

Background Material for Boceprevir Advisory Committee
Division of Antiviral Products (DAVP)
April 27, 2011

I. Introduction

Boceprevir is a direct-acting antiviral agent active against hepatitis C virus (HCV) genotype 1. Boceprevir is an NS3/4a serine protease inhibitor in the ketoamide class, studied in combination with pegylated interferon and ribavirin for treatment of chronic hepatitis C. The primary endpoint for the key clinical trials was sustained virologic response (SVR), measured 24 weeks after the end of therapy. This background document focuses on key clinical pharmacology, efficacy and safety findings for boceprevir, with emphasis on the issues for discussion with the Advisory Committee. Please note that analyses presented herein by DAVP may differ somewhat from those presented by the Applicant.

II. Summary of Efficacy

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. Details regarding study designs were provided by the Applicant. 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. Note that DAVP asked the Applicant to use an HCV RNA cutoff of < 25 IU/mL (lower limit of assay quantification, LLOQ) for defining SVR. 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. DAVP believes that using the 25 IU/mL cut-off will offer a more efficient review process going forward; while still providing an accurate representation of efficacy. Both Phase 3 trials for boceprevir included a 4-week lead-in treatment period with pegylated interferon alfa-2b and ribavirin prior to addition of boceprevir in each of the treatment arms.

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[®] 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; while for those with detectable HCV RNA at Week 8 but undetectable at Week 24, 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.

Please see the Applicant’s background document for further details on study design, inclusion and exclusion criteria, demographics, and subject disposition.

We 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 1. 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.

Please see discussion regarding response-guided therapy in section 4d below.

Subset Analysis in Treatment-Naïve Subjects (P05216)

As shown in the following table, SVR rates were lower 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 2. 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= HCV RNA at end-of-treatment < 10 IU/mL and at end of follow-up > 25 IU/mL

^Virologic relapse= HCV RNA undetectable (< 10 IU/mL) at end of treatment and > 25 IU/mL at end of followup.

In Cohort 2 (blacks) the 11% numerical difference in SVR between the RGT boceprevir arm and the 48 week boceprevir arm is of some concern and will be an issue for discussion.

In the Division’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, and 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).

b. Efficacy in Previous Treatment-Failure Subjects (P05101)

In P5101, chronic hepatitis C subjects (HCV genotype 1) who had previously failed treatment with pegylated interferon and ribavirin were enrolled. This study enrolled subjects who would generally be classified as previous partial responders (≥ 2 log₁₀ 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 log₁₀ decline in HCV RNA at Week 12 of prior therapy) were excluded from the trial. The Applicant’s term, “non-responders” will be referred to as previous partial responders in this document. Relapsers were defined as subjects with HCV RNA undetectable at the end of treatment, with a subsequent detectable HCV RNA during follow-up.

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; while those with detectable HCV RNA at Week 8, but undetectable HCV RNA at Week 12 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 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.

Please see the Applicant's background document for further details on study design, inclusion and exclusion criteria, demographics, and subject disposition.

In general, we 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 DAVP's 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 3. 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.

For additional discussion of response-guided therapy in this population please see section 4d 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 4. 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 DAVP’s subset analyses, within the boceprevir treatment arms subjects who were previous relapsers, those with lower baseline HCV RNA ($\leq 800,000$ IU/mL), lower baseline Metavir fibrosis scores (F0, F1, and F2 combined), 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), and HCV subtype 1a; while no significant difference in SVR was observed with gender and age.

c. Null Responders and Interferon Responsiveness

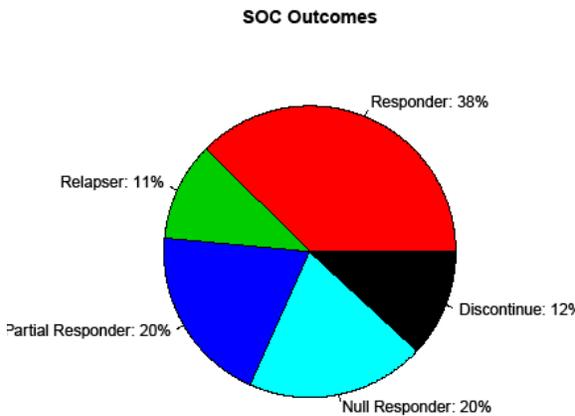
The Applicant has proposed that prior null responders not be excluded from the indication even though they were not eligible for enrollment in the phase 3 treatment-failure trial, P5101. Enrolled subjects in this trial were referred to as “non-responders” and were either partial responders ($\geq 2 \log_{10}$ 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 P5101.

Null responders were not included in P5101 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 FDA 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 (Fig. 1) 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 1. 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-naïve subjects with genotype 1. Subjects were randomized 1:1:1 to either: peginterferon alfa-2b 1.5 µg/kg/wk or peginterferon alfa-2b 1.0 µg/kg/wk, both with weight-based dosing of ribavirin (800-1400 mg/day), or to peginterferon alfa-2a 180 µg/kg/wk plus ribavirin 1000-1200 mg/day. Subjects with a $< 2.0 \log_{10}$ decline in HCV RNA at treatment Week 12 discontinued due to futility.

In IDEAL, 679 subjects had a $< 2 \log_{10}$ decline at treatment Week 12. Subjects with a $< 1.0 \log_{10}$ decline in HCV RNA at treatment Week 4 had 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 $\geq 1.0 \log_{10}$ 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 5. 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 $\geq 1.0 \log_{10}$ 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 (21.5%) of these subjects had a $\geq 1 \log_{10}$ decline in HCV RNA at Week 4. Similarly, 705 subjects had a $< 1 \log_{10}$ decline in HCV RNA at treatment Week 4, but 172 (24.4%) of these subjects had a $\geq 2 \log_{10}$ decline at treatment Week 12.

Analysis of PR lead-in responses in the Phase 3 trial (P05101) in treatment-experienced subjects also raises questions about using PR lead-in responsiveness as a surrogate for

prior treatment history. Although this trial specifically excluded prior PR null responders (based on the $< 2 \log_{10}$ at Week 12 definition), 25% (102/403) of all subjects enrolled achieved a $< 1 \log_{10}$ HCV RNA decline at treatment Week 4 (end of PR lead-in). Of the 102 subjects who achieved a $< 1 \log_{10}$ HCV RNA decline at treatment Week 4, 46 (45%) were prior relapsers. In other words, the Applicant’s proposed surrogate indicator of PR “null responder” does not adequately differentiate prior partial responders and relapsers from prior null responders.

d. Response-Guided Therapy

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

Table 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 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.

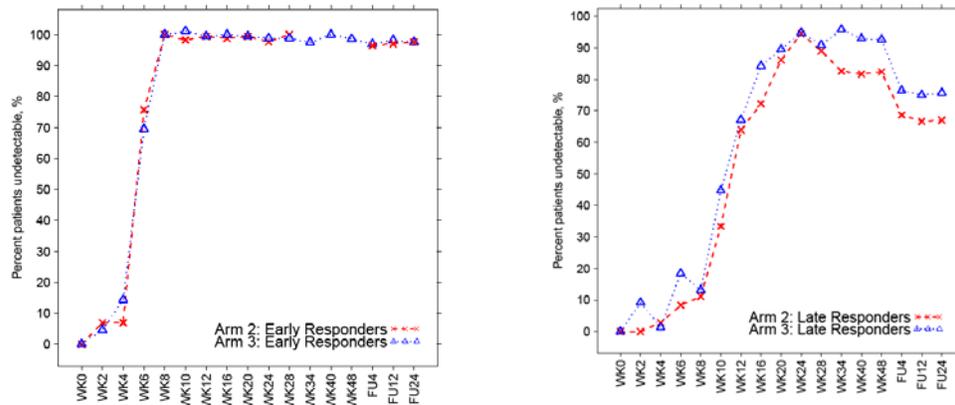
Subjects were discontinued for futility at Week 24 in all treatment arms if HCV RNA was detectable.

This 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.

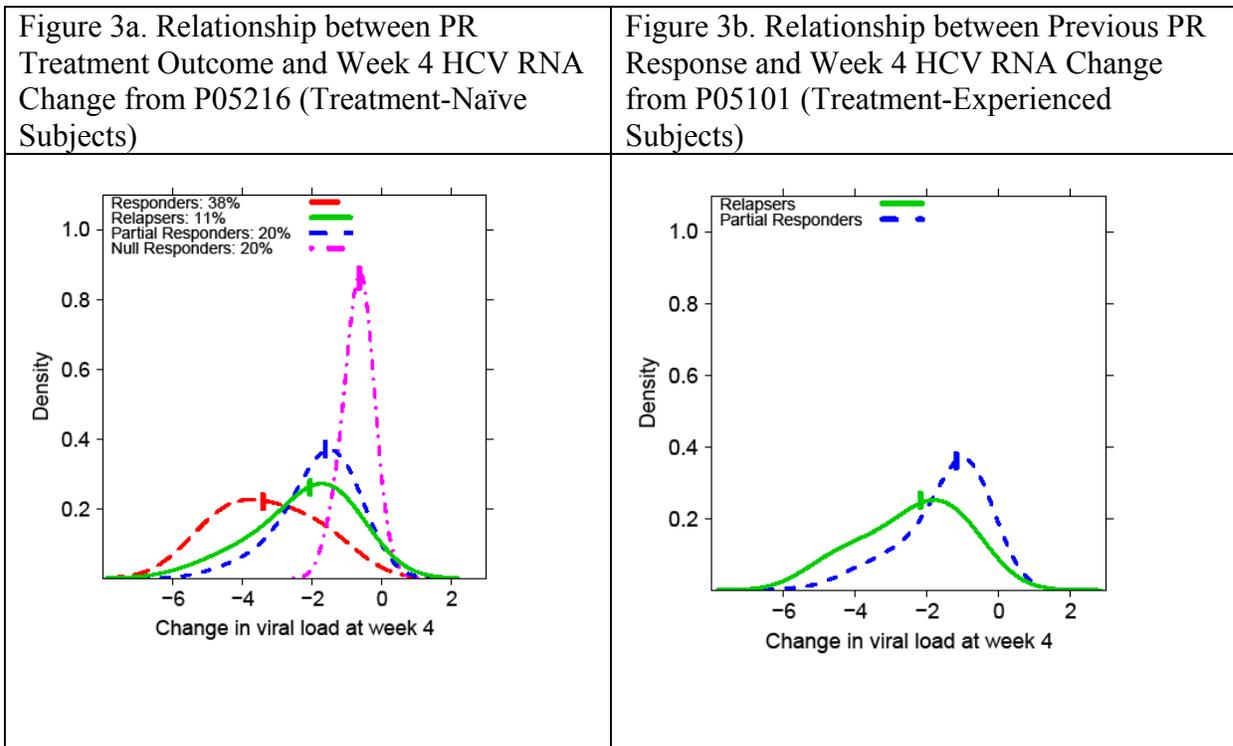


FDA analyses suggest that treatment-naïve subjects with detectable HCV RNA at Treatment Week 8 but undetectable at Week 24 (i.e., late responders not meeting futility rule) may benefit from receiving a longer duration (for example, 32 or 44 weeks of boceprevir plus PR), rather than boceprevir plus PR 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 may come at the cost of prolonged anemia. Another option could be giving treatment-naïve late responders a total of 32 weeks of boceprevir followed by PR alone for 12 weeks, as was studied in the treatment-experienced trial (P05101). This approach may allow for improved SVR while limiting the duration of anemia compared to a full 48 weeks of triple therapy.

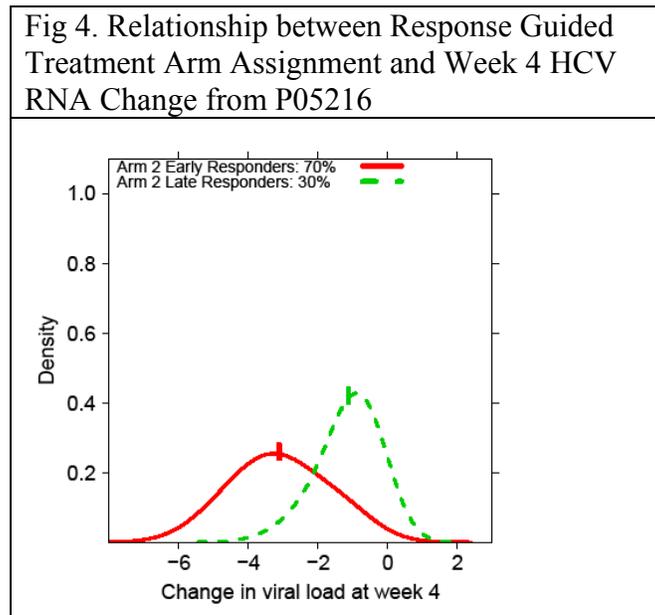
To support a 32 week duration of boceprevir treatment (i.e. through Week 36) followed by PR alone, data from studies P05216 and P05101 were bridged. This “bridging” analysis demonstrates that late responders among the treatment-naïve population are fairly similar in characteristics to that of previously-treated 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 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 log₁₀ decrease) at Week 4 are more likely to be SVR responders and those with smaller Week 4 viral load changes (median=0.7 log₁₀ decrease) are more likely to be null responders to PR (<2 log₁₀ decline at Week 12) (Figure 3a). The relapser (median=2.1 or 2.2 log₁₀ decreases) and partial responder (median=1.6 or 1.2 log₁₀ decreases) populations also demonstrate similar viral load decreases as expected, for both treatment-naïve (Fig. 3a) and treatment-experienced (Fig. 3b) populations, respectively. Hence, the Week 4 response is a good predictor of PR treatment outcome in treatment-naïve subjects and a similar PR Week 4 response is maintained if subjects classified as relapsers or partial responders are retreated with PR.



An additional analysis of the boceprevir RGT arm in P05216 based on Week 4 response identified those subjects with >2.0 log₁₀ 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 (Fig. 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.



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 a 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 (PR4/BOC-PR32/PR12)	BOC44 (PR4/BOC-PR44)
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 SOC 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.

Response Guided Therapy: SVR by Race in P05216

As discussed in section II 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]
Overall			
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.

Response Guided Therapy: SVR in Subjects with Advanced Fibrosis Stage or Cirrhosis (Metavir Scores F3 or F4) in P05216

In the treatment-naïve 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)

Response-Guided Therapy: 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).

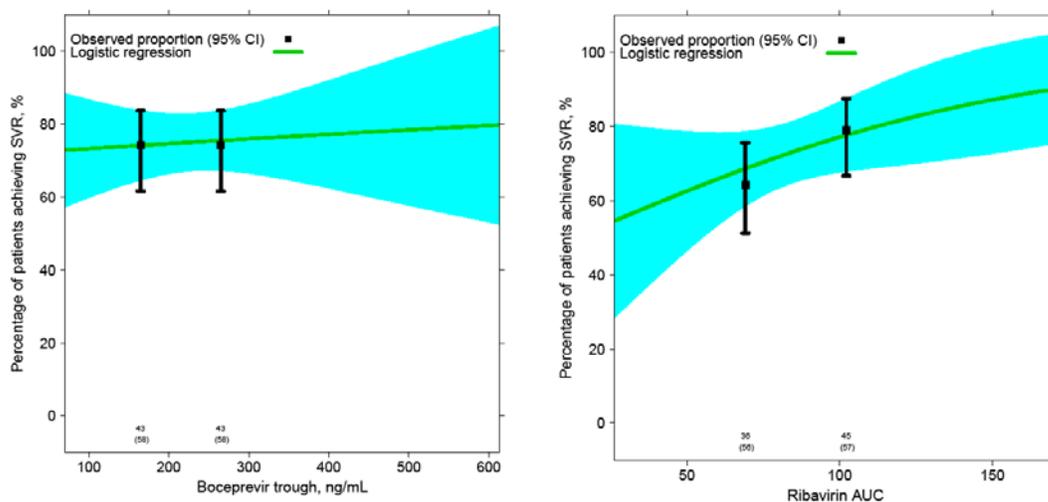
In the Boc/PR48 arm, all subjects, both early and late responders received 44 weeks Boc/PR after 4 week lead-in treatment with PR.

e. Exposure-Response Relationships for Efficacy

The Applicant's proposed boceprevir dose is based on Phase 2 trials in which doses lower than 800 mg three times daily were associated with lower efficacy rates. In the two pivotal Phase 3 trials, pharmacokinetic (PK) data were available for 67 of 734 treatment-naïve subjects (P05216) and 49 of 323 treatment-experienced subjects (P05101). C_{trough} and AUC were estimated using sparse PK samples. At the 800 mg three times daily dose of boceprevir evaluated in these trials, a shallow and non-significant relationship was identified between boceprevir exposure and SVR (Fig. 5, left). These results indicate that higher exposures to boceprevir are not expected to result in greater efficacy.

A non-significant but upward trending relationship between ribavirin steady-state AUC (AUC_{τ}) and SVR was observed in the same Phase 3 PK population (Figure 5, right). These results indicate that ribavirin exposure may be an important factor in achieving SVR in the setting of boceprevir treatment, despite dosing ribavirin based on weight.

Figure 5: Percentage of Subjects Achieving SVR from P05101 and P05216 Versus Boceprevir Trough Concentration (left) or Ribavirin Steady-State AUC (right).*



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

III. Virology Summary (P05216 and P05101)

a. 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.

b. Treatment-emergent Resistance

In our analysis of genotypic resistance data for this application, DAVP 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 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.

IV. Summary of Safety

The Division's primary safety analysis evaluated adverse events (AEs), serious adverse events (SAEs), severe and life-threatening adverse events, deaths, and laboratory abnormalities in the key Phase 2 and Phase 3 clinical trials of boceprevir in treatment-naïve (P03523 and P05216) and treatment-failure (P05101) trials. In general, the Division agrees with the Applicant's assessment of safety in these trials; but several important differences will be pointed out in this summary. Please see the Applicant's background document for description of boceprevir exposure, AEs, SAEs, deaths, severe and life-threatening adverse events, and discontinuations or dose-modifications due to adverse events.

Overall, most of the adverse events reported in these trials have been well-described for pegylated interferon and ribavirin therapy. The most important safety concern during the clinical development of boceprevir has been the decrease in hemoglobin above and beyond that observed with pegylated interferon and ribavirin alone. The anemia appears to be part of an overall bone marrow suppressive effect of boceprevir as evidenced by the increased frequency of neutropenia and thrombocytopenia in boceprevir-treated subjects compared to PR-treated controls. Further details regarding anemia observed in this development program are described detail below.

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

Dysgeusia (alteration of taste) was a common adverse event reported at an increased frequency in boceprevir-treated subjects as compared to control (37% in boceprevir-containing arms versus 16% in control arm); however, the majority of dysgeusia events were mild-moderate in intensity and were not treatment-limiting.

a. Anemia

As reported by the Applicant, no significant declines in hemoglobin or significant adverse events of anemia were reported in healthy volunteers. A study conducted in healthy men with boceprevir alone (P05351), determined that the mechanism of anemia was not due to RBC hemolysis, as observed with ribavirin. Instead, anemia was thought to be the result of a bone-marrow suppressive effect associated with boceprevir. In the key 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, as shown in the Applicant's background document. 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.

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

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

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

1. Subjects with hemoglobin ≤ 10 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 ≤ 10 g/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

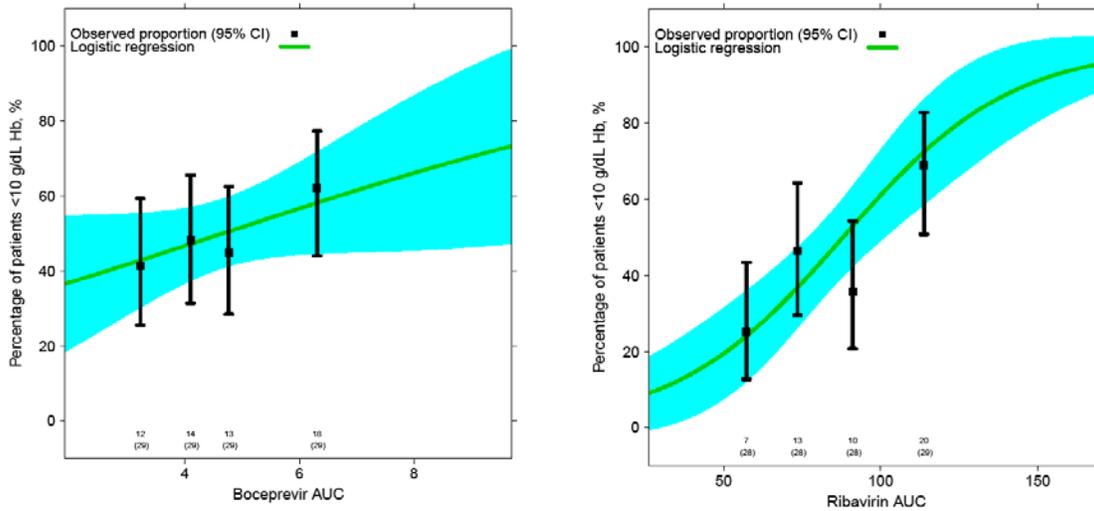
A non-significant upward trend of increasing incidence of anemia (Hgb < 10 g/dL) was observed with increasing boceprevir AUC_{τ} in the Phase 3 PK population (Figure 6, left). Boceprevir AUC_{τ} was used as the PK parameter for the exposure-response safety analysis; however, similar relationships were 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 $\mu\text{g}\cdot\text{hr}/\text{mL}$) was 48%. Similarly, the predicted incidence of anemia at the lowest and highest exposure quartiles (3.2 and 6.3 $\mu\text{g}\cdot\text{hr}/\text{mL}$) 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; $p<0.0001$) (Figure 6, right).

This finding is not unexpected, given ribavirin’s known hematological effects, with an observed incidence rate of ~30% in the standard of care (SOC) population. Indeed, a similar exposure-response relationship is observed if the analysis is performed for subjects randomized to SOC (n=51; $p = 0.001$). The relationships between ribavirin exposure and efficacy and ribavirin exposure and safety may explain why higher SVR rates were observed in subjects who develop anemia.

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

Figure 6: Percentage of Subjects with Anemia from P05101 and P05216 Versus Boceprevir (left) or Ribavirin Steady-State AUC (right).*



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

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

Anemia reported as an Adverse Event

The following table shows the DAVP 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 (of ribavirin, boceprevir or pegylated interferon) in boceprevir treatment arms than PR control arms across the Phase 3 trials.

Table 11. Adverse Events: Anemia in Phase 3 trials

Anemia* Adverse Events	P5101 Boceprevir arms N=323 (%)	P5101 PR arms N=80 (%)	P5216 Boceprevir arms N=734 (%)	P5216 PR arms N=363 (%)	P5216+P5101 Boceprevir Arms N= 1057 (%)	P5216+P5101 PR arms N=443 (%)
Anemia as AE*	157 (49)	17 (21)	392 (53)	114 (31)	548 (52)	131 (30)
Anemia as serious AE*	5 (2)	0	7 (1)	1 (<1)	12 (1)	0
Anemia as Grade 3 or 4 AE*	21 (7)	0	24 (3)	7 (2)	45 (4)	7 (2)
Anemia resulting in Study Drug discontinuation*	5 (2)	0	14 (2)	4 (1)	19 (2)	4 (1)
Anemia resulting in dose reduction*	69 (21)	7 (9)	195 (27)	51 (14)	264 (25)	58 (13)
Anemia resulting in dose interruption*	9 (3)	0	22 (3)	9 (3)	31 (3)	9 (2)

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

Lowest Hemoglobin Values during Treatment

Please see the Applicant's table showing the distribution of subjects' lowest hemoglobin values during treatment using the WHO grading criteria. Additionally, the following table shows the DAVP analysis of the number and proportion of subjects who reached hemoglobin nadirs of ≤ 10 g/dL and ≤ 8.5 g/dL in the Phase 3 Trials (P05216, and P05101). Hemoglobin values of < 10 and < 8.5 are those recommended in the approved ribavirin package inserts for ribavirin dose-reduction and discontinuation, respectively. A higher proportion of boceprevir/PR recipients than subjects who received PR alone experienced hemoglobin nadirs of ≤ 10 g/dL and ≤ 8.5 g/dL in the Phase 3 trials. As discussed 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 12. Hemoglobin Nadir during Phase 3 Trials (P05216 and P5101)

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

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

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 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 \leq 10 g/dL, ribavirin dose reduction and/or use erythropoietin (or both) recommended;
- Hemoglobin \leq 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 13. Use of Erythropoietin and/or Ribavirin Dose Reduction in Phase 3 Trials (P05216 and P05101)

Treatment Arm (Pooled)	Erythropoietin Use n (%)	Ribavirin Dose Reduction n (%)	Erythropoietin Use or ribavirin dose reduction n (%)	Erythropoietin Use and ribavirin dose reduction n (%)	RBC Transfusion n (%)
All Boceprevir-treated Subjects (N=1057)	458 (43)	327 (31)	543 (51)	242 (23)	39 (4)
All PR-treated subjects (N=443)	104 (24)	81 (18)	135 (31)	50 (11)	2 (<1)

Adverse Events Associated with ESA Use

Erythropoietin use was permitted, at the investigator’s discretion, with or without ribavirin dose reduction in the boceprevir clinical trials as a supportive therapy for the management of anemia. 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.

b. 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.

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

Table 14. 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.

c. Thrombocytopenia

Thrombocytopenia was more common among subjects receiving boceprevir/PR than in those receiving PR alone in the pivotal Phase 3 trials as part of the overall bone marrow suppressive effect. 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, as a severe (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, a higher proportion of subjects in boceprevir-containing arms than the PR arms experienced Grade 3 or 4 thrombocytopenia.

Table 15. Lowest Absolute Platelet Count on Treatment in Phase 3 Trials (P05216 and P05101)

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

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

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 platelet transfusions because of severe thrombocytopenia.

d. Neuropsychiatric Events

In the pooled Phase 2 and Phase 3 boceprevir trials analyzed for safety, an increased number of subjects reported psychiatric symptoms of suicidal and homicidal ideation in boceprevir-containing arms as compared to control. This finding is of concern due to its potential life-threatening implications. Suicidal ideations were reported in 12/1548 (1%) boceprevir-treated subjects compared to 2/547 (<1%) subjects in control arm; homicidal ideations were reported in 4/1548 boceprevir-treated subjects compared to none of the subjects in control arm. Adverse events such as anxiety (19% vs. 15%), depression (29% vs. 26%) and insomnia (48% vs. 41%) were noted in a somewhat higher proportion of boceprevir-treated subjects compared to subjects treated with PR alone, respectively. However, life-threatening or fatal neuropsychiatric events, including suicide, suicidal and homicidal ideation, depression, and relapse of drug addiction/overdose have been reported in patients with and without a previous psychiatric disorder with pegylated interferon therapy. Additionally, these data are confounded to some degree due to the shorter overall PR exposure in the PR control Arm than in the boceprevir treatment arms in P5101, due to more discontinuations at Week 12 due to futility. *Based on the currently available data, it is difficult to make any meaningful clinical conclusions from this observation.*

e. Dysgeusia

In the key trials, dysgeusia was reported in increased frequency in boceprevir-treated subjects as compared to control (37% in boceprevir-containing arms versus 16% in control arm); however, the majority of dysgeusia events were mild-moderate in intensity.

V. Clinical Pharmacology Summary

a. 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. However, insufficient information is available 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 methadone and buprenorphine PK, two important medications for the intended patient population. Although methadone is metabolized partially by CYP3A4, DDI studies with other potent inhibitors of CYP3A4, including ritonavir-boosted HIV protease inhibitors, have demonstrated unanticipated decreases in methadone exposure, possibly due to mixed inhibition and induction effects on CYP450 enzymes or uncharacterized transporter effects. Thus, the effect of boceprevir on methadone exposure cannot be accurately predicted based on *in vitro* experiments. Buprenorphine is less sensitive to interactions via CYP3A4, given its alternative glucuronidation pathway; however, the impact of boceprevir on glucuronidation has not been characterized.
- A DDI study was not performed to characterize the effect of boceprevir on a sensitive P-glycoprotein (P-gp) substrate, such as digoxin. Based on *in vitro* experiments, boceprevir has the potential to inhibit P-gp, particularly in the gut, which may result in clinically significant increases in the exposure of digoxin and other sensitive substrates.
- The safety and efficacy of combined oral contraceptive (COC) use during boceprevir coadministration have not been sufficiently characterized. The completed DDI study conducted with Yaz® (ethinyl estradiol/drospirenone) showed a 24% decrease in ethinyl estradiol (EE) exposure and a 100% increase in drospirenone (DRSP) exposure during boceprevir administration. The magnitude of increase in DRSP exposure may increase the risk of adverse events, including hyperkalemia and thromboembolism. It is unknown if the doubling of exposure would necessarily occur with other progestational components (e.g. norgestimate or norethindrone). The 25% decrease in EE exposure may result in breakthrough bleeding and may theoretically impact COC efficacy, though there is limited information on which to draw a conclusion. Further, because of deficiencies in the design of the completed DDI study, reliability of the PK results and interpretation of the findings are in question. Because it may be challenging for women of child-bearing potential to rely on two barrier methods while on concomitant treatment with ribavirin, the safety and efficacy implications of boceprevir coadministration with COCs should be further characterized. The Applicant has acknowledged these concerns and plans to conduct a clinical DDI study with another progestin-containing COC.

- *In vitro* experiments to evaluate the potential impact of boceprevir on liver and gut transporters OATP1B1, OATP1B3 and BCRP were not performed. The results of such experiments are important for characterizing possible DDIs with potential concomitant medications, including statins, angiotensin II receptor blockers (ARBs) and some antidiabetic agents.
- A DDI study was not conducted to assess the effect of boceprevir on antidepressant exposure. Unanticipated decreases in the exposure of selective serotonin reuptake inhibitors (SSRIs), including paroxetine, sertraline and escitalopram, have been observed in DDI studies conducted with other HCV and HIV protease inhibitors. Because the mechanism of these observed decreases have not been characterized, and given the importance of these agents in HCV patient care, an *in vivo* study is considered important to rule-out a potentially significant interaction.

b. IL28B Pharmacogenetics

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

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

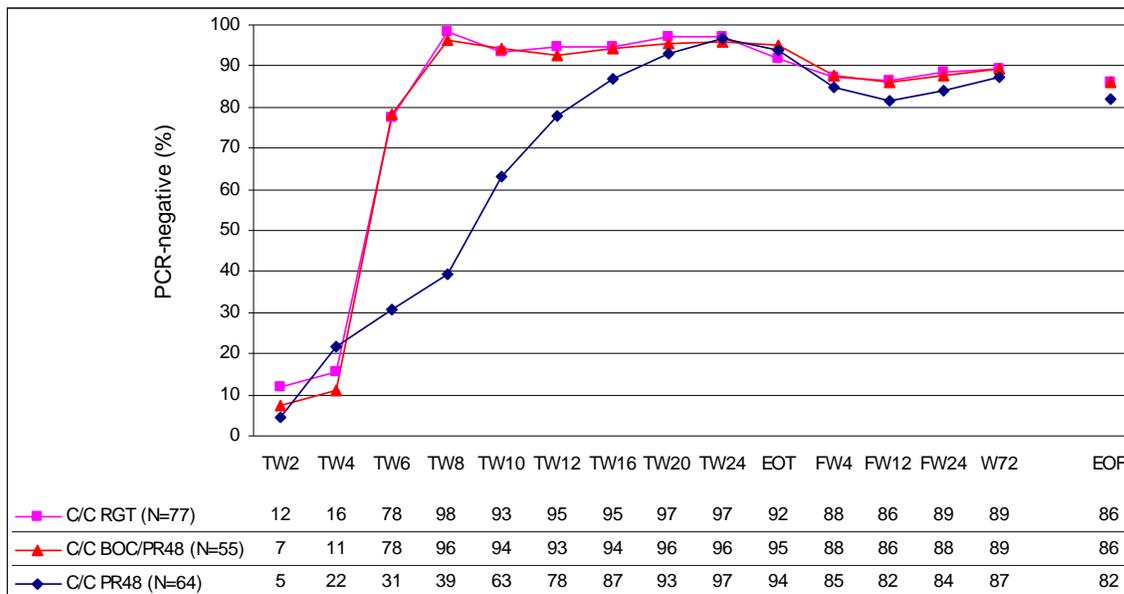
The Applicant’s genetic substudy confirms previous reports of IL28B genotype effects on PR responses (**Table 16**). In treatment-naïve subjects with the C/T and T/T genotypes, boceprevir-containing regimens resulted in significantly higher SVR rates than PR alone, whereas SVR rates did not differ significantly between the boceprevir-containing arms and PR alone in the C/C genotype subgroup (genotype x treatment interaction $P=0.005$). Among C/T and T/T subjects, the number-needed to treat (NNT) with boceprevir to achieve one additional SVR was approximately 3 to 4 depending on the boceprevir regimen; among C/C subjects the NNT was 27 for boceprevir response-guided therapy (RGT) and 53 for boceprevir/PR48. In treatment-failure subjects, IL28B genotype effects were less pronounced and thus treatment effects did not differ significantly based on IL28B genotype (genotype x treatment interaction $P=0.60$). However, the lack of significant genotype effects within the P05101 treatment arms may be related to the smaller sample size and enrichment for prior PR partial responders and relapsers.

Table 16. Treatment Comparisons by IL28B Genotype and Treatment

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

While SVR rates were similar for boceprevir-containing regimens and PR48 in treatment-naïve C/C subjects, responses to boceprevir occurred more rapidly in subjects with the C/C genotype in arms 2 and 3 relative to PR48 (Figure 7). The majority of C/C subjects treated with boceprevir had undetectable HCV-RNA by Treatment Week 8, whereas similar response rates were not achieved until Treatment Week 24 for those treated with PR48. These data suggest that IL28B C/C genotype subjects could potentially benefit from a shorter course of boceprevir/PR therapy and still achieve SVR. This hypothesis has not been tested.

Figure 7. Virologic Response over Time by Genotype and Treatment in Treatment-Naïve Subjects (P05216)



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.

VI. Issues for Discussion

DAVP analyses of efficacy and safety are ongoing; and additional data may be presented at the Advisory Committee if any pertinent results are noted. The following major issues for discussion at the Advisory Committee meeting are presented below. Please note that the final questions for the Committee may change based on additional analyses.

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

Background Information for Consideration (Issue 1): In the Phase 2 and 3 clinical trials, treatment with boceprevir in combination with pegylated interferon/ribavirin was associated with decline in hemoglobin in proportionally more subjects than in subjects treated with pegylated interferon/ribavirin alone. The absolute magnitude of hemoglobin decline with boceprevir is difficult to assess in these clinical trials because of differences in the way individual investigators chose to manage anemia.

In addition, boceprevir in combination with pegylated interferon/ribavirin treatment was associated with higher rates of neutropenia and thrombocytopenia than with pegylated interferon/ribavirin alone. In several cases, neutropenia was associated with severe or life-threatening infections; but no cases of significant bleeding events were reported in association with thrombocytopenia. Please refer to section IV a, b, and c above for a more detailed discussion of anemia, neutropenia, and thrombocytopenia, and associated adverse events.

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

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

Background Information for Consideration (Issue 2): This will be the official yes/no vote for marketing approval for boceprevir for treatment of chronic hepatitis C. As the question states, we are asking the committee to weigh all the risks and benefits in the vote for approval. Please note that a vote for approval, in general terms, doesn't mean that one must agree with all of the proposed dosing recommendations or that one must define all labeling recommendations. The questions that follow the general approval question/vote will give the committee a chance to provide opinions on more granular issues and

labeling recommendations, if there is consensus that the overall risk-benefit is positive and supportive of approval for use in treatment of hepatitis C. If not, please consider what additional studies should be recommended.

Issue 3: Please comment on the strength of the evidence for use of boceprevir in combination with pegylated interferon/ribavirin in prior null responders (patients with $< 2 \log_{10}$ decrease in HCV RNA at 12 weeks), who were not included in the treatment-experienced population in the Phase 3 trial, P5101 .

Background Information for Consideration (Issue 3): To help guide the committee discussion of this question, please refer to the following definitions of treatment response to prior pegylated interferon plus ribavirin therapy. These definitions are included in the September 2010 draft FDA Guidance for Industry entitled “Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Agents for Treatment”:

- **Null Responder:** less than $2 \log_{10}$ reduction in HCV RNA at Week 12 of a pegylated interferon/ribavirin regimen
- **Partial Responder:** greater than or equal to $2 \log_{10}$ reduction in HCV RNA at Week 12, but not achieving HCV RNA undetectable at the end of treatment with a pegylated interferon/ribavirin
- **Responder-Relapser:** HCV RNA undetectable at the end of treatment with a pegylated interferon-based regimen, but HCV RNA detectable within 24 weeks of treatment follow-up.

Please also refer to section IIc of this background document for discussion of null responders and interferon responsiveness.

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

a. Treatment-naïve patients:

i. Should treatment-naïve patients with detectable HCV RNA at Week 8 and undetectable at Week 24 (i.e., late responders not meeting futility rule) receive longer durations of boceprevir plus PR?

ii. Black patients

iii. Patients with more advanced fibrosis stage or cirrhosis (Metavir scores F3 or F4)

b. Patients who have previously failed treatment with pegylated interferon/ribavirin, including relapsers, partial responders, and null responders

Background Information for Consideration (Issue 4): Please refer to section II d of this background document for discussion of response-guided therapy.

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

Background Information for Consideration (Issue 5): A number of boceprevir clinical trials are ongoing, including long-term follow-up study 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 are possible studies for consideration:

- 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 boceprevir/PR vs. PR alone in treatment-naïve subjects with IL28B C/C genotype
- A randomized, controlled trial evaluating different durations of triple therapy for late responders
- Drug-drug interaction studies, as discussed in section Va above