mean and median hemoglobin change for the maximum absolute decline of hemoglobin concentration for each treatment group for those with a baseline hemoglobin concentration of ≤ 14 g/dL and also for those with a baseline hemoglobin concentration of ≥ 16 g/dL. This analysis shows that subjects with higher baselines experienced a greater magnitude of decline in hemoglobin concentrations.

Table 15. Mean and Median Maximum Change in Hemoglobin by Baseline and Arm in g/dL

	Baseline Hgb ≤ 14 g/dL		Baseline Hgb ≥ 16 g/dL	
	Median	Mean	Median	Mean
Arm 1	-3.2	-3.2	-4.6	-4.7
Arm 2	-3.8	-3.5	-6.2	-5.0
Arm 3	-4	-3.8	-5.5	-5.6

Arm 1=peg/ribavirin; Arm 2=peg/ribavirin/boceprevir response guided therapy; Arm 3= peg/ribavirin/boceprevir

Assessment of Anemia by Adverse Events

MedDRA and Adverse Event Coding

MedDRA terminology version 13.0 was used for adverse event coding. All anemia adverse events were coded to one of four MedDRA terms: Anaemia, Haemolytic anaemia, Haematocrit decreased, Haemoglobin decreased. The distribution of terms is presented in **Table 15**.

Table 15. Distribution of Reported Anemia Adverse Events

MedDRA Term	Arm 1 – PR *	Arms 2, 3 – BOC *
Anaemia	208	901
Haemolytic anaemia	0	2
Haematocrit decreased	2	9
Haemoglobin decreased	7	43

*Counts represent total number of events.

Note: subjects may have experienced more than one event. For example: subject P05216-0113-002082 was reported as having experienced 22 Anaemia events, although none were serious.

Overall Rates of AEs

Table 16 shows a summary of anemia adverse events, serious events, Grade 3 or 4 events as well as those resulting in study drug discontinuation, dose reduction or interruption. In this analysis, each subject was counted only one time per adverse event type. For example, a subject who was reported as having had more than one anemia adverse event is counted only one time.

Table 16 shows that increased proportions of boceprevir-treated subjects experienced a Grade 3 or 4 anemia event as well as events resulting in dose reduction, discontinuation, or interruptions. Overall, rates of serious adverse events and study drug discontinuation were relatively limited in boceprevir treated subjects.

Table 16. Adverse Events: Anemia in Phase 3 trials

Anemia* Adverse Events	P05101 Boceprevir arms N=323 n(%)	P05101 PR arms N=80 (%)	P05216 Boceprevir arms N=734 (%) n(%)	P05216 PR arms N=363 (%) n(%)	P05216+P05101 Boceprevir Arms N= 1057 n(%)	P05216+P05101 PR arms N=443 n(%)
Anemia as AE*	157 (49)	17 (21)	392 (53)	114 (31)	548 (52)	131 (30)
Anemia as serious AE*	5 (2)	0	7 (1)	1	12 (1)	1
Anemia as Grade 3 or 4 AE*	21 (7)	0	24 (3)	7 (2)	45 (4)	7 (2)
Anemia resulting in Study Drug discontinuation*	5 (2)	0	14 (2)	4 (1)	19 (2)	4 (1)
Anemia resulting in dose reduction*	69 (21)	7 (9)	195 (27)	51 (14)	264 (25)	58 (13)
Anemia resulting in dose interruption*	9 (3)	0	22 (3)	9 (3)	31 (3)	9 (2)

* MedDRA Preferred Terms including Anaemia, Haemoglobin decreased, Haematocrit decreased, Haemolytic anaemia,
n= number of subjects who experienced adverse event.

Serious Adverse Events

The occurrence of serious anemia adverse events was low, although more such events occurred in boceprevir-treated subjects (**Table 16**).

There were no deaths related to anemia events. The most common reason for a serious anemia event was hospitalization and transfusion and all serious events, except one described in this section, were reported as having resolved by the end of follow up.

There were 27 subjects who received transfusions with packed red blood cells (PRBCs) but whose anemia event was not categorized as being serious. **Table 17** shows a comparison of subjects with a serious anemia adverse event and subjects with a serious anemia event as well as an anemia event requiring transfusion.

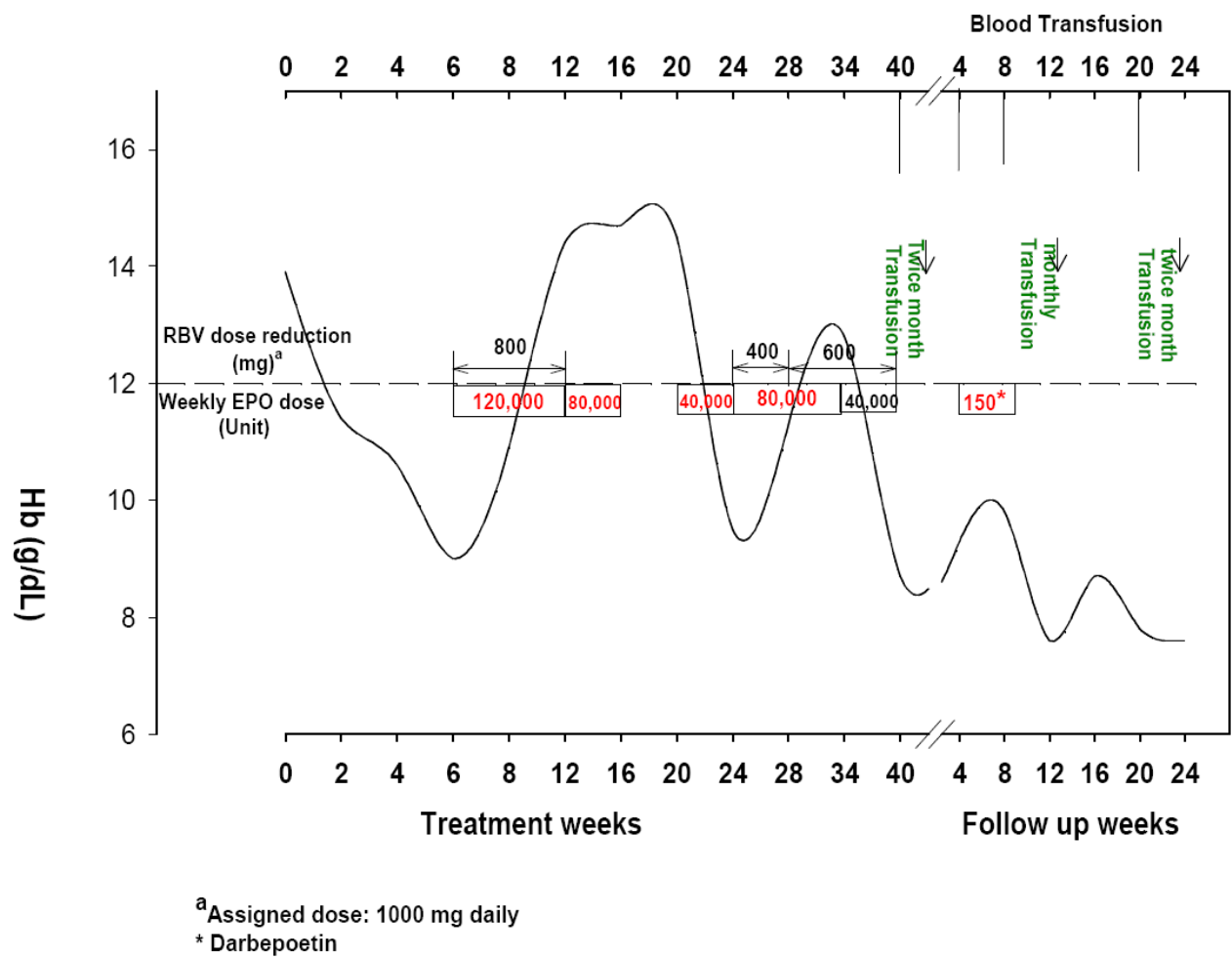
Table 17. Serious Anemia-related Adverse Events and Transfusion

Anemia* Adverse Events	5101 Boceprevir arms N=323 (%)	5101 PR arms N=80 (%)	5216 Boceprevir arms N=734 (%)	5216 PR arms N=363 (%)	5216+5101 Boceprevir Arms N= 1057	5216+5101 PR arms N=443
Anaemia as serious AE	5 (2)	0	7 (1)	1 (<1)	12 (1)	1 (<1)
Anemia as serious AE or resulting in transfusion	17 (5)	0	21 (3)	2 (<1)	38 (4)	2 (<1)

* MedDRA Preferred Terms including Anaemia, and Anaemia resulting in PRBC transfusion

One subject from Study 5216 (800002163) experienced severe anemia that did not respond to interventions. **Figure 9** shows this subject's hemoglobin concentrations over time in relation to various interventions including ribavirin dose reduction, EPO administration, and transfusion. This patient initially responded well to RBV dose reduction and EPO, however, anemia recurred after discontinuation of these interventions. Subsequent courses of RBV dose reduction and EPO produced smaller response of less duration. Ultimately, the subject underwent bone marrow biopsy and anti-EPO antibodies which were consistent with pure red blood cell aplasia related to EPO exposure. The subject's event was ongoing at the time of end of study, and the subject was being treated with intermittent red blood cell transfusions. This figure shows that the subject was treated with EPO beyond the time point at which her hemoglobin concentration had reached 12g/dL and that she was treated with a high dose of EPO.

Figure 9. Hemoglobin Concentration, EPO dosing, and Tranfusions over Time for Subject 80002163



Brief Summary of Reported Anemia-related Serious Adverse Events

Study P05216:
 91002078: PR; Hospitalization/transfusion; 60 year old female who was hospitalized on day 116 for severe abdominal pain and was noted at that time to have anemia (Hgb on day 113 was 9.1 g/dL). Patient was evaluated and diagnosed with vitamin B deficiency for which she was treated. Her anemia worsened and on day 169, her hemoglobin was 8.6 g/dL and all study medications were discontinued. On day 197, her hemoglobin had declined to 7.1 g/dL requiring hospitalization and transfusion. By day 344, her anemia had resolved.

6001953: Arm 2/RGT; Hospitalization/transfusion; 76 year old female with a past history of thalassaemia beta was hospitalized on day 64 for transfusion (hemoglobin 8.6 g/dL). At that time, study drugs were discontinued. Anemia was considered resolved on day 83.

32007491: Arm 2/RGT: Hospitalization/transfusion; 67 year old female with history of anemia, erosive gastritis and diabetes mellitus. Patient was hospitalized and transfused on 4 occasions and ultimately study drugs were discontinued due to anemia on day 99. Her hemoglobin measurements on days 15, 70, 92 were 8.0, 6.3, and 6.0 g/dL. Anemia was resolved by day 230 (Hgb 11.5)

54002169: Arm 2/RGT: Hospitalization/transfusion; 54 year old male with no history of anemia, was hospitalized and transfused on day 84 (Hgb 5.6). Study drug was stopped at that time. Anemia was resolved on day 93.

21002043: Arm 3: Hospitalization/transfusion; 52 year old female who developed neutropenia on day 57 requiring G-CSF and worsening anemia and thrombocytopenia on day 64. PEG2b was reduced and RBV interrupted and patient was discontinued from the study due to fatigue. On day 157, anemia and thrombocytopenia worsened and resulted in hospitalization at which time EPO and G-CSF were discontinued and subject received transfusion with 4 units packed red blood cells (PRBCs) for Hgb of 6.3 g/dL. Anemia was resolved on day 366.

26007459: Arm 3: Hospitalization/transfusion; 55 year old male with history of diabetes mellitus who developed neutropenia on day 169. G-CSF was initiated on day 243 and he was hospitalized on day 251 for anemia and transfusion (Hgb 8.2 g/dL). Subject was treated with darbopoeitin. Study drugs were discontinued on day 316 due to declining Hgb and subject was admitted again on day 327 for anemia and transfusion (Hgb 8.2 g/dL). Anemia resolved by day 391.

51000136: Arm 3: Hospitalization. 43 year old female for whom PEG2b was reduced due to leukopenia. Patient experienced anemia on day 69 (Hgb 10.2 g/dL) resulting in hospitalization, ribavirin dose reduction and EPO administration. Anemia resolved by day 365 and the subject completed study drug treatment and follow up.

800002163: Arm 3: Hospitalization/transfusion/ongoing PRCA. 56 year old female with no other past medical history who, due to anemia with Hgb of 9.0g/dL on day 43, was started on therapy with EPO (day47). She later developed neutropenia on day 169 with subsequent PEG2b dose reduction. On day 272, on visit to primary care physician was found to have Hgb of 6.0g/dL and PLT of 38.4×10^9 . All study drugs and EPO were discontinued at that time and patient was admitted to the hospital where she received 2 units PRBCs. On day 304, darbopoietin was started and the patient was re-admitted on day 313 with Hgb of 6.6g/dL at which time the darbopoietin was discontinued. Bone marrow biopsy was done and revealed pure red blood cell aplasia and subsequent EPO antibody test was obtained and confirmed as positive for the presence of anti-EPO antibodies. The patient was then managed with periodic symptomatic PRBC transfusions (approximately twice/month). At the time of the last visit on day 503, the event was still ongoing. In total, the subject was treated with EPO from study day 47 to 140, and then from 176 to 271 followed by darbopoietin from study day 304 to 313.

Study P05101

90013026: Arm 3: Hospitalization/transfusion. 61 year old male with a history of diabetes and macrocytic anemia who was diagnosed with anemia on day 61 at which time Hgb was found to be 7.7g/dL. Patient was transfused at that time and subsequently was treated with EPO from study day 215 to 292. Study drug was completed on day 334. The anemia event was reported as having resolved as of the last visit.

260012035: Arm 3: Transfusion. 55 year old female who developed neutropenia on day 14 requiring dose reduction of PEG2b and treatment with GCSF. Anemia was reported on day 84 and worsened on day 240 requiring dose reduction of boceprevir. Anemia worsened by day 285 with Hgb of 6.7g/dL with subsequent discontinuation of all study drugs and GCSF on day 286. Leukopenia, neutropenia, and thrombocytopenia all resolved by day 305 and anemia resolved by day 378.

330011004: Arm 3: Hospitalization/transfusion. 61 year old male with diabetes on pioglitazone and glyburide/metformin who developed severe anemia on day 104 with Hgb of 6.4g/dL. Subject was hospitalized and transfused at that time and all study drugs were discontinued. On day 197, anemia was resolved.

350010120: Arm 3: Hospitalization/transfusion. 57 year old male developed anemia on day 61 which worsened by day 210 (Hgb 8.0g/dL) requiring hospitalization and transfusion. Study drug was complete by day 337 and anemia resolved by day 365.

690011093: Arm 3: Hospitalization/transfusion. 57 year old male who was diagnosed with anemia on day 85 which worsened requiring treatment with darbopoeitin from day 127-174. Anemia recurred on day 215 and Hgb decreased to 8.6 by day 292 requiring hospitalization and treatment interruption. Anemia resolved by day 299, and treatment with study drugs was re-started on day 293 and completed on day 338.

Anemia-related AEs

An assessment of adverse events potentially associated with anemia was done for phase 3 studies (P05216 and P05101 combined) as seen in **Table 18**. Of the most common adverse events possibly associated with anemia, dyspnoea/exertional dyspnoea occurred more often in boceprevir treated patients, 330/1057 (31.2%) vs. 107/443 (24.2%). Dizziness occurred in a higher proportion of boceprevir-treated subjects, 199/1057 (18.8%) vs. 68/443 (15.3%). Syncope was also reported more often in boceprevir-treated subjects, 23/1057 (2.2%) vs. 3/443 (0.7%). Other events of interest, such as myocardial infarction and ischaemia occurred too infrequently to make a meaningful comparison (2 events in boceprevir-treated subjects vs. 2 events in PR-treated subjects).

The phase 3 studies were not specifically designed to prospectively collect anemia-related symptoms or adverse events.

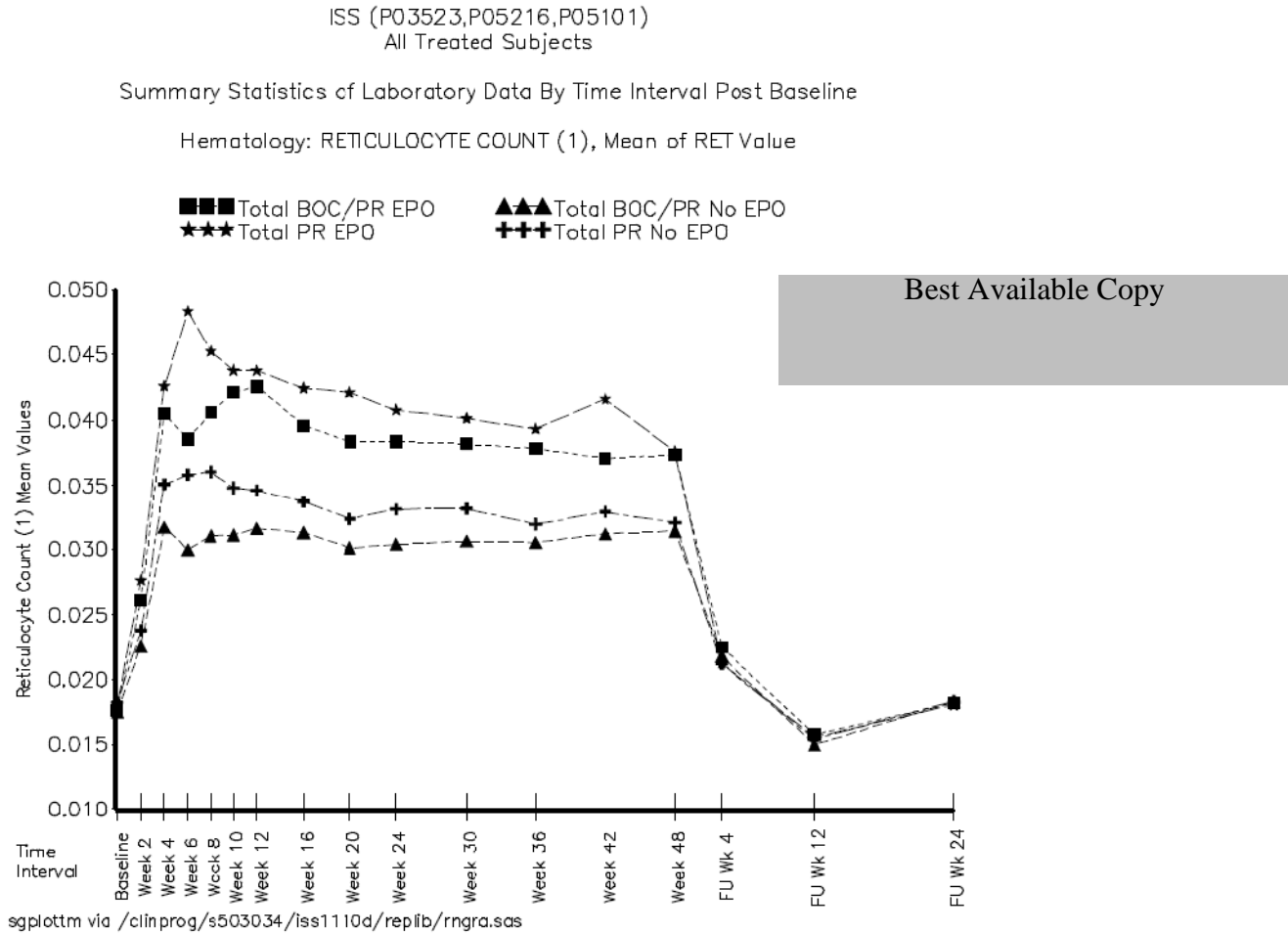
Table 18. Adverse Events Possibly Associated with Occurrence of Anemia by Treatment Arm

decoded meddra preferred term	Arm 1 PR	Arm 2 BOC/ PR 28/48	Arm 2 BOC/ PR 36/48	Arm 3 BOC/PR
FATIGUE	257 (58.0%)	196 (53.3%)	87 (53.7%)	301 (57.1%)
DYSпноEA	73 (16.5%)	68 (18.5%)	29 (17.9%)	124 (23.5%)
ASTHENIA	83 (18.7%)	55 (14.9%)	31 (19.1%)	108 (20.5%)
DIZZINESS	68 (15.3%)	80 (21.7%)	26 (16.0%)	93 (17.6%)
DYSпноEA EXERTIONAL	34 (7.7%)	42 (11.4%)	22 (13.6%)	45 (8.5%)
CHEST PAIN	15 (3.4%)	13 (3.5%)	3 (1.9%)	16 (3.0%)
CHEST DISCOMFORT	10 (2.3%)	7 (1.9%)	2 (1.2%)	14 (2.7%)
MALAISE	6 (1.4%)	11 (3.0%)	4 (2.5%)	11 (2.1%)
SYNCOPE	3 (0.7%)	6 (1.6%)	6 (3.7%)	11 (2.1%)
WHEEZING	3 (0.7%)	7 (1.9%)	2 (1.2%)	8 (1.5%)
MUSCULOSKEL CHEST PAIN	3 (0.7%)	4 (1.1%)	2 (1.2%)	8 (1.5%)
TACHYCARDIA	5 (1.1%)	4 (1.1%)	1 (0.6%)	7 (1.3%)
LETHARGY	5 (1.1%)	4 (1.1%)	1 (0.6%)	5 (0.9%)
SOMNOLENCE	5 (1.1%)	0 (0.0%)	0 (0.0%)	6 (1.1%)
PRESYNCOPE	3 (0.7%)	4 (1.1%)	1 (0.6%)	2 (0.4%)
HYPERSONNIA	2 (0.5%)	1 (0.3%)	1 (0.6%)	3 (0.6%)
PALLOR	2 (0.5%)	3 (0.8%)	1 (0.6%)	1 (0.2%)
MUSCLE FATIGUE	1 (0.2%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
ORTHOSTATIC HYPOTENSION	0 (0.0%)	2 (0.5%)	0 (0.0%)	3 (0.6%)
CARDIOVASCULAR DISORDER	1 (0.2%)	1 (0.3%)	0 (0.0%)	2 (0.4%)
HEART RATE INCREASED	1 (0.2%)	3 (0.8%)	0 (0.0%)	0 (0.0%)
DIZZINESS POSTURAL	0 (0.0%)	0 (0.0%)	1 (0.6%)	2 (0.4%)
CORONARY ARTERY DISEASE	0 (0.0%)	2 (0.5%)	0 (0.0%)	1 (0.2%)
COPD	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
MYOCARDIAL INFARCTION	1 (0.2%)	0 (0.0%)	1 (0.6%)	0 (0.0%)
SINUS TACHYCARDIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
MYOCARDIAL ISCHAEMIA	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
MENTAL STATUS CHANGES	1 (0.2%)	0 (0.0%)	1 (0.6%)	0 (0.0%)
ATRIAL FIBRILLATION	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.2%)
ASTHENOPA	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.2%)
ACUTE MYOCARDIAL INFARC	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
CARDIAC ARREST	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
VENTRICULAR EXTRASYSTOLES	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ATRIAL FLUTTER	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
CEREBRAL ISCHAEMIA	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
TACHYPNOEA	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
EMPHYSEMA	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
CARDIO-RESPIRATORY ARREST	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CARDIAC FLUTTER	0 (0.0%)	0 (0.0%)	1 (0.6%)	0 (0.0%)
EXERCISE TOLERANCE DECR	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ANGINA PECTORIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
CARDIAC FAILURE CONGESTIVE	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
LISTLESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
FEELING ABNORMAL	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
TRANSFUSION REACTION	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Subjects	443 (100.0%)	368 (100.0%)	162 (100.0%)	527 (100.0%)

Reticulocytosis

Figure 10 shows an analysis of reticulocyte count (sponsor’s ISS page 225) which shows mean visit reticulocyte count by study drug vs. comparator according to EPO use. This graph shows that boceprevir treated subjects experienced less reticulocytosis compared to PR-treated subjects for both EPO-treated subjects and non-EPO treated subjects. This is consistent with the possible mechanism of anemia involving bone marrow suppression.

Figure 10. Mean Reticulocyte Count by Therapy According to ESA Use



Mean Reticulocyte Count by Erythropoietin Use by Treatment Arm

Protocol Nos. [P03523](#), [P05216](#), and [P05101](#) (PR=peginterferon alfa-2b plus ribavirin; BOC=boceprevir; Source Data: [Section 8.4.1.24](#)

INTERVENTIONS

For protocols P05216 and P05101, several different approaches to anemia management were allowable including: initiation of erythropoiesis stimulating agents, ribavirin dose reduction (or interruption), red blood cell transfusion, and boceprevir dose reduction. The majority of subjects who required an intervention for anemia received either an ESA or ribavirin dose modification with a small number of subjects receiving either a transfusion or boceprevir dose reduction. **Table 19** shows all subjects according to the intervention or combination of interventions received. This table shows that the majority of subjects who received an intervention, 621/680 (91.3%) received either an ESA, RBV dose reduction, or combination of both.

Table 19. Interventions for Anemia in Studies P05101 and P05216*				
ESA	RBV Dose Modification	Boceprevir Dose Reduction	Transfusion	n
No Interventions				820
Yes				262
Yes	Yes			246
	Yes			113
Yes	Yes		Yes	25
Yes	Yes	Yes		17
Yes			Yes	7
Yes	Yes	Yes	Yes	4
	Yes		Yes	2
			Yes	1
		Yes		1
	Yes	Yes		1
Yes		Yes		1
				1500

* each subject is represented once

Table 20 shows a comparison of ESA use and/or Ribavirin dose reduction as well as RBC transfusion. This shows that there were substantially more boceprevir-treated subjects receiving these interventions compared to control-treated subjects.

Table 20. Use of Erythropoietin and Ribavirin Dose Reduction in Phase 3 Trials (P05216 and P05101)

Treatment Arm (Pooled)	Erythropoietin Use n (%)	Ribavirin Dose Reduction n (%)	Erythropoietin Use or ribavirin dose reduction n (%)	Erythropoietin Use and ribavirin dose reduction n (%)	RBC Transfusion n (%)
All Boceprevir-treated Subjects (N=1057)	458 (43)	327 (31)	543 (51)	242 (23)	37 (3.5)
All PR-treated subjects (N=443)	104 (24)	81 (18)	135 (31)	50 (11)	2 (<1)

Table 21 shows the numbers of subjects from each arm according to length of treatment with ESA. This table shows that Arm 3, which had the longest exposure to boceprevir, had a larger proportion of subjects with prolonged exposure to ESA than Arms 1 or 2.

Table 21. Length of ESA Exposure by Study and Arm

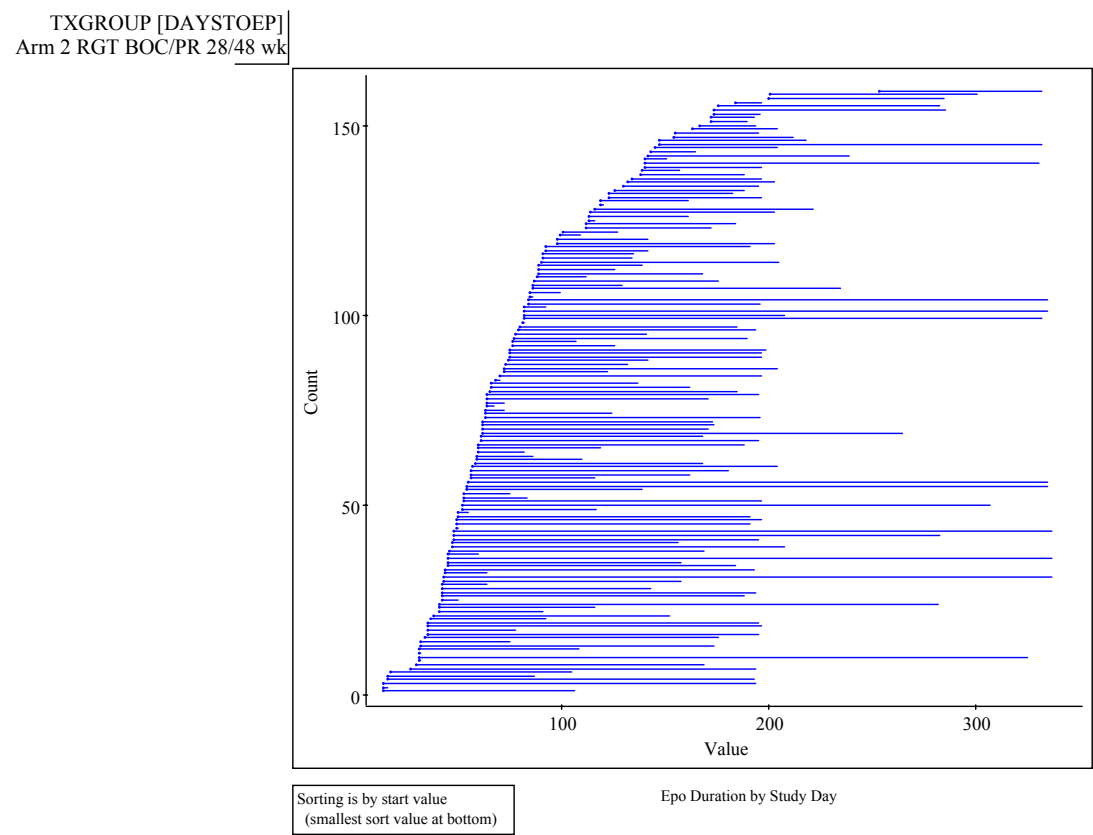
Study	Arm 1*	Arm 2*	Arm 3*
>250 Days Epo Treatment			
P05101	0/80 (0)	4/162 (3)	16/161 (10)
P05216	13/363 (4)	10/368 (3)	37/366 (10)
Total	13/443 (3)	14/530 (3)	53/527 (10)
> 200 Days Epo Treatment			
P05101	0/80 (0)	12/162 (7)	22/161 (14)
P05216	22/363 (6)	13/368 (4)	59/366 (17)
Total	22/443 (5)	25/530 (5)	81/527 (15)
>150 Days Epo Treatment			
P05101	2/80 (3)	34/162 (21)	29/161 (18)
P05216	31/363 (9)	23/368 (6)	79/366 (22)
Total	33/443 (8)	57/530 (11)	108/527 (21)
>100 Days Epo Treatment n/N (%)			
P05101	4/80 (5)	41/162 (25)	35/161 (22)
P05216	46/363 (13)	71/368 (20)	108/366 (30)
Total	50/443 (11)	112/530 (21)	143/527 (27)

*n/N (%) n= number of subjects with ESA exposure of specified duration; N=total number of subjects in that arm

ESA Discontinuation

Figures 11 and 12 are delta graphs which provide an overview of the timing of when ESA use was discontinued for subjects in the Response Guided Therapy arms. Each line in these figures represents a single subject with the x-axis as study day. These figures reveal that for the RGT arms, a clear pattern of ESA discontinuation is seen occurring around week 28 for study P05216 and week 36 for study P05101. For subjects in Arm 3, a large number continued ESA use until the end of study therapy (**Figure 13**). These figures show that for a number of subjects, ESA use is continued for as long as the subject is being treated with boceprevir, which explains why subjects in Arm 3 experienced more prolonged ESA exposure.

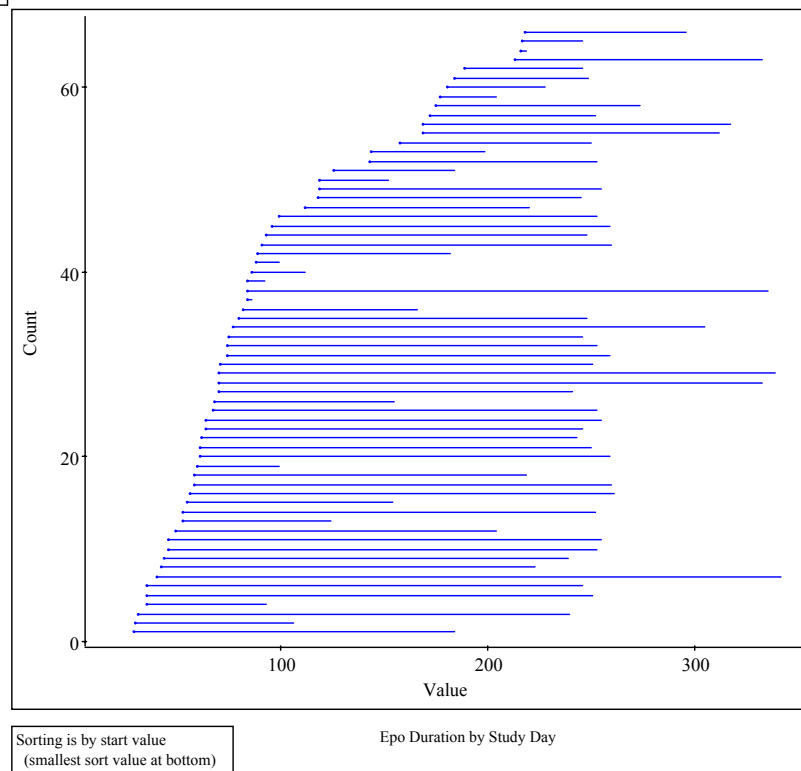
Figure 11. Timing of ESA Use by Subject in Study P05216, Arm 2*



*x-axis is study day and y-axis is number of subjects. Each line represents a single subject with left most point representing study day of ESA start and right most point representing study day of ESA stop

Figure 12. Timing of ESA Use by Subject in Study P05101, Arm 2*

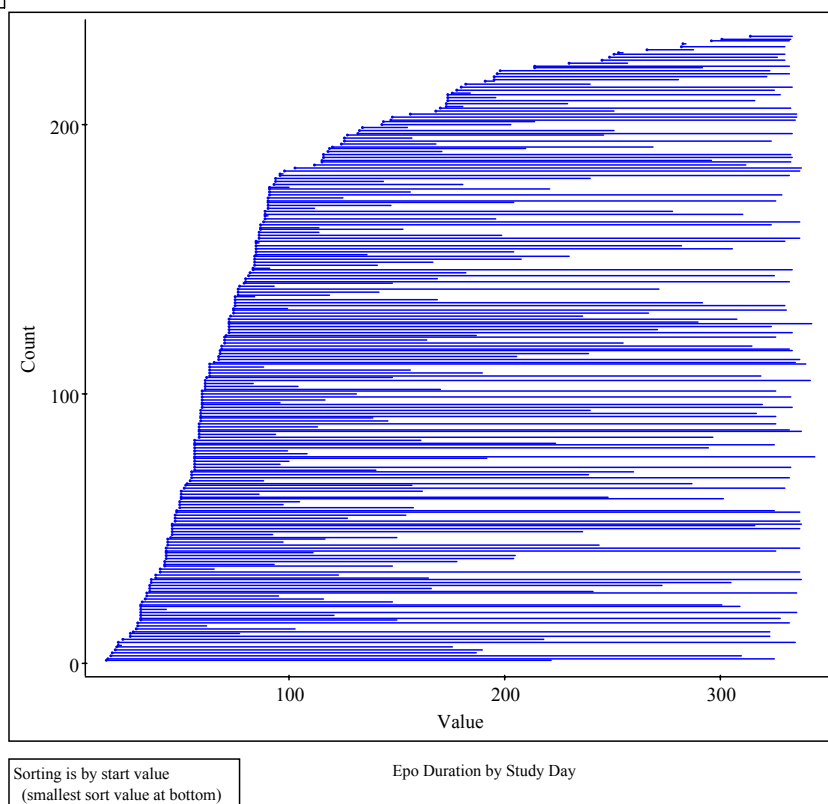
TXGROUP [DAYSTOEP]
Arm 2 RGT BOC/PR 36/48 wk



*x-axis is study day and y-axis is number of subjects. Each line represents a single subject with left most point representing study day of ESA start and right most point representing study day of ESA stop

Figure 13. Timing of ESA Use by Subject in Studies P05216, P05101, Arm 3*

TXGROUP [DAYSTOEP]
Arm 3 BOC/PR 48 wk



*x-axis is study day and y-axis is number of subjects. Each line represents a single subject with left most point representing study day of ESA start and right most point representing study day of ESA stop

Timing of ESA Administration

The timing for when ESA interventions were initiated was explored. Subjects who experienced ESA administration earlier in the course of the study, potentially, may have experienced less overall hemoglobin decline, since such intervention is likely to slow, halt, or reverse declines in hemoglobin concentrations. **Table 22** shows the mean and median for study day of ESA start by study and treatment arm. For boceprevir-treated subjects, ESA use was initiated earlier in study P05216 compared to study P05101. This finding has the potential to obscure true differences that may exist in rates of anemia.

Table 22. Mean and Median Number of Days to Start of ESA by Arm and Protocol

	n	Mean (days)	Median (days)
Arm 1			
P05101	17	100.5	71
P05216	87	89.3	71
Total	104	91.1	71
Arm 2			
P05101	66	95.8	77
P05216	159	80.3	66
Total	225	84.8	71
Arm 3			
P05101	74	100.5	76.5
P05216	159	79.9	64
Total	233	86.4	70

Arm 1=peg/ribavirin; Arm 2=peg/ribavirin/boceprevir response guided therapy; Arm 3=peg/ribavirin/boceprevir

One possible explanation for this finding is that there were a larger proportion of subjects in Study P05216 with lower baseline hemoglobin levels. These subjects would be expected to reach the intervention trigger point of a Hgb of $\leq 10\text{g/dL}$ sooner and, as shown previously in **Table 14**, are more likely to experience an intervention as well as a reported adverse event. **Table 23** shows the proportion of subjects with baseline hemoglobin $\leq 14\text{g/dL}$ by protocol and treatment arm.

Table 23. Proportion of Subjects with Baseline Hemoglobin Concentrations $\leq 14\text{g/dL}$ by Arm and Protocol

	n/N (%)
Arm 1	
P05101	18/80 (23)
P05216	114/363 (31)
Arm 2	
P05101	29/162 (18)
P05216	90/368 (25)
Arm 3	
P05101	30/161 (19)
P05216	100/366 (27)

Arm 1=peg/ribavirin; Arm 2=peg/ribavirin/boceprevir response guided therapy; Arm 3= peg/ribavirin/boceprevir

Transfusions by Protocol and Treatment Arm

As described in **Table 16** previously, boceprevir-treated subjects required more red blood cell transfusions than control-treated subjects. Subjects in Arm 3 of study P05101 had the highest proportion of subjects receiving transfusion.

Table 24. Proportion of Subjects who Received PRBC Transfusion by Arm and Protocol

	n/N (%)
Arm 1	
P05101	0/80 (0)
P05216	2/363 (1)
Arm 2	
P05101	3/162 (2)
P05216	11/368 (3.0)
Arm 3	
P05101	14/161 (9)
P05216	9/366 (3)

Arm 1=peg/ribavirin; Arm 2=peg/ribavirin/boceprevir response guided therapy; Arm 3= peg/ribavirin/boceprevir

Overall Conclusions regarding Anemia

Boceprevir exposure was associated with higher incidence of anemia when compared to standard of care of pegylated interferon/ribavirin. Anemia which required an intervention in the phase 3 studies was managed in most patients with either ESA administration, ribavirin dose reduction, or a combination of both in the majority of subjects (over 90%). More boceprevir-treated subjects required these interventions, and required a longer duration of ESA exposure. Investigator directed interventions were largely successful in limiting the incidence of serious adverse events, transfusion, and discontinuations. A single case of pure red cell aplasia was reported in a boceprevir-treated subject, although because interferons have also been associated with PRCA, the case is confounded. Assessment of risk factors and sub-groups associated with boceprevir-associated anemia was limited by underlying confounding by hemoglobin baseline and by variability in anemia management and adverse event reporting.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHARLES K COOPER
04/15/2011

MARY E SINGER
04/15/2011

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202258

**Applicant: Schering-
Plough (SP)**

**Stamp Date: Received
November 15, 2010**

Drug Name: Boceprevir (SCH 503034, VICTRELIS™)

**NDA/BLA Type: Original
Submission/NME**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				Electronic CTD format
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			An application orientation meeting with the sponsor is scheduled on December 20, 2010
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Module 2 Clinical Overview, Section 6.0
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505 (b)(1)

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
DOSE					
13	<p>If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (<i>i.e.</i>, appropriately designed dose-ranging studies)?</p> <p>Study Number: <u>P03659</u></p> <p>Study Title: <u>PEGINTRON/REBETOL vs PEGINTRON/SCH 503034 with and without Ribavirin in Chronic Hepatitis C HCV-1 PEGINTERFERON/Ribavirin nonresponders: A SCH 503034 dose-finding Phase 2 study</u></p> <p>Sample Size: N=357</p> <p>Arms: 6 initially, Arm 7 added as an amendment</p> <p>Location in submission: Module 5</p> <p><u>P03523</u> Only used the boceprevir 800 mg TID dose.</p>	X			<p>Boceprevir 100, 200 and 400 mg TID doses initially explored in combination with PegIntron +/- ribavirin.</p> <p>Amendment 1 added an open label Arm 7, all to receive PegIntron/Boceprevir 800 mg TID.</p> <p>Subsequently the Data Review Advisory Board determined (1) lower boceprevir doses had poor anti-HCV activity and (2) resistance developed rapidly in groups without ribavirin; therefore, Amendment 2 switched all continuing eligible subjects to 800 mg tid plus PegIntron/ribavirin</p>
EFFICACY					
14	<p>Do there appear to be the requisite number of adequate and well-controlled studies in the application?</p> <p><u>Pivotal Study #1 P05216</u></p> <p>Indication: A Phase 3, safety and efficacy study of Boceprevir (SCH 503034) in previously untreated subjects with chronic hepatitis C genotype 1</p> <p>Double-blind, placebo-controlled study</p>	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	<p>comparing two regimens of boceprevir response-guided therapy (RGT) treatment paradigm of BOC/PR (28/48 wk) and BOC/PR (48 wk) to PR (48 wk).</p> <p>Treatment Regimen: BOC 800 mg TID (or placebo) PEG 2b 1.5 µg/kg QW RBV 600 to 1400 mg/day</p> <p>No. of Subjects Treated: 1097</p> <p><u>Pivotal Study #2 P05101</u></p> <p>Indication: A Phase 3, safety and efficacy study of Boceprevir (SCH 503034) in subjects with chronic hepatitis C genotype 1 who failed prior treatment with peginterferon/ribavirin</p> <p>Double-blind, placebo-controlled study comparing two regimens of boceprevir response-guided therapy (RGT) treatment paradigm of BOC/PR (36/48 wk) and BOC/PR (48 wk) to PR (48 wk).</p> <p>Treatment Regimen: BOC 800 mg TID (or placebo) PEG 2b 1.5 µg/kg QW RBV 600 to 1400 mg/day</p> <p>No. of Subjects Treated: 403</p> <p><u>Supportive Phase 2b Study P03523</u></p> <p>Phase 2, open-label, two-part study in treatment-naïve</p> <p><u>Part 1</u> included five treatment arms with BOC/PR for 28 or 48 weeks, with and without a 4-week lead-in with PR.</p> <p><u>Part 2</u> included exploration of BOC/P/low-dose RBV (400 to 1000 mg/day) for 48 weeks.</p> <p>Treatment Regimen:</p>				

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Part 1 BOC 800 mg TID PEG2b 1.5 µg/kg QW RBV 800 to 1400 mg/day Part 2 BOC 800 mg TID PEG2b 1.5 µg/kg QW RBV 400 to 1000 mg/day No. of Subjects Treated: Part 1: 520 Part 2: 75				
15	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
18	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (<i>e.g.</i> , QT interval studies, if needed)?	X			
20	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21	For chronically administered drugs, have an	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?				
22	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?		X		We have sent an information request to the applicant to submit the coding dictionary.
24	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
25	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
30	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
31	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34	Are all datasets to support the critical safety analyses available and complete?	X			
35	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			Submitted for Phase 3 trials and in P03523. Selected CRFs submitted for non-pivotal trial P03659.
37	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	All CRFs appear to be available for the Phase 3 trials.
FINANCIAL DISCLOSURE					
38	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___ Yes ___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please submit the coding dictionary used for mapping investigator verbatim terms to preferred terms. The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this is submitted as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

Please also submit the “Sponsor UTD Dictionary” which has been referred to in some studies and also provide any dictionaries that have been used. Please provide an explanation for how the different dictionaries were integrated into the ISS datasets with a focus on the implications for analyses across studies.

Poonam Mishra, M.D.

Sarah Connelly, M.D.

December 13, 2010

Reviewing Medical Officer

Date

Mary Singer, M.D., PhD.

December 13, 2010

Clinical Team Leader

Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

POONAM MISHRA
12/13/2010

SARAH M CONNELLY
12/13/2010

MARY E SINGER
12/13/2010