CENTER FOR DRUG EVALUATION AND RESEARCH

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	April 21, 2011
From	Mary Singer, M.D., Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 202-258
Applicant	Merck/Schering-Plough
Date of Submission	November 10, 2011
PDUFA Goal Date	May 15, 2011
Proprietary Name / Established (USAN) names	Victrelis™/boceprevir
Dosage forms / Strength	200 mg capsules
Proposed Indication(s)	Treatment of chronic hepatitis C genotype 1 in adults
Recommended:	Approval

1. Introduction

Boceprevir is an NS3/4a serine protease inhibitor in the ketoamide class of direct-acting antiviral agents active against hepatitis C virus (HCV) genotype 1. Boceprevir is the first direct-acting antiviral agent submitted for marketing approval for treatment of chronic hepatitis C. An NDA for a second direct-acting antiviral agent in the same pharmacologic class, telaprevir, was submitted shortly after boceprevir; and a regulatory action regarding telaprevir is also pending. Neither drug has been marketed internationally to date. The pivotal trials in the development programs for both drugs were based on superiority trials (add-on of new drug to standard of care) in subjects with chronic hepatitis C who were treatment-naïve or treatment-experienced (received prior pegylated interferon/ribavirin therapy) with the goal of improving SVR, and potentially shortening treatment duration. Because direct-acting antiviral agents may address an unmet medical need, particularly in patients who previously failed pegylated interferon/ribavirin therapy, both boceprevir and telaprevir were given a priority review designation.

Boceprevir was studied in combination with pegylated interferon and ribavirin (PR) for treatment of chronic hepatitis C because of the rapid development of virologic resistance when used as monotherapy for this class of antiviral agents. The primary endpoint for the pivotal clinical trials was sustained virologic response (SVR), measured 24 weeks after the end of therapy. Sustained virologic response (undetectable HCV RNA at the end of therapy and remaining undetectable through 24 weeks of follow-up) is generally considered a cure for hepatitis C infection; and recent studies have shown that achievement of SVR is associated with halting the progression of liver disease and decreasing the frequency of chronic hepatitis C the complications, including cirrhosis, hepatic decompensation, hepatocellular carcinoma, and liver-related mortality.

2. Background

The current standard of care for treatment of chronic hepatitis C genotype 1 is pegylated interferon plus ribavirin for 48 weeks. Overall SVR rates for pegylated interferon and ribavirin alone range from 40 to 45% in patients infected with HCV genotype 1. SVR rates are even lower in patients who are HIV/HCV-coinfected, black, cirrhotic, or have other unfavorable prognostic factors, such as an unfavorable IL28B genotype (C/T or T/T). The Applicant has demonstrated that addition of boceprevir to pegylated interferon and ribavirin results in significant improvement in SVR rates in subjects who are treatment-naïve and in subjects who have previously failed therapy and were either relapsers (undetectable HCV RNA at end-of-treatment, but with detectable HCV RNA within 24 weeks after stopping treatment) or partial responders ($\geq$2 $\log_{10}$ reduction in HCV RNA at treatment week (TW)12, but not achieving undetectable HCV RNA at the end of treatment). The Applicant identified anemia and dysgeusia as the major adverse reactions associated with boceprevir.

This review will focus on overall efficacy, efficacy in pertinent subgroups, appropriate duration of therapy for various subgroups, and the question of whether null responders who were not studied in Phase 3, should be included in the treatment indication as proposed by the Applicant. Additionally, this review will also discuss the Division's safety findings, including anemia, neutropenia, thrombocytopenia, HCV resistance, and important issues with drug-drug interactions, particularly oral contraceptives, as well as labeling issues.

3. CMC and Biopharmaceutics

Please see details regarding CMC and biopharmaceutics findings for this application in Dr. Mark Seggel's 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) . 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.

ONDQA CMC and Biopharmaceutics reviewers identified a potential issue with (b) (4) Available data for (b) (4) indicates a potential for genotoxicity, although the evidence is mixed (Ames negative, clastogenicity positive). After discussions with the Pharmacology/Toxicology review team, it was agreed that a limit of (b) (4) was acceptable.

ONDQA CMC and Biopharmaceutics reviewers have found that this NDA has provided sufficient information to assure identity, strength, quality, purity, potency and bioavailability of the drug product; and the Office of Compliance has issued an overall recommendation of "Acceptable" based on the satisfactory cGMP status of the manufacturing facilities.

4. Nonclinical Pharmacology/Toxicology

Please see details nonclinical pharmacology/toxicology findings in reviews by Drs. Christopher Ellis and Dr. Hanan Ghantous. In the preclinical toxicology studies, the finding of testicular toxicity in rats was of some concern for clinical use of boceprevir. Testicular degeneration occurred in rats at boceprevir exposures less than clinical boceprevir 800 mg three times daily (TID) exposures. In a 3-month rat study, there were signs that this toxicity was reversible following a 2-month treatment free period. Testicular findings were not associated with alterations in FSH, LH or testosterone; and the Sertoli cell appeared to be the primary target. Testicular findings were not observed in mice or monkeys administered boceprevir for 3 months at exposures approximately 7- and 4-fold higher, may be species-specific. See section 8 for clinical evaluation of this potential safety signal.

Although there was evidence of liver toxicity in mice and rats, there was minimal liver toxicity observed in monkeys, and there has been no evidence of liver toxicity in boceprevir clinical trials to date. In addition, there was also no evidence of significant hematologic toxicity in preclinical studies, except for mild, reversible anemia in monkeys.

Boceprevir was not genotoxic in 3 separate *in vitro* assays. Two-year mouse and rat carcinogenicity studies were negative for boceprevir-related tumors at exposures similar to humans (rats) or at exposures 2 to 6-fold higher than those expected with the proposed human dose in male and female mice, respectively.

In female rats, although reversible effects on fertility and early embryonic development were observed at 150 mg/kg boceprevir, no effects were observed at a 75 mg/kg dose, providing an approximately 1.4-fold rat to human AUC exposure multiple. No adverse findings regarding embryo-fetal development or teratogenicity were observed in rats or rabbits at boceprevir doses of up to 600 and 300 mg/kg, respectively.

It should be noted that ribavirin is embryocidal and teratogenic, and is considered a pregnancy category X drug. Interferons, considered pregnancy category C, are arbortifacients. At this time, because boceprevir should be used only in combination with pegylated interferon and ribavirin, its use will be contraindicated in pregnant women. The boceprevir Package Insert will also include appropriate warnings and precautions about use in pregnancy, and information regarding appropriate contraception methods to avoid pregnancy.

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 was not 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. No evidence of thyroid toxicity associated with boceprevir has been observed in clinical trials in adults; and the Applicant plans to monitor thyroid function closely in the proposed pediatric trials.

5. Clinical Pharmacology

Please see details regarding clinical pharmacology in the joint review of Clinical Pharmacology, Pharmacometrics, and Pharmacogenomics by Drs. Ruben Ayala, Sarah Robertson, Jeffry Florian, Pravin Jadhav, Shashi Amur, and Michael Pacanowski.

Boceprevir is a racemic mixture of two diastereomers: SCH534128 and SCH534129. Boceprevir capsules contain a diastereomer ratio of 1:1. In plasma, the diastereomer ratio converts to a stable ratio of 2:1, in favor of SCH534128. SCH534128 is the active stereoisomer of boceprevir.

With multiple dosing, boceprevir has a mean half-life of approximately 2-4 hours that allows steady-state concentrations to be reached within 1 day of TID dosing. With multiple dosing, boceprevir steady-state exposures increase linearly and proportionally to dose from 200 mg to 800 mg TID, but increase less than dose proportionally with doses greater than 800 mg TID.

Boceprevir exposures are similar between healthy subjects and HCV-infected patients. Food increases the mean exposures (AUC) of boceprevir by approximately 50% relative to fasting conditions, and thus boceprevir should be administered with food. Dose adjustment of boceprevir is not necessary based on age, gender, race, or body weight.

Plasma protein binding of boceprevir is low (approximately 77%). The mean steady-state apparent volume of distribution is large, suggesting that boceprevir distributes extensively in tissues. In animals, liver concentrations of boceprevir were 11 to 49-fold higher relative to concentrations in blood; however, the liver concentrations of boceprevir in humans are unknown.

In the Phase 3 clinical trials, based on sparse pharmacokinetic (PK) data, no significant exposure-response relationship between boceprevir AUC and efficacy was shown. Results indicate that higher boceprevir exposures than those delivered with boceprevir 800 mg TID may not result in greater efficacy.

Boceprevir undergoes hepatic and renal elimination, but most elimination occurs hepatically. Dose adjustment of boceprevir is not necessary in patients with any degree of hepatic impairment or in those with any degree of renal impairment.

The Interdisciplinary review team (IRT), in consultation with DAVP, found that boceprevir did not prolong the QT or QTc interval at doses of 800 mg TID or 1200 mg TID, based on results from a multiple dose thorough QTc trial conducted in healthy subjects (P04489). The trial had a 4-way crossover design with placebo, an active control (moxifloxacin), a therapeutic dose, and a supratherapeutic dose of boceprevir. The largest upper bound of the 2-sided 90% CI for the mean difference post-dose between boceprevir (800 mg and 1200 mg TID) and placebo was below 10 ms, the threshold for regulatory concern, as described in ICH E14 guidelines.

Drug-Drug Interaction Potential

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. The following conclusions could be drawn by the clinical pharmacology reviewers regarding potential drug interactions with boceprevir:

- Boceprevir is a strong inhibitor of CYP3A4; thus, sensitive substrates of CYP3A4 with a narrow therapeutic index should not be coadministered. Other CYP3A4 substrates should be used with caution.

- Boceprevir is a substrate of CYP3A4; thus, moderate and strong inducers of CYP3A4 should not be co-administered due to the potential for loss of efficacy. Boceprevir may be coadministered with strong inhibitors of CYP3A4 and P-gp, but patients should be monitored closely because increased levels of boceprevir may increase the risk of anemia.

- Boceprevir is a substrate for P-gp and may be an inhibitor of P-gp, based on *in vitro* study results. A drug interaction trial was not conducted to assess the effect of boceprevir on a sensitive P-gp substrate (e.g. digoxin).

- Oral hormonal contraceptives may not be as effective during concomitant boceprevir therapy due to decreases in ethinyl estradiol concentrations. The Applicant plans to conduct an additional oral contraceptive drug interaction trial to better characterize the effect of boceprevir on the PK of oral contraceptives.

However, insufficient information is available with this NDA to characterize the effect of boceprevir on other likely coadministered agents. Outstanding DDI issues include the following:

- DDI studies were not performed to assess the effect of boceprevir on PK of methadone, an important medication 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.
- 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.

- 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.

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, 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, as shown in the following table. 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; while

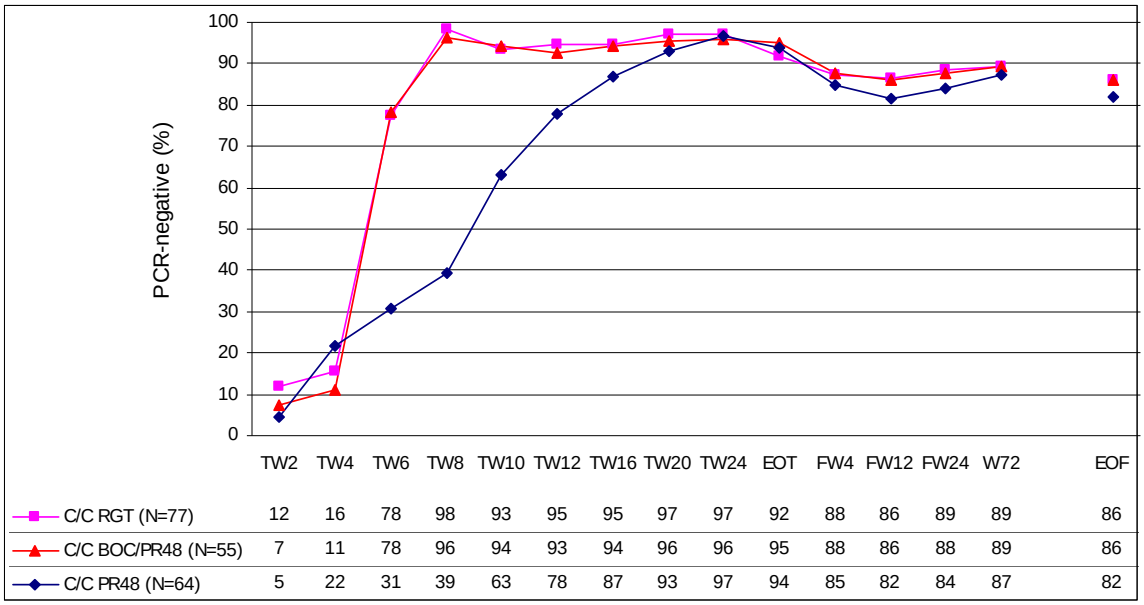
among C/C subjects the NNT was 27 for boceprevir response-guided therapy (RGT) and 53 for boceprevir/PR48. In treatment-failure subjects (P05101), IL28B genotype effects were less pronounced and thus treatment effects did not differ significantly based on IL28B genotype (genotype x treatment interaction 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 1. Treatment Comparisons by IL28B Genotype and Treatment

Trial (population)	IL28B Genotype	N	SVR, n/N (%)		
			Arm 1 PR	Arm 2 RGT	Arm 3 Boc/PR48
P05216 (treatment-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 (prior treatment-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)

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, as shown in the following figure. 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 TW 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 1. Virologic Response over Time by Genotype and Treatment in Treatment-Naïve Subjects (P05216)



	TW2	TW4	TW6	TW8	TW10	TW12	TW16	TW20	TW24	EOT	FW4	FW12	FW24	W72	EOF
C/C RGT (N=77)	12	16	78	98	93	95	95	97	97	92	88	86	89	89	86
C/C BOC/PR48 (N=55)	7	11	78	96	94	93	94	96	96	95	88	86	88	89	86
C/C PR48 (N=64)	5	22	31	39	63	78	87	93	97	94	85	82	84	87	82

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.

6. Virology

Summary of Virologic Resistance in Phase 3 Trials P05216 and P05101

Please see Virology reviews by Drs. Patrick Harrington and Julian O'Rear for further details regarding preclinical and clinical virology findings.

Baseline Resistance

DAVP agreed that boceprevir resistance-associated substitutions were detected infrequently as baseline polymorphisms using a population-based assay. Among subjects who had a relatively poor response to the PR lead-in therapy, these baseline polymorphisms (specifically V36M, T54A, T54S, V55A or R155K) were associated with reduced boceprevir efficacy. Thus, pegylated interferon/ribavirin responsiveness appears to play a role in reducing the impact of these polymorphisms on treatment outcome.

Treatment-emergent Resistance

In Dr. Harrington's analysis of genotypic resistance data for this application, he concluded that the majority of boceprevir-treated subjects who did not achieve SVR (and for whom samples were analyzed) had one or more specific treatment-emergent NS3 amino acid substitutions, most of which have been previously shown to reduce the anti-HCV activity of boceprevir.

These included V36A, V36M, T54A, T54S, V55A, V107I, R155K, A156S, A156T, A156V, V158I, D168N, I/V170A, and I/V170T. Rates of detection of boceprevir treatment-emergent substitutions were similar for the response-guided therapy (RGT) and Boc/PR48 arms. Detection of these substitutions was most common among subjects who experienced virologic breakthrough or incomplete virologic response as defined by the Applicant. Among boceprevir-treated subjects who did not achieve SVR, those who demonstrated lower pegylated interferon/ribavirin responsiveness during the PR lead-in period were more likely to have the emergence of detectable boceprevir resistance-associated substitutions at the time of treatment failure.

After stopping therapy, certain post-baseline boceprevir treatment-emergent substitutions persisted. Among subjects with available data, 25% of subjects with treatment-emergent substitutions still had at least one such substitution detected by population sequencing after 2.5 years of follow-up in the Applicant's long-term follow-up study (P05063). The most common NS3 substitutions detected after 2.5 years of follow-up were T54S and R155K. The loss of detection of an amino acid substitution in a patient sample based on a population-based assay does not necessarily indicate that viral subpopulations carrying that substitution have declined to a background level that existed prior to treatment in that patient.

7. Clinical/Statistical: Efficacy

Details on study design, inclusion and exclusion criteria, demographics, subject disposition, and statistical analysis are included in the Clinical Review by Drs. Poonam Mishra and Sarah Connelly, and the Statistical Review by Drs. Wen Zeng and Guoxing Soon.

Major Efficacy Findings

The two Phase 3 boceprevir studies were: 1) P05216 in treatment-naïve subjects; and 2) P05101 in subjects who had previously failed pegylated interferon alfa plus ribavirin therapy. In both trials, the primary endpoint was sustained virologic response, SVR, defined as undetectable HCV RNA (< 10 IU/mL) measured 24 weeks after the end of therapy. For the purposes of discussion and labeling, DAVP asked the Applicant to use an HCV RNA cutoff of < 25 IU/mL (lower limit of assay quantification, LLOQ) for defining SVR. Note that this cutoff only applies to HCV RNA level off-treatment; while the most appropriate HCV RNA cutoff to guide treatment duration or futility decisions remains under discussion. This decision was made because of issues with suspected false positive HCV RNA results that were reported as detectable but < LLOQ for post-treatment follow-up samples in the telaprevir clinical trials. DAVP believes that using the 25 IU/mL cut-off offers a more efficient review process going forward; while still providing an accurate representation of efficacy. In the boceprevir trials, no differences were found in SVR using the < 10 IU/mL or the < 25 IU/mL HCV RNA cutoff.

a. **Efficacy in Treatment-Naïve Subjects (P05216)**

Study P05216 was a randomized, double-blind, placebo-controlled Phase 3 trial of treatment-naïve subjects with chronic hepatitis C (HCV genotype 1). In order to enroll more black subjects who are often underrepresented in clinical trials, two separate population cohorts were enrolled: Cohort 1 (non-black subjects), and Cohort 2 (black subjects). However, for the primary endpoint analysis, Cohorts 1 and 2 were combined. All subjects received a 4 week

lead-in period of pegylated interferon-alfa and ribavirin prior to addition of boceprevir or placebo. The three treatment arms were:

- Arm 1: Pegylated interferon alfa-2b (PegIntron®) plus ribavirin (Rebetol®) 48 weeks control (PR48)
- Arm 2: Boceprevir plus PegIntron®/ Rebetol®l response-guided therapy (RGT) (described below)
- Arm 3: Boceprevir plus PegIntron® plus Rebetol® (Boc/PR48)

The same dose of boceprevir, 800 mg administered orally three times a day, was used in both boceprevir treatment arms. PegIntron® was dosed at 1.5 µg/kg subcutaneously weekly, and Rebetol® was administered as (600 to 1400 mg/day orally) on the basis of weight. Note that the 600 mg daily Rebetol® dose is not an FDA-approved dose for use with PegIntron®; however, only 18 subjects in this trial received the Rebetol® 600 mg daily dose.

In Arm 2 (RGT), all subjects received 24 weeks of boceprevir in combination with PR (after the 4 week PR lead-in period). For subjects with undetectable HCV at treatment Week 8 through Week 24, all 3 drugs were stopped at Week 28 (early responders); while for those with detectable HCV RNA at Week 8 but undetectable at Week 24 (late responders), boceprevir was stopped and subjects received an additional 20 weeks of PR and placebo. For subjects in each of the treatment arms, all treatment was discontinued for futility if HCV RNA was detectable at Week 24.

The clinical and statistical review teams agree with the Applicant's analysis of the primary efficacy endpoint, SVR, using an HCV RNA of < 25 IU/mL as the cutoff for undetectable. The Division's analysis of the key efficacy endpoints is shown in the following Table.

Table 2. Key Efficacy Endpoints in Treatment-Naïve Subjects (P05216) (Combined Cohorts 1 and 2)*

Efficacy Parameter	Arm 1 PR48 control (N=363)	Arm 2 RGT (combined short and long treatment arms) (N=368)	Arm 3 Boc/PR48 (N=366)
SVR† n(%)	138 (38)	233 (63)	242 (66)
Virologic Relapse^	39/176 (22)	24/257 (9)	24/265 (9)

* Results shown from full analysis set, defined as all randomized subjects who received at least one dose of study medication.
†SVR= sustained virologic response (HCV RNA < 25 IU/mL) at 24 weeks after the end of treatment. HCV RNA was imputed from follow-up Week 12 if Week 24 data was missing.
^Virologic relapse= HCV RNA undetectable (< 10 IU/mL) at end of treatment and > 25 IU/mL at end of followup.

Response-guided therapy is discussed further below.

Subset Analysis in Treatment-Naïve Subjects (P05216)
As shown in the following table, SVR rates were lower and relapse rates were higher in Cohort 2 (black subjects) than in Cohort 1 (non-blacks) for both boceprevir treatment groups (Arms 2 and 3) and for the PR control; however, within each cohort SVR was higher in both boceprevir treatment arms than in the PR control arm.

Table 3. SVR by Race: Cohort 1 (non-black) vs. Cohort 2 (blacks) in P05216

Efficacy Parameter	Cohort 1 (non-black subjects			Cohort 2 (black subjects)		
	Arm 1 PR48 (control) (N=311)	Arm 2 RGT (N=316)	Arm 3 Boc/PR48 (N=311)	Arm 1 PR48 (control) (N=52)	Arm 2 RGT (N=52)	Arm 3 Boc/PR48 (N=55)
SVR† n(%)	126 (41)	211 (67)	213 (69)	12 (23)	22 (42)	29 (53)
Virologic Relapse^ n/N(%)	37/162 (23)	21/232 (9)	18/230 (8)	2/14 (14)	3/25 (12)	6/35 (17)

†SVR= sustained virologic response (HCV RNA < 25 IU/mL) at 24 weeks after the end of treatment (EOT). HCV RNA imputed from follow-up Week 12 if Week 24 data was missing.
^Virologic relapse= HCV RNA undetectable (< 10 IU/mL) at end of treatment and > 25 IU/mL at end of followup.

In Cohort 2 (blacks), although not statistically significant, the 11% numerical difference in SVR between the RGT boceprevir arm and the 48 week boceprevir arm is of some concern and will be discussed further below.

In the statistical reviewer's subset analysis, within the boceprevir treatment arms no differences in SVR were observed for gender, age, or location (US vs. non-US sites). SVR was higher in subjects with baseline HCV RNA ≤ 800,000 IU/mL than in those with baseline HCV RNA > 800,000 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 Metavir fibrosis score (F0, F1, and F2 combined) than in those with higher Metavir fibrosis scores (F3 or F4 combined); and in subjects who had cirrhosis at baseline, compared to no cirrhosis (by investigator's designation).

Efficacy in Previous Treatment-Failure Subjects (P05101)
In P05101, chronic hepatitis C subjects (HCV genotype 1) who had previously failed treatment with pegylated interferon and ribavirin were enrolled. This study enrolled subjects whom the Applicant referred to as "non-responders", who would generally be classified as previous partial responders (≥ 2 $\log_{10}$ decline in viral RNA at Week 12, but never achieving undetectable HCV RNA) and relapsers (undetectable HCV RNA at the end of therapy, but detectable HCV RNA during follow-up). Prior null responders (< 2 $\log_{10}$ decline in HCV RNA at Week 12 of prior therapy) were excluded from the trial.

Subjects were randomized to one of 3 treatment arms:

Arm 1: pegylated interferon alfa-2b (PegIntron®) plus ribavirin (Rebetol®) alone (PR48),
Arm 2: boceprevir plus PR response-guided therapy (RGT), as described below
Arm 3: boceprevir plus PR (Boc/PR48)

All subjects received a 4 week lead-in treatment phase with PR alone. In the RGT arm, subjects with an undetectable HCV RNA at Week 8 completed all therapy at Week 36 (early responders); while those with detectable HCV RNA at Week 8, but undetectable HCV RNA at Week 12 (late responders) received triple therapy through Week 36, followed by an additional 12 weeks of PR alone (total of 48 weeks therapy). In all treatment arms, subjects with detectable HCV RNA at Week 12 discontinued all therapy for treatment futility, and were considered treatment failures. The boceprevir, pegylated interferon alfa-2b and ribavirin dosing regimens were the same as those evaluated in P05216. In this trial, only 1 subject received the 600 mg daily ribavirin dose.

In general, the clinical and statistical review teams agreed with the Applicant's analysis of the primary efficacy endpoint, SVR, defined as HCV RNA of < 25 IU/mL at Week 24 after the end of treatment. The Division's analysis of the key efficacy endpoints is shown in the following Table. SVR was higher and relapse rates were lower in both boceprevir arms than in the PR control arm in this treatment-experienced 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 our analysis, in the subgroup of cirrhotic subjects (cirrhosis present, based on liver biopsy results reported by local pathologist) 2/17 (12%) in Arm 2 (RGT) and 14/22 (64%) in Arm 3 (Boc/PR48) had an undetectable HCV RNA at Week 8 and reached Week 36 while receiving triple therapy. The difference in response prior to Week 36 between these subgroups remains unexplained.

Table 4. Key Efficacy Endpoints in Previous Treatment-Failure Subjects (P05101)*

Efficacy Parameter	Arm 1 PR 48 control (N=80)	Arm 2 (RGT) (N=162)	Arm 3 Boc/PR48 (N=161)
SVR† n(%)	18/80 (23)	96/162 (59)	107/161 (66)
Virologic Relapse^ n/N(%)	7/25 (28)	16/111 (14)	14/121 (12)

* In full analysis set (all randomized subjects who received at least one dose of any study drug
†SVR= sustained virologic response (HCV RNA < 25 IU/mL) at 24 weeks after the end of treatment (EOT). HCV RNA imputed from follow-up Week 12 if Week 24 data was missing.
^Virologic Relapse= undetectable HCV RNA at end of treatment and HCV RNA > 25 IU/mL at end of follow-up.

Response-guided therapy in this population is discussed below.

Subset Analysis

Black and non-black subjects were not enrolled in separate cohorts in P05101, as was done in P05216. As a result, the subset of black subjects in this study is relatively small, and results of this analysis should be interpreted with caution. As shown in the following table, 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. However, in both subsets, SVR was higher in both boceprevir arms than in the control arm.

Table 5. Subset Analysis: SVR in Black vs. non-Black Subjects in P05101

Efficacy Parameter	Blacks Subset			Non-Blacks Subset		
	Arm 1 PR48 (control) n/N (%)	Arm 2 RGT n/N (%)	Arm 3 Boc/PR48 n/N (%)	Arm 1 PR48 (control) n/N (%)	Arm 2 RGT n/N (%)	Arm 3 Boc/PR48 n/N (%)
†SVR	1/12 (8)	11/18 (61)	10/19 (53)	16/68 (24)	84/144 (58)	97/142 (68)
Virologic Relapse^	0/1 (0)	0/11 (0)	0/10 (0)	7/24 (29)	16/100 (16)	14/111 (13)

†SVR= sustained virologic response (HCV RNA < 25 IU/mL) at 24 weeks after the end of treatment. HCV RNA imputed from follow-up Week 12 if Week 24 data was missing.
^Virologic Relapse= undetectable HCV RNA at end of treatment and HCV RNA > 25 IU/mL at end of follow-up.

In the statistical reviewer's subset analyses, within the boceprevir treatment arms subjects who were previous relapsers, those with lower baseline HCV RNA (≤ 800,000 IU/mL), lower baseline Metavir fibrosis scores (F0, F1, and F2 combined), no cirrhosis, and HCV subtype 1b, had higher response rates (SVR) than those who were previous partial responders, subjects with higher baseline HCV RNA (>800,000 IU/mL), higher Metavir scores (F3 and F4 combined), cirrhosis, and HCV subtype 1a; while no significant difference in SVR was observed with gender and age.

It should also be noted that although PegIntron® and Rebetol® were used in combination with boceprevir in these clinical trials, similar efficacy would be expected if Pegasys® and Copegus® had been used, based on previous data from the Applicant's IDEAL study, and on data from the Applicant's recently completed trial (P05685) which evaluated boceprevir in combination with Pegasys® and Copegus®. Although the complete study report and datasets have not been submitted, the Applicant submitted a summary of efficacy in P05685 with the safety update report, as requested at the pre-NDA meeting. Based on the Applicant's analysis, SVR rates were higher and relapse rates were lower in the boceprevir/ Pegasys® and Copegus® arms than in the Pegasys® and Copegus® control arms, similar to that observed with boceprevir in combination with PegIntron® and Rebetol®.

Efficacy Issues:
Although boceprevir in combination with pegylated interferon and ribavirin was clearly superior to PR alone in both treatment-naïve subjects and in subjects who had previously failed PR therapy (partial responders and relapsers), there remain several efficacy issues, including optimal duration of boceprevir/PR in treatment-naïve subjects who are "late responders"; optimal duration of therapy for certain subgroups, and inclusion of prior null responders to PR in the boceprevir treatment indication.

Response Guided Therapy: Treatment-Naïve Subjects
In trial P05216, subjects in both boceprevir/PR treatment arms had a higher rate of SVR than those who received PR48 alone. Subjects considered early responders (undetectable HCV RNA at TW8 through TW24) had similar rates of SVR whether they received a shorter course of treatment (4 weeks PR followed by 24 weeks boceprevir/PR) or a longer course of therapy (4 weeks PR followed by 44 weeks boceprevir PR triple therapy), as shown in the following table. However, SVR was numerically higher in the Boc/PR48 Arm 3 than the RGT Arm 2 in subjects who were late responders (defined as detectable at TW8 but undetectable at TW24), and thus received longer durations of therapy. In late responders, subjects received 4 weeks PR followed by 24 weeks boceprevir/PR followed by 20 weeks PR, and 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 represents a true difference, it would probably be considered clinically relevant. Note that this analysis excludes 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. The Applicant included these 14 subjects in the RGT late responder arm even though they received the longer duration of therapy and were determined to be early responders upon repeat HCV RNA testing.

Table 6. SVR by Virologic Response on Treatment (P05216) Cohorts 1 and 2 Combined

Virologic Response	Arm 2 (RGT) SVR n/N (%)	Arm 3 Boc/PR48 SVR n/N (%)	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]

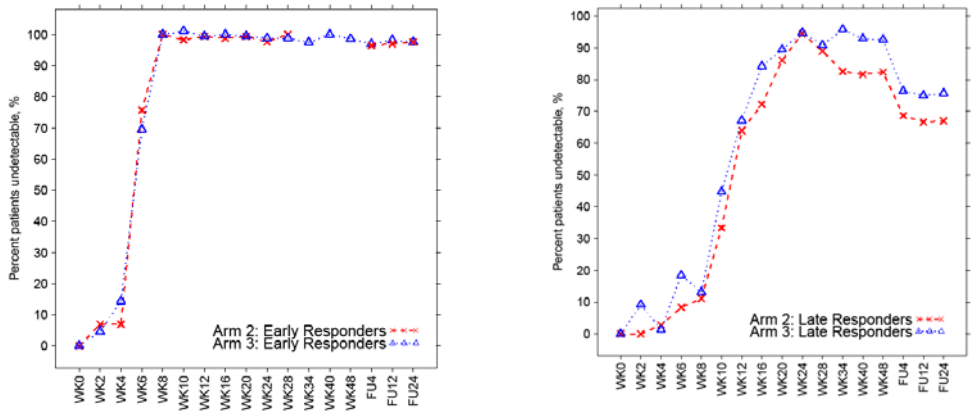
[*]Early Responders: Undetectable HCV RNA treatment Week 8 through 24 (In RGT Arm, early responders received BOC/PR through Week 28).
[#]Late Responders: Detectable HCV RNA Week 8, but undetectable by Week 24 (In RGT Arm, late responders received 28 weeks BOC/PR, followed by 20 weeks of PR for total of 48 weeks).
Subjects were discontinued for futility at Week 24 in all treatment arms if HCV RNA was detectable.

In this subset analysis, virologic relapse rates were similar in early responders who received either 24 weeks of triple therapy in RGT Arm (4/160, 3%) or 44 weeks of triple therapy in BOC/PR 48 Arm (2/157, 1%). There was also no difference in relapse rates between late responders in the RGT Arm who received 24 weeks boceprevir/PR followed by 20 weeks PR (7/52, 13%) compared to the 44 weeks of triple therapy in BOC/PR 48 Arm (9/64, 14%).

The numeric difference in SVR between late responders in Arms 2 and 3 (and the similar SVR between Arms 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 2, 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: 45/68 (66%); and Arm 3 late responders: 55/73 (75%) (Figure 2, right). It appears that this difference can be attributed largely to virologic breakthrough while on PR after stopping boceprevir.

Figure 2: Percentage of Treatment-Naïve Subjects with Undetectable Viral Load at Different Treatment Time Points for Early Responders (Left) or Late Responders (Right) From P05216.



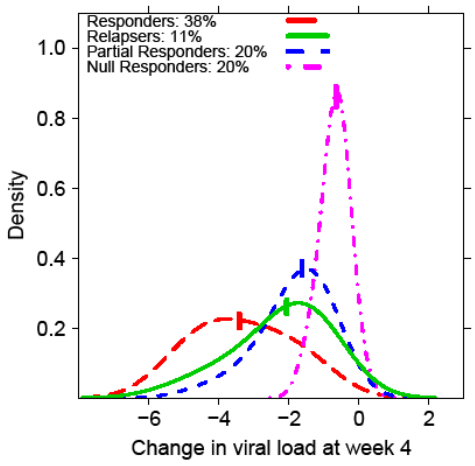
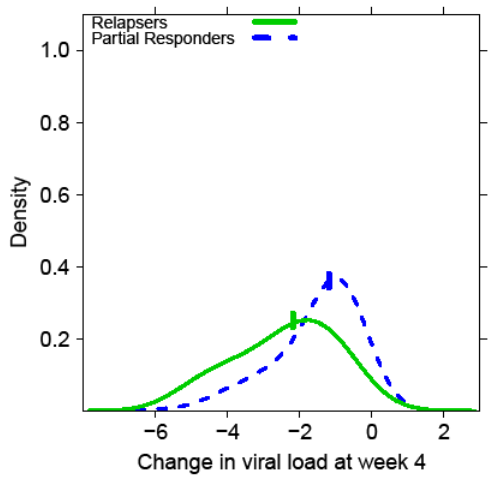
These analyses suggest that treatment-naïve subjects with detectable HCV RNA at Treatment Week 8 but undetectable at Week 24 (i.e., late responders not meeting futility rule) may

benefit from receiving a longer duration (for example, 32 or 44 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 could come at the cost of prolonged anemia. Another option may 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.

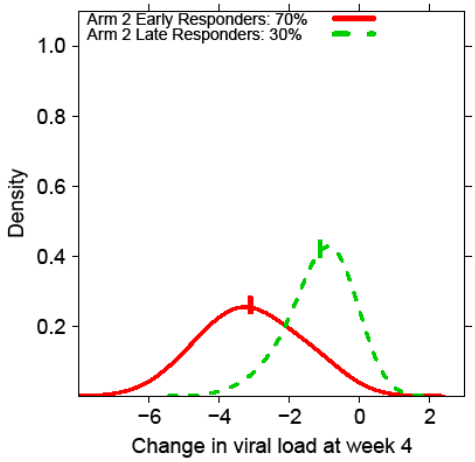
To support a 32 week duration of boceprevir treatment (i.e. through Week 36) followed by PR alone, data from studies P05216 and P05101 were bridged. This "bridging" analysis demonstrates that late responders among the treatment-naïve population are fairly similar in characteristics to that of previously-treated 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 standard of care (SOC) 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 $\log_{10}$ decrease) at Week 4 are more likely to be SVR responders and those with smaller Week 4 viral load changes (median=0.7 $\log_{10}$ decrease) are more likely to be null responders to PR (<2 $\log_{10}$ decline at Week 12) (Figure 3a). The relapser (median=2.1 or 2.2 $\log_{10}$ decreases) and partial responder (median=1.6 or 1.2 $\log_{10}$ decreases) populations also demonstrate similar viral load decreases as expected, for both treatment-naïve (Figure 3a) and treatment-experienced (Figure 3b) populations, respectively. Hence, the Week 4 response is a good predictor of PR treatment outcome in treatment-naïve subjects and a similar Week 4 response is maintained if subjects classified as relapsers or partial responders are retreated with PR.

Figure 3a. Relationship between PR Treatment Outcome and Week 4 HCV RNA Change from P05216 (Treatment-Naïve Subjects)	**Figure 3b. Relationship between Previous PR Response and Week 4 HCV RNA Change from P05101 (Treatment-Experienced Subjects)**
	

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 4). 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 SOC treatment.

Figure 4. Relationship between Response Guided Treatment Arm Assignment and Week 4 HCV RNA Change from P05216



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, as shown in the following table. Taken together, these analyses indicate that 24 weeks duration of boceprevir (i.e. 4 weeks PR followed by 24 weeks triple therapy, followed by 20 weeks PR) was not sufficient in late responders based on P05216, while P05101 suggests that 32 weeks boceprevir (i.e. 4 weeks PR followed by 32 weeks triple therapy, followed by 12 weeks PR) may be sufficient in this group. However, this analysis is not conclusive as P05101 did not include previous null responders, and it is currently unresolved whether longer treatment duration (44 weeks of boceprevir) would be necessary to achieve optimal SVR rates in these patients.

Table 7. Response Rates (SVR) for Early and Late Responders from P05101[a]

Study and Treatment Group	RGT	Boc/PR48
P05101 Late Responders*	79% (27/34)	73% (29/40)
P05101 Early Responders[#]	91% (62/68)	97% (68/70)

[a] Subjects who had a treatment duration of less than 36 weeks were removed from this analysis.
*Late Responders: detectable HCV RNA at Week 8, but undetectable at Week 12
[#]Early Responders: undetectable HCV RNA at Week 8 and Week 12

To summarize, the link between data from PR48 and RGT Arms from P05216 and late responders from P05101 demonstrates that:

- Patients with poor response to PR alone at Week 4 are most likely to be partial responders, null responders, or relapsers if they continued on SOC.
- Patients with poor response to SOC at Week 4 are most likely to receive treatment as late responders in RGT.

- For subjects in P05101, which included prior partial responders and relapsers, late responders required 32 weeks of boceprevir treatment to achieve SVR rates similar to those observed for late responders treated with boceprevir for 44 weeks.
- Thus, a minimum of 32 weeks of boceprevir in combination with pegylated interferon/ribavirin may be necessary in order to achieve optimal SVR rates in treatment-naïve late responders.

Duration of treatment in pertinent subgroups: SVR by Race in P05216
As discussed above, in the subset analysis of blacks vs. non-blacks in the treatment-naïve trial, P05216, boceprevir in combination with PR provided a treatment benefit over the standard of care (PR) within each cohort. Additionally, as described previously in multiple studies of treatment with PR alone, SVR is generally lower in black than non-black subjects.

A similar analysis to that described above for early and late responders was performed to evaluate the efficacy of response-guided therapy in Cohorts 1 (non-blacks) and 2 (blacks) in the treatment-naïve study P05216. In Cohort 1 (non-blacks), early responders had similar SVR rates with 28 weeks (4 lead-in PR plus 24 weeks triple therapy) in comparison to early responders that received 48 weeks triple therapy (4 week lead-in PR plus 44 weeks triple therapy). In Cohort 2 (blacks), early responders had higher rates of SVR (numerically, but not statistically significant) with longer triple therapy than with the shorter course. Late responders in both Cohorts had higher rates of SVR with 48 week triple therapy (though not statistically significant) than with 24 weeks boceprevir plus 12 weeks PR; and this difference was much greater in blacks than non-blacks. The number of subjects in this subset was very small and these are post-hoc subset analyses; however these analyses raise the issue of whether black patients should receive a shortened course of therapy.

Table 8. RGT vs. Boc48 (Cohort 1 vs. Cohort 2) in P05216

Virologic Response	Arm 2 (RGT) SVR n/N (%)	Arm 3 (Boc/PR48) SVR n/N (%)	Treatment Difference Arm 2-Arm 3 [95% CI two sided]
Cohort 1 (non-Blacks)	N=316	N=311	
*Early Responders	143/146 (97.9)	137/142 (96.5)	1.5 [-2.8, 6.2]
#Late Responders	38/56 (67.9)	48/65 (73.8)	-6.0 [-22.5, 10.7]
Cohort 2 (Blacks)	N=52	N=55	
*Early Responders	13/15 (86.7)	18/19 (94.7)	-8.1 [-37.0, 14.8]
#Late Responders	7/12 (58.5)	7/8 (87.5)	-29.2 [-65.1, 16.1]

*Early Responders: Undetectable HCV RNA treatment Weeks 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.

Duration of Treatment: SVR in Subjects with Advanced Fibrosis Stage or Cirrhosis (Metavir Scores F3 or F4) in P05216

In the treatment-naive study, P05216, subset analysis showed that SVR in the boceprevir treatment arms was similar in subjects with baseline Metavir fibrosis scores of F0, F1, and F2 (minimal to moderate fibrosis stage) to that observed in the full-analysis set. However, subjects with baseline Metavir fibrosis scores of F3 or F4 (more advanced fibrosis stage or cirrhosis, respectively) had a lower SVR rate in the boceprevir treatment arms than that observed in the subset of subjects with Metavir scores of F0, F1, and F2 or in all boceprevir-treated subjects. Because the number of subjects with baseline Metavir F3 or F4 scores was small, analysis of SVR in early vs. late responders between Arms 2 and 3 was not conducted to assess whether shorter duration of boceprevir is warranted in early responders. These results are based on a small number of subjects, so the lower response rates in this group should be viewed with caution.

Table 9. SVR by Baseline Metavir Fibrosis Scores in P05126

Parameter	Arm 1 (PR48) SVR n/N (%) N=363	Arm 2 (RGT) SVR n/N (%) N=368	Arm 3 (Boc/PR48) SVR n/N (%) N=366
Overall	138 (38)	233 (63)	242 (66)
Baseline Metavir Fibrosis Score F0, F1, or F2 n/N (%)	124/328 (38)	213/319 (67)	211/313 (67)
Baseline Metavir Fibrosis Score F3 or F4 n/N (%)	9/24 (38)	14/34 (41)	22/42 (52)

Duration of Treatment: Previous Partial Responders and Relapsers (P05101)

A similar analysis to that shown above for study P05216 was performed with data from this trial to compare SVR in early responders (undetectable HCV RNA Weeks 8 through 12), and late responders (detectable HCV RNA Week 8, but undetectable at Week 12) to determine whether a shorter duration of boceprevir was reasonable in subjects who had previously failed PR treatment. The following table shows no significant difference in SVR rates for early responders who received 32 weeks boceprevir/PR in RGT Arm vs. 44 weeks boceprevir/PR (both after 4 weeks PR lead-in therapy). These data suggest that the extra 12 weeks triple therapy in the Boc/PR48 Arm did not result in higher SVR in early responders. Additionally, no significant difference was observed in SVR for late responders who received RGT (32 weeks Boc/PR plus 12 additional weeks of PR) vs. those who received 44 weeks Boc/PR (both after 4 week lead-in with PR). These data suggest that 32 weeks triple therapy plus 12 weeks PR may be sufficient for late responders in this population.

Table 10. SVR by Virologic Response on Treatment in Study P05101 (RGT vs. Boc/PR48)

Virologic Response	Arm 2 (RGT) SVR n/N (%)	Arm 3 (Boc/PR48) SVR n/N (%)	Treatment Difference Arm 2-3 [95% 2-sided CI]
Overall	96/162 (59.3)	107/161 (66.5)	-7.2 [-17.7, 3.5]
Early Responders#	62/68 (91.2)	68/70 (97.1)	-6.0 [-15.6, 2.2]
Late Responders*	27/34 (79.4)	29/40 (72.5)	6.9 [-14.0, 26.7]

#Early Responders: Subjects with undetectable HCV RNA (<10 IU/mL) Weeks 8 through 12 (In RGT Arm received a total of 32 weeks boceprevir/PR after 4-week lead-in treatment with PR.)
*Late Responders: Subjects with detectable HCV RNA (> 10 IU/mL) at Week 8 but undetectable at Week 12 (In RGT Arm received a total of 32 weeks boceprevir/PR after 4-week lead-in treatment with PR, followed by an additional 12 weeks PR).
In the Boc/PR48 Arm, all subjects, both early and late responders received 44 weeks Boc/PR after 4 week lead-in treatment with PR.

Null Responders and Interferon Responsiveness

The Applicant has proposed that prior null responders not be excluded from the indication even though they were not eligible for enrollment in the Phase 3 treatment-failure trial, P05101. Enrolled subjects in this trial were referred to as "non-responders" and were either partial responders ($\geq$ 2 $\log_{10}$ decline in HCV RNA at week 12, but never achieving undetectable HCV RNA), or relapsers (HCV RNA undetectable at the end of treatment but HCV RNA detectable during follow-up). As shown above, a 36-43% treatment benefit was shown over pegylated interferon/ribavirin alone for the boceprevir treatment arms in the populations studied in P05101.

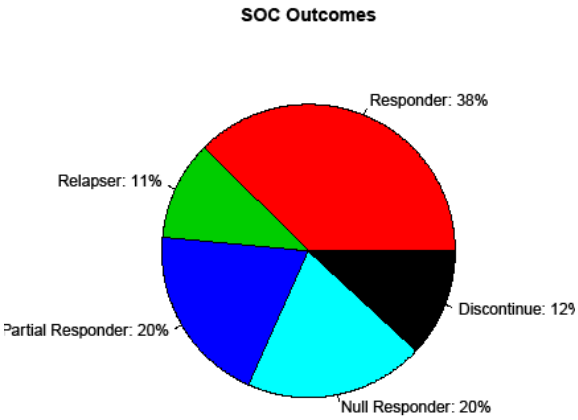
Null responders were not included in P05101 because at the time, there appeared to be insufficient support from the Phase 2 trial in the treatment-experienced population to embark on a larger study for the null response subgroup; and the Applicant and FDA concurred that it was prudent to first see the results from Phase 3 trials evaluating relapsers and partial responders. The Applicant's Phase 2 trial (P03659) enrolled previous treatment-failure subjects who never achieved undetectable HCV RNA while receiving pegylated interferon/ribavirin therapy, including null responders and partial 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 assessed.

Based on the DAVP and Applicant's analyses, an important concept for consideration is the view that treatment-naïve patients are comprised of a spectrum of potential responders and nonresponders. In fact it can be predicted that more than half of treatment-naïve patients will eventually be proven to be pegylated interferon plus ribavirin treatment failures, 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, and therefore considering prior treatment history is less important than the current response to PR at treatment Week 4.

The following figure (Figure 5) shows the outcomes reported for subjects enrolled in the PR48 (control) treatment arm in P05216. Note that subjects who relapsed, or who had a partial response, or null response comprised 51% of those who received PR therapy alone. Because the trial was randomized, presumably a similar distribution of subjects (as in the PR48 Arm) would have been included in the boceprevir treatment arms in that trial.

Figure 5. Treatment Outcomes with Pegylated Interferon/ribavirin (Arm 1) in Treatment- Naïve Subjects (P05216)



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-naive 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, 679 subjects had a < 2 $\log_{10}$ decline in HCV RNA at treatment Week 12. Subjects with a < 1.0 $\log_{10}$ decline in HCV RNA at treatment Week 4 had SVR rates 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 treatment Week 4 did not achieve SVR. In addition in boceprevir trials P05216 (treatment-naïve) and P05101 (partial responders and relapsers), subjects in the PR48 control arms with a < 1.0 $\log_{10}$ decrease in HCV RNA after 4 weeks PR lead-in therapy had SVR rates of 4%, and 0%, respectively. These data show that subjects 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 a <1 $\log_{10}$ HCV RNA treatment Week 4 response to PR therapy could be considered a surrogate for null response to prior PR therapy (defined as < 2 $\log_{10}$ HCV RNA decline at treatment Week 12).

The Division confirmed that in the treatment-naïve trial P05216, interferon-responsive subjects, i.e. those who had a ≥ 1.0 $\log_{10}$ decline in HCV RNA by treatment Week 4, had a higher rate of SVR than subjects who were poorly interferon-responsive (< 1.0 $\log_{10}$ decline at treatment Week 4) as shown in the following table.

Table 11. SVR by Virologic Response to 4 week Lead-in Treatment with PR in Treatment-Naïve Trial (P05216)

Treatment Week 4 Virologic Response	SVR Arm 1 (PR48) N=363	SVR Arm 2 (RGT) N=368	SVR Arm 3 (Boc/PR48) N=366
Poorly interferon responsive (HCV RNA < 1.0 $\log_{10}$ decline)	3/83 (4)	27/97 (28)	36/95 (38)
Interferon responsive (HCV RNA ≥ 1.0 $\log_{10}$ decline)	134/260 (52)	203/252 (81)	200/254 (79)

SVR= sustained virologic response (HCV RNA < 25 IU/mL) at 24 weeks after the end of treatment. HCV RNA was imputed from follow-up Week 12 if Week 24 data were missing.

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 subjects across a range of interferon responsiveness, including poorly interferon responsive subjects, a proportion of whom would eventually be classified as null responders to current treatment.

There are some weakness 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 (22 %) of these subjects had a ≥ 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 ≥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 period). 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.

The Pharmacometrics reviewers have proposed that boceprevir be approved for use in null responders based on an additional analysis of data from the treatment-naïve study P05216, showing the benefit of boceprevir/PR over PR alone in null responders identified by using a lower HCV RNA cut-off at TW4 (≤ 0.5 $\log_{10}$ decline in HCV RNA) for viral load to define null responders). Using this HCV RNA cut-off, 22/25 (88%) subjects who had an HCV RNA ≤ 0.5 $\log_{10}$ decline at TW4 were also null responders to PR (< 2 $\log_{10}$ decline at TW 12 and 0% SVR. In the boceprevir treatment arms, SVR among subjects with a ≤ 0.5 $\log_{10}$ decline HCV RNA at in TW4 was 11/37 (30%) in the RGT Arm, and 13/47 (28%) in the Boc/PR48 Arm in this trial. Although this is a post-hoc subset analysis, and the numbers are small, it would appear that boceprevir provides some benefit in null responders over the current standard of care. The optimal duration of therapy in this group is not known; however, it may be prudent to treat late responders who also have a TW4 response of < 1 $\log_{10}$ HCV RNA with a longer course of triple therapy (i.e. 44 weeks boceprevir/PR after the 4 week lead-in period with PR).

8. Safety

For details of clinical safety, see Clinical Reviews by Drs. Poonam Mishra, Sarah Connelly, and Charles Cooper. Dr. Charles Cooper's safety review focuses specifically on anemia in the Phase 3 trials. In the boceprevir clinical trials, 1033 subjects received boceprevir at the proposed dose (800 mg TID) for a minimum of 24 weeks; 608 subjects received boceprevir for at least 32 weeks; and 370 subjects received boceprevir for at least 44 weeks. The safety database is considered adequate to assess safety of boceprevir in this population.

The major safety signal to emerge from boceprevir clinical trials was anemia, which was seen at a higher frequency and at a greater magnitude (at least 1 g/dL hemoglobin [Hgb] greater) than that observed with PR alone. Additionally, neutropenia, sometimes in association with serious and life-threatening infections, and thrombocytopenia were found at higher rates in

subjects treated with boceprevir/PR than in those treated with PR alone. Certain gastrointestinal adverse events, namely dysgeusia (taste alteration), nausea, vomiting and diarrhea, were reported more commonly in boceprevir/PR-treated than in PR-treated subjects; however, these adverse events (AEs) were generally mild or moderate in severity.

Psychiatric serious adverse events (SAEs), including suicidal and homicidal ideation were reported somewhat more frequently in boceprevir/PR-treated than PR (alone)-treated subjects; however these events are also associated with PR use and the imbalance seen may have been related to the shorter duration of PR therapy (due to higher proportions of discontinuations in that arm) due to treatment futility in P05101.

Because of the preclinical findings of testicular toxicity in rats, potential effects on male fertility were evaluated in Phase 1 and 2 clinical trials by monitoring inhibin B, a surrogate marker of testicular function, and analysis of sperm counts in semen. No evidence for boceprevir-related testicular toxicity was observed in these trials, and with the agreement of DAVP, further monitoring of inhibin B or semen analysis was not studied in the later boceprevir clinical development program.

The major safety concerns with boceprevir are summarized below.

Anemia
Treatment of chronic hepatitis C with pegylated interferon and ribavirin is itself associated with development of anemia and significant declines in hemoglobin concentration. Ribavirin causes a dose-related hemolysis which is exacerbated by interferon-related bone marrow suppression, resulting in blunted reticulocytosis. Typical hemoglobin concentration declines of approximately 3 g/dL may require ribavirin dose reduction or discontinuation. In a study in healthy volunteers, the Applicant demonstrated that boceprevir-associated anemia is not associated with hemolysis, but rather, appears to be due to bone marrow suppression. In the Phase 2 and 3 trials, mean hemoglobin concentration in boceprevir treatment arms reached a nadir approximately 4-8 weeks after starting boceprevir, and was reversible after stopping treatment. Because anemia resolved in these trials after stopping all treatment, there may be some benefit in terms of safety for shorter vs. longer durations of treatment with boceprevir in combination with pegylated interferon/ribavirin for patients in whom efficacy is predicted to be similar.

In the boceprevir clinical trials, anemia management was left up to the discretion of investigators. Guidelines were provided in the protocols for ribavirin dose reduction or discontinuation (as per the approved Rebetol® Package Insert) or for erythropoietin use for hemoglobin $\leq$ 10 g/dL. In these trials, anemia was managed by ribavirin dose reduction or discontinuation, and/or erythropoietin use; and/or blood transfusion. It should be noted that erythropoietin is not FDA-approved for treatment of anemia in patients with chronic hepatitis C.

The Applicant reported 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.

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 ≤10g/dL in the Phase 3 trials.

Because investigators weren't required to intervene upon development of a hemoglobin ≤ 10g/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 g/dL were not always reported as having had an anemia adverse event 108/688 (16%).
2. Subjects with hemoglobin ≤10 g/dL 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 ≤ 10g/dL as a protocol-specified intervention trigger added additional bias by increasing the likelihood that subjects, 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 subjects, 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.

Exposure-Response Relationships for Anemia

The pharmacometrics reviewers, Drs. Jeffry Florian and Pravin Jadhav found a non-significant upward trend of increasing incidence of anemia (Hgb < 10 g/dL) was observed with increasing boceprevir AUC_τ in the Phase 3 pharmacokinetics (PK) population. Boceprevir AUC_τ 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_τ was observed in the Phase 3 PK population receiving triple therapy (n=113; $p<0.0001$). This finding is not unexpected, given ribavirin's known hematological effects, with an observed incidence rate of ~30% in the 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 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.

Anemia reported as an Adverse Event

The following table shows the clinical reviewer's analysis of anemia reported as an adverse event in the Phase 3 trials (P05216 and P05101). Anemia was reported as an adverse event (regardless of causality) in a higher proportion of subjects in the boceprevir-containing arms than in the PR control arms 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 boceprevir/PR recipients than in PR controls. Likewise, anemia resulted in more frequent dose reduction or interruption or discontinuation (of

ribavirin, boceprevir or pegylated interferon) in boceprevir treatment arms than PR control arms across the Phase 3 trials. It should be noted that because of confounding and misclassification bias with regard to reporting anemia as an adverse event in the Phase 3 clinical trials, the numbers and proportion of subjects with anemia shown in the table below is likely an underestimate.

Table 12. Adverse Events: Anemia in Phase 3 trials

Anemia* Adverse Events	P05216+P05101 Boceprevir Arms N= 1057 (%)	P05216+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,

Lowest Hemoglobin Values during Treatment

The following table shows the clinical reviewer's 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 g/dL and < 8.5 g/dL 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 above, because of confounding and potential bias due to individual investigator's management of anemia, the hemoglobin values shown below probably do not reflect the true magnitude of hemoglobin decline with boceprevir or pegylated interferon and ribavirin treatment.

Table 13. Hemoglobin Nadir during Phase 3 Trials (P05216 and P05101)

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

Adverse Events Associated with Anemia

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, 330/1057 (31%) vs. 107/443 (24%). Dizziness also occurred in a higher proportion of boceprevir/PR-treated subjects than PR controls, 199/1057 (19%) vs. 68/443 (15%), respectively; and although uncommon, syncope was reported more often in boceprevir/PR-treated subjects, 23/1057 (2%) vs. 3/443 (<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 (2 events in boceprevir-treated subjects vs. 2 events in PR-treated subjects).

Anemia management in key Phase 2 and 3 trials
In the Phase 3 trials, management of anemia was left up to individual investigators. The protocol provided guidelines for anemia management as follows:

- Hemoglobin ≤10 g/dL, ribavirin dose reduction and/or use erythropoietin (or both) recommended;
- Hemoglobin ≤8.5 g/dL ribavirin interruption or discontinuation recommended

Erythropoietin was provided at no cost to subjects by the Applicant in these trials. 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. However, in clinical practice, off-label use of ESAs in this population is common and at the discretion of the treating physician. Erythropoietin use and/or ribavirin dose reduction or both in the Phase 3 trials is shown in the following table. Note that erythropoietin use and/or ribavirin dose reduction or both was reported in a higher proportion of boceprevir-treated than PR control-treated subjects**.** Additionally, although blood transfusions were not commonly required in these trials, they were more frequent in boceprevir recipients.

Table 14. Use of Erythropoietin and/or Ribavirin Dose Reduction in Phase 3 Trials (P05216 and P05101)

Treatment Arm (Pooled)	Erythropoietin Use **or** ribavirin dose reduction n (%)	Erythropoietin Use **and** ribavirin dose reduction n (%)	RBC Transfusion n (%)
All Boceprevir-treated Subjects (N=1057)	543 (51)	242 (23)	39 (4)
All PR-treated subjects (N=443)	135 (31)	50 (11)	2 (<1)

Adverse Events Associated with Erythropoiesis-Stimulating Agents (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. ESA use has been associated with a number of serious adverse events, including death, cardiovascular events, thromboembolic events, stroke, and risk or tumor progression or

recurrence (in patients with underlying cancer). 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 included 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. The Applicant is currently conducting a randomized clinical trial to evaluate strategies for anemia management (i.e. ribavirin dose reduction or erythropoietin use) in subjects with chronic hepatitis C treated with boceprevir/PR.

ITPA Polymorphism and Anemia
ITPA polymorphisms have been associated with a lower risk for developing anemia in the course of PR therapy. In addition to IL28B, three ITPA polymorphisms were assayed in the genetic substudies of P05216 and P05101 as follows: rs1127354 (C>A, missense P32T), rs7270101 (A>C, intronic splice-altering), and rs6051702 (A>C, tagging SNP). The missense and splice-altering polymorphisms are putative ITPA deficiency alleles; subjects were grouped according to the presence or absence of either or both of these alleles. Baseline hemoglobin did not differ according to the composite ITPA genotype. The incidence of anemia-related adverse events (i.e., hemoglobin nadir, absolute and percent change in hemoglobin, erythropoietin use, and DAIDS grade 3/4 anemia) was significantly lower among individuals with ITPA polymorphisms in both PR and the pooled boceprevir/PR arms (P<0.001).

Neutropenia
Neutropenia was more common among subjects receiving boceprevir plus PR than in those receiving PR alone in the Phase 3 trials. Neutropenia was reported as an adverse event in 231/1057 (22%) subjects in boceprevir- containing arms versus 85/443 (19%) subjects in PR arm, as a serious AE in 3 subjects (<1%) in boceprevir-containing arms compared to none (0%) in control arm, as a severe (Grade 3 and 4) AE in 84 subjects (8%) in boceprevir-containing arms compared to 28 subjects (6%) in the control arm. Neutropenia resulted in study drug discontinuation in 8/1057 (<1%) subjects in boceprevir containing arms and in none (0%) of the subjects in the PR alone arm. G-CSF use was allowed in the Phase 3 trials, and was used in 96/1057 (9%) boceprevir-treated, and 26/443 (6%) PR-treated subjects.

As shown in the following table, based on laboratory data, a higher proportion of boceprevir recipients experienced Grade 3 and 4 neutropenia than subjects who received PR alone.

Table 15. 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.

Three subjects (all in boceprevir-containing arms), experienced severe infections; these include epiglottitis requiring tracheostomy, upper respiratory infection, and salmonella gastroenteritis/diarrhea. These adverse events were reported within two weeks of Grades 3 and 4 neutropenia. Additionally, two cases of life-threatening neutropenia (both in boceprevir-treated subjects) were reported. One subject developed multi-organ system failure due to sepsis, and the other experienced a fever of 104.5°F. A specific infection was not reported in these cases.

Thrombocytopenia

Thrombocytopenia was also more common among subjects receiving boceprevir/PR than in those receiving PR alone in the pivotal Phase 3 trials. Thrombocytopenia was reported as an adverse event in 49/1057 (5%) subjects in boceprevir-containing arms versus 7/443 (2%) subjects in the PR arms, as a serious AE in 3 subjects (<1%) in boceprevir-containing arms compared to none (0%) in PR arms, and as a severe or life-threatening (Grade 3 and 4) AE in 15 subjects (1%) in boceprevir-containing arms compared to 3 subjects (<1%) in the PR arm. Thrombocytopenia resulted in study drug discontinuation in 4/1057 (<1%) subjects in boceprevir containing arms and in none (0%) of the subjects in the PR alone arm. As shown in the following table, based on laboratory data, a higher proportion of subjects in boceprevir-containing arms than the PR arms experienced Grade 3 or 4 thrombocytopenia.

Table 16. Lowest Absolute Platelet Count on Treatment in Phase 3 Trials (P05216 and P05101)

Lowest absolute Platelet count on Treatment	Boceprevir/PR N=1050 n(%)	PR 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

Both of the boceprevir-treated subjects with grade 4 thrombocytopenia were reported to have epistaxis which was considered mild and no intervention was needed. No cases of significant bleeding were reported in Phase 3 trials; however, one of the subjects received numerous platelet transfusions because of severe thrombocytopenia.

9. Advisory Committee Meeting

An Advisory Committee meeting is scheduled for April 27, 2011. The major issues/questions for discussion, as outlined in the background document provided to the Committee include the following:

1. Please comment on the safety of boceprevir in patients with chronic hepatitis C genotype 1, focusing mainly on the hematological effects of boceprevir in combination with pegylated interferon and ribavirin (PR).

2. Considering the overall potential risk and benefits of boceprevir, 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?

VOTE: Yes/No/Abstain

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

3. Please comment on the strength of the evidence for use of boceprevir in combination with pegylated interferon/ribavirin in prior null responders (defined as less than 2 $\log_{10}$ decrease in HCV RNA at 12 weeks during previous course of PR therapy), who were not included in the Phase 3 trial, P5101 in subjects who had previously failed PR therapy.

4. Please comment on the strength of the evidence to support response-guided therapy (RGT) with boceprevir in combination with pegylated interferon and ribavirin. Should certain groups of patients receive longer durations of boceprevir plus PR therapy than that evaluated in RGT arms?

a. Treatment-naïve patients with detectable HCV RNA at Week 8 and undetectable at Week 24 (late responders)

b. Patients such as blacks or those with advanced fibrosis or cirrhosis

c. Null responders (if recommended for inclusion in the indication)

d. Other groups, such as patients with poor interferon responsiveness (i.e. < 1 $\log_{10}$ HCV RNA decline after the 4 week lead-in therapy with PR)

5. In addition to pediatric studies, are there any other postmarketing studies you would recommend to further define risks or optimal use of boceprevir in clinical practice?

10. Pediatrics

No systematic surveillance of chronic HCV infection among pediatric patients is available making an accurate assessment of prevalence and severity in this age group difficult. The primary mode of HCV transmission to children is via vertical transmission. The rate of vertical transmission is estimated to be about 5% but may be increased in the presence of HIV infection. Among vertically infected patients, an estimated 20-30% will have spontaneous clearance of HCV and clearance is more likely in the first 2-3 years of life. Severe manifestations or complications of infection are unusual in infants and young children and pediatric hepatologists acknowledge a lack of consensus regarding when to begin treatment in pediatric patients. Although most pediatric patients with chronic HCV infection will remain asymptomatic for many years, up to 30% will have chronic active infection during pediatric period and an unknown proportion will go on to develop serious complications of chronic HCV including cirrhosis, hepatocellular carcinoma, or need for transplantation. The goals of treatment are to clear virus and prevent these complications.

Pediatric studies have not been initiated at this time. The Applicant submitted a Proposed Pediatric Study Request to IND 69,027. The PPSR is currently under discussion regarding the types of pediatric PK and antiviral activity studies which should be performed; (b) (4) The Applicant submitted a request for a deferral of pediatric studies in patients 3 to 18 years old; and a waiver for pediatric studies in patients < 3 years old. DAVP agrees that the deferral in patients ages 3 to 18 years old should be granted because the adult studies have been completed and approval of boceprevir in adults is recommended at this time. DAVP also agrees that a waiver should be granted in pediatric patients < 3 years old because studies in this age group would not be feasible, given that the number of pediatric patients < 3 years old with chronic hepatitis C is small and geographically dispersed; and because the rate of spontaneous clearance of HCV in this age group is variable and cannot be predicted for individual patients. These requests were brought to the Pediatric Review Committee (PeRC), who agreed with the Applicant's deferral and waiver requests. There was some discussion with PeRC regarding the Applicant's pediatric investigation plan, particularly regarding whether a single arm safety and antiviral activity study in pediatric patients would be sufficient, or whether an active comparator arm (pegylated interferon/ribavirin) is necessary. No consensus was reached on the appropriate trial design in this population at this time.

11. Other Relevant Regulatory Issues

The protocol and informed consent documents were reviewed and approved by the Institutional Review Boards and Independent Ethics Committees for each of the investigational sites 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.

Financial disclosures for clinical trial investigators were reviewed, and no significant conflicts of interest were identified.

Four clinical investigator sites, two domestic and two foreign sites were inspected by the Division of Scientific Investigation (DSI) in support of this application. The inspections of Drs. Gordon, Bourliere, McCone, and Savino revealed no significant problems that would adversely impact data acceptability. Overall, the data collected in support of this application are considered reliable and acceptable.

12. Labeling

The trade name for boceprevir, Victrelis™, was found to be acceptable upon review by Division of Medication Error Prevention and Analysis (DMEPA). Consults regarding Victrelis™ labeling from the Division of Drug Marketing, Advertising and Communications (DDMAC) and the Office of Surveillance and Epidemiology (OSE) are pending at this time.

The major labeling issues include the indication for Victrelis™, the duration of dosing in treatment naïve late responders and in certain subpopulations, as well as inclusion of contraindications to the use of CYP3A4/5 sensitive substrates and potent CYP3A4/5 inducers, and the inclusion of neutropenia and thrombocytopenia in the Warnings and Precautions section (5). In addition, DAVP plans to remove (b) (4) except for those related to ribavirin use in pregnancy. Because ribavirin is a pregnancy category X drug, this information will be included in Contraindications (4), Warnings and Precautions (5), Use in Specific Populations (8), and Nonclinical Toxicology (13). References to pegylated interferon and ribavirin Package Inserts and Medication Guides will be included in several sections of the Victrelis™ Package Insert and Medication Guide.

Because of the drug interaction of boceprevir with the oral contraceptive, Yaz® (ethinyl estradiol/drosperinone) which resulted in significantly increased drosperinone concentrations and decreased ethyinyl estradiol concentrations, DAVP, in consultation with the Division of Reproductive and Urology Products (DRUP), was concerned that systemic hormonal contraceptives may not be as effective in women taking Victrelis, and because Victrelis must be taken in combination with pegylated interferon and ribavirin, DAVP has proposed including this information in the Warnings and Precaution section (5.1) in conjunction with the warning regarding use of ribavirin in pregnancy until further DDI studies with other oral contraceptives have been completed by the Applicant, as follows:

5 WARNINGS AND PRECAUTIONS

5.1 Use with Ribavirin and Peginterferon alpha:
Pregnancy

Ribavirin may cause birth defects and/or death of the exposed fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin therapy should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Women of childbearing potential and men must use at least two forms of effective contraception during treatment and for at least 6 months after treatment has concluded. Routine monthly pregnancy tests must be performed during this time. Systemic hormonal contraceptives may not be as effective in women while taking VICTRELIS. Two alternative effective methods of contraception, including intrauterine devices and barrier methods, should be used in women during treatment with VICTRELIS and concomitant ribavirin.

In addition, extensive changes have been proposed by the Clinical Pharmacology and Virology review teams to Warning and Precautions/ Drug Interactions (5.7), Clinical Pharmacology/Pharmacokinetics (12.3), Clinical Pharmacology/Pharmacogenomics (12.5), and Microbiology sections (12.4).

The Applicant has proposed the following in the Indications and Usage section (1):

Indications and Usage

(b) (4)

Whether Victrelis™ should be indicated all patients who have failed previous therapy, including prior null responders or should be limited to partial responders and relapsers in addition to treatment-naïve patients, as studied, will be discussed with the Advisory Committee. In the Dosage and Administration section (2), the Applicant has proposed the following guidelines for response-guided therapy in previously untreated subjects:

Dosage and Administration

(b) (4)

Whether treatment-naïve late responders should receive a longer course of triple therapy (b) (4) as proposed, will be discussed with the Advisory committee. Additionally, whether treatment futility should be assessed at (b) (4) in treatment naïve patients, as proposed, or should be assessed earlier (b) (4)) is currently under discussion within DAVP and with the Applicant.

In general, DAVP agrees with the proposed guidelines for response guided therapy in treatment experienced patients. However, whether certain subgroups within both treatment naïve and treatment-experienced populations (e.g. black patients or those with advanced fibrosis or cirrhosis) should receive longer duration of triple therapy will be discussed with the Advisory Committee.

In the Nonclinical Toxicology section (13), DAVP has proposed extensive changes to include information regarding genotoxicity of ribavirin, and impairment of fertility in animal studies with ribavirin (reversible testicular toxicity in male animals), pegylated interferon (impairment of fertility and early embryonic development in female rats) and boceprevir (testicular toxicity in male animals).

In the Clinical Studies section (14), DAVP has proposed extensive changes to the description of the efficacy results from the Phase 3 clinical trials. These changes are currently under discussion with the Applicant.

(b) (4)

Drs. Andrew Dmytrijuk and Kathy Robie-Suh, in the Division of Hematology Products, in their consultation regarding the anemia associated with boceprevir, stated that:

> *"While some mention of epoetin alfa use in the clinical trials should be included in the clinical studies section, the studies were not designed to provide information for the dosing and safety of EPO in these patients. The use and safety of EPO in this clinical setting would need to be studied in an appropriately designed trial to support labeling which is more than descriptive in the Clinical Studies Section of the proposed B label and Medguide."*

(b) (4)
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With regard to the proposed Medication Guide, DAVP has proposed changes to the

What is the most important information I should know about TRADENAME?
section (b) (4) as well as extensive changes to the
What should I tell my healthcare provider before taking TRADENAME? Medicines you should not use when prescribed TRADENAME sections. The proposed Medication Guide is currently under review by DRISK.

The container and carton labels were reviewed by DMEPA, who have recommended a number of labeling changes to the Applicant. The DMEPA reviewers voiced concern regarding potential medication errors and/or overdosage because the current packaging consists of a single bottle containing the total daily dose of Victrelis (12 capsules), and have recommended labeling on each bottle with instructions for use. DAVP agreed that although this packaging may be convenient for patients, and these patients generally receive extensive counseling on how take these medications, there is some concern for medication errors; and has proposed including language in the Patient Counseling Information of the Package Insert as well as in the Medication Guide in the interim, until the Applicant can further address this packaging issue.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action: Approval of boceprevir for treatment of adults with chronic hepatitis C and compensated liver disease.

Risk Benefit Assessment:

Based on the review of data presented in the application, the benefits 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. Overall, boceprevir in combination with pegylated interferon and ribavirin was superior in efficacy to the standard of care (pegylated interferon and ribavirin alone) in both previously untreated (treatment-naïve) and previous treatment failure (partial responders and relapsers) subjects. The higher sustained virologic response was mainly driven by higher end-of-treatment response; but relapse rates were also substantially lower in boceprevir-treated subjects The incremental benefit (as measured by SVR) of adding boceprevir to the current standard of care was 25-28 % in treatment naïve subjects and 38-45% in treatment-experienced subjects overall. The benefit afforded by boceprevir in improving SVR over the standard of care in the treatment-experienced population should answer, at least in part, a significant unmet medical need in this population.

Achievement of SVR is generally considered a cure of HCV infection, and has been associated with decreased progression of liver fibrosis and cirrhosis, as well as decreased incidence of hepatocellular carcinoma, liver-related complications and death. Liver disease due to hepatitis C is one of the major reasons for liver transplantation in this country, and addition of boceprevir to the current standard of care would, in the long term, be expected to result in decreased requirement for liver transplants for chronic hepatitis C, decreased incidence of hepatocellular carcinoma, and decreased liver-related mortality.

The use of boceprevir in the clinical trials was associated with an incremental decrease in hemoglobin above and beyond that observed with standard of care therapy (pegylated interferon and ribavirin) alone. In the clinical trials, anemia appeared to be managed effectively with ribavirin dose reduction or discontinuation and/or use or erythropoietin and/or blood transfusion. None of the deaths reported in the clinical trials was related either directly

or indirectly to anemia. The potential risks 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. Although erythropoietin is not FDA-approved for use in this population, it is frequently used off-label for anemia related to pegylated interferon and ribavirin use in clinical practice. ESA use, itself, is associated with additional potential safety risks, including thrombotic events, stroke, and pure red cell aplasia, and others. Although some of these adverse events were reported in boceprevir clinical trials, most of them were confounded by underlying diseases and by the concurrent use of pegylated interferons. The Applicant is currently evaluating use of erythropoietin vs. ribavirin dose reduction or discontinuation for anemia management in a randomized controlled trial in chronic hepatitis C subjects receiving boceprevir plus pegylated interferon and ribavirin, and thus additional safety information regarding use of ESAs in this population will be available in the future.

The anemia observed with boceprevir appears to be part of an overall bone marrow suppressive effect of the drug as evidenced also by the increased frequency of neutropenia and thrombocytopenia in boceprevir-treated subjects compared to PR-treated controls. These cytopenias are also associated with pegylated interferons alone. In these clinical trials there were several cases of serious and life-threatening infections in association with neutropenia among subjects treated with boceprevir. Anemia, neutropenia and thrombocytopenia will be included in the Warnings and Precautions section of the Package Insert, and frequent (at least monthly) monitoring of CBC will be recommended, particularly during the first 12 weeks of treatment. Anemia, (b) (4) will also be prominently presented in the Medication Guide.

Recommendation for Post-marketing Risk Evaluation and Management Strategies

A number of boceprevir clinical trials are ongoing, including long-term follow-up of subjects who achieved SVR, evaluation of boceprevir/PR in subjects with HIV/HCV coinfection, evaluation of anemia management strategies (ribavirin dose-reduction vs. erythropoietin use) and effect on SVR, evaluation of pegylated interferon alfa-2a/ribavirin in combination with boceprevir (recently completed), and evaluation of boceprevir/PR in subjects who previously failed PR treatment in another boceprevir clinical trial. Pediatric studies will be required to assess safety and activity of boceprevir under PREA regulations.

The following post-marketing commitments and requirement have been proposed and are currently under discussion with the Applicant. Final decisions regarding post-marketing commitments (PMCs) or post-marketing requirements (PMRs) will be made after discussion with the Advisory Committee and with the Applicant.

Clinical Review Team (proposed PMCs):

- A trial of boceprevir in combination with PR in previous null responders to PR (null responders defined as < 2 $\log_{10}$ decline in HCV RNA at Week 12)
- A trial evaluating different durations of triple therapy for late responders

The rationale for these studies is to confirm efficacy of boceprevir in null responders and to determine optimal duration of triple therapy in patients who are late responders.

Virology Review Team

Proposed PMCs and PMRs:

- PMR: Conduct a study to assess the impact of boceprevir treatment-emergent NS3 amino acid substitutions (those that have been observed but not characterized phenotypically) on the anti-HCV activity of boceprevir in the HCV replicon system. Potentially novel resistance-associated substitutions should also be evaluated. The HCV replicon genotype/subtype background used should be consistent with the background in which the specific substitutions have been observed in treated patients. Evaluations should include HCV replicons with previously characterized resistance-associated substitutions spanning the range of susceptibilities as reference standards. Specific examples of substitutions to be assessed include the following:
  a. D168N, with and without linked R155T, genotype 1a replicon
  b. V107I, with and without linked V36M+R155K, genotype 1a replicon
  c. P146S, with and without linked V36M+R155K, genotype 1a replicon
  d. I170V, genotype 1a replicon
  e. V36M, R155K and V36M+R155K, genotype 1a replicon

This study will provide more complete information regarding the effect of specific boceprevir treatment-emergent amino acid substitutions on boceprevir anti-HCV activity.

- PMC: Conduct a study to assess phenotypic susceptibility of baseline and treatment-failure isolates from boceprevir-treated subjects using the HCV replicon system. These analyses could focus on a subset of subjects whose virologic responses and genotypic resistance patterns are representative of the subject populations studied in the Phase 3 boceprevir trials. Baseline isolates from a few boceprevir-treated subjects who achieved SVR should be included in these assessments for comparison. Entire NS3 protease or NS3/4A cassettes should be amplified from patient isolates and cloned into an appropriate HCV replicon.

This trial will provide information regarding the variability of boceprevir phenotypic susceptibility of clinical isolate-derived HCV variants, and how phenotypic susceptibility is associated with treatment outcome.

- PMR: Report results from P05063 regarding the long term persistence (≥2 years following end of treatment) of amino acid substitutions that emerged in boceprevir-treated subjects in Phase 2 and Phase 3 trials conducted to date. For analyses going forward, ideally the same assay/vendor used initially to identify the treatment-emergent substitutions will continue to be used to monitor the persistence of the substitutions in the follow-up period. A subset of subjects whose virologic responses and genotypic resistance patterns are representative of the subject populations studied in the Phase 3 boceprevir trials should have long term follow-up samples characterized genotypically using a sensitive and quantitative nucleotide sequencing assay to characterize the dynamics of the complex viral populations

over time. The possibility of compensatory substitutions associated with persistence of resistance-associated substitutions should also be explored.

This study will provide insight into the long term persistence of HCV viral populations harboring resistance-associated substitutions that may impact virologic responses to future treatment with boceprevir or other NS3/4A protease inhibitors.

- PMR: Conduct a pooled analysis of completed and currently ongoing clinical trials to characterize the impact of detectable baseline boceprevir resistance-associated polymorphisms on the efficacy of boceprevir + Peg-IFNα/RBV treatment regimens among subjects who (1) respond relatively poorly to the Peg-IFNα/RBV 4-week lead-in (e.g., <1 $\log_{10}$ IU/mL decline, ≥1 $\log_{10}$ IU/mL to <2 $\log_{10}$ IU/mL decline, etc.), or (2) have an unfavorable IL28B genotype.

This study will enhance our understanding of the impact, on boceprevir-based treatment efficacy, of having detectable, pre-treatment, boceprevir resistance-associated substitutions.

- PMR: Conduct a study to analyze NS3/4A protease cleavage sites for the presence of boceprevir treatment-emergent substitutions for a selected subset of samples representative of the virologic failure responses and NS3 protease resistance patterns observed in Phase 3 trials. A representative subset of samples from subjects who experienced virologic failure, but for whom no clear resistance-associated substitutions in NS3/4A were detected, should also be analyzed for the presence of substitutions in NS3/4A protease cleavage sites.

This study will be an initial investigation to determine whether boceprevir treatment-emergent substitutions are detected in NS3/4A protease cleavage sites, which are domains of the HCV polyprotein that interact with the NS3/4A protease drug target.

Clinical Pharmacology Review Team:

Proposed PMRs:

- Conduct an *in vivo* drug-drug interaction trial between boceprevir and an oral contraceptive containing a progesterone component other than drospirenone.
- Conduct an *in vivo* drug-drug interaction trial between boceprevir and methadone.
- Conduct an *in vivo* drug-drug interaction trial between boceprevir and a sensitive substrate of p-glycoprotein (e.g. digoxin).
- Conduct an *in vivo* drug-drug interaction trial between boceprevir and a commonly used selective serotonin reuptake inhibitor (SSRI) (e.g. escitalopram).

These studies should be conducted because insufficient information was included in the NDA to fully evaluate potentially important drug interactions with boceprevir.

Proposed PMCs:

- Conduct a trial evaluating shorter treatment durations of pegylated interferon and ribavirin with and without boceprevir in patients with the IL28B rs12979860 C/C genotype.

This trial may elucidate whether patients with the IL28B C/C genotype, in whom no incremental benefit of boceprevir was noted over pegylated interferon in the retrospective analysis performed with this NDA, could benefit from shorter courses of triple therapy; or whether shorter courses of boceprevir/PR therapy are superior to shorter courses of PR alone in this population.

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/s/

MARY E SINGER
04/21/2011