

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202258Orig1s000**

**MICROBIOLOGY REVIEW(S)**

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)**  
**VIROLOGY REVIEW (ADDENDUM)**  
**NDA: 202258 SDN: 003 DATE REVIEWED: 05/11/2011**  
**Virology Reviewer: Patrick R. Harrington, Ph.D.**

**NDA#:** 202285    **SDN:** 003    **eCTD:** 0001  
**Reviewer's Name(s):** Patrick R. Harrington, Ph.D.

**Sponsor's Name and Address:** Schering-Plough Corporation  
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**Initial Submission Dates:**  
**Correspondence Date:** 11/10/2010  
**CDER Receipt Date:** 11/15/2010  
**Assigned Date:** 11/17/2010  
**Review Complete Date:** 04/14/2011 (Addendum 5/12/2011)  
**PDUFA Date:** 5/15/2011

**Amendments:** none

**Related/Supporting Documents:**

- IND 69027
- NDA 202285 SDNs 56, 58, 61, 64, 65 and 67 (eCTDs 54, 56, 59, 62, 63 and 65, respectively)

**Product Name(s)**

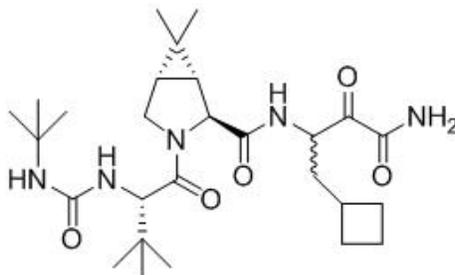
**Proprietary:** Victrelis™  
**Non-Proprietary/USAN:** boceprevir  
**Code Name/Number:** SCH 503034

**Chemical Name:** (1R,5S)-N-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(S)-[[[(1,1-dimethylethyl)amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2(S)-carboxamide

**Molecular Weight:** 519.7

**Molecular Formula:** C<sub>27</sub>H<sub>45</sub>N<sub>5</sub>O<sub>5</sub>

**Structural Formula:**



**SCH 503034 (boceprevir, Victrelis™)**

**Dosage Form/Route of Administration:** 200 mg capsule /Oral

**Dispensed:** Rx  OTC

**Abbreviations:** BLOQ, below limit of quantification; BT, breakthrough; HCV, hepatitis C virus; LLOQ, lower limit of quantification; LOD, limit of detection; Peg-IFN $\alpha$ , pegylated interferon alfa; PMC, post-marketing commitment; PMR, post-marketing requirement; RBV, ribavirin; RGT, response-guided therapy; SOC, standard of care; SVR, sustained virologic response;

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***ADDENDUM***

This review is an addendum to the Clinical Virology review of the Original NDA for boceprevir (Victrelis™). The purpose of this addendum is to document the following information:

- Virology-related post-marketing requirements (PMRs) and post-marketing commitments (PMCs) agreed to by the sponsor.
- Final version of Virology-related sections of the Victrelis™ label.
- Results from additional exploratory analyses to assess the clinical relevance of HCV RNA results that are detectable but below the lower limit of assay quantification.

**VIROLOGY-RELATED PMRs**

1. **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**

**Merck Response (SDN 67/eCTD 65):**

Merck agrees to perform this study. The proposed dates are as follows:

A summary of the study plan will be submitted by the end of June 2011.

Analyses will begin in 2011.

Expected completion time is end of June, 2012.

The final report will be submitted by end of July 2012.

2. **Report results from ongoing clinical trial P05063 regarding the long term persistence of amino acid substitutions that emerged in boceprevir-treated subjects from the following Phase 2 and Phase 3 trials conducted to date: P03523, P03659, P05216 and P05101. For long-term follow-up analyses of subjects from the Phase 3 trials (P05216 and P05101), if available, the same assay/vendor used initially to identify the treatment-emergent substitutions should continue to be used to monitor the persistence of the substitutions in the follow-up period. The persistence of detectable amino acid substitutions should be assessed for a treatment-free follow up period of approximately 2 years.**

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**Merck Response (SDN 67/eCTD 65):**

Merck will continue to report analyses from PN05063 for patients that enrolled in PN03523, PN03659, PN05216, and PN05101 according to the protocol outlined in PN05063. In this study, resistance variants will be followed by population sequencing.

For patients enrolled in the long-term follow-up study (PN05063) from Phase 3 studies, resistance analysis will be performed by the same vendor that initially identified the variants.

A study plan will be submitted by the end of July 2011.

The date of study completion, based on the last patients dosed in PN05126 and PN05101 is estimated to be late December, 2011.

The final report on the 2 year follow-up on resistance data will be submitted by end of July 2012.

- 3. Conduct pooled analyses to characterize the impact of detectable baseline boceprevir resistance-associated polymorphisms on the efficacy of boceprevir + Peg-IFN $\alpha$ /RBV treatment regimens among subjects who (1) respond relatively poorly to the Peg-IFN $\alpha$ /RBV 4-week lead-in (e.g.,  $<1 \log_{10}$  IU/mL decline,  $\geq 1 \log_{10}$  IU/mL to  $<2 \log_{10}$  IU/mL decline, etc.), or (2) have an unfavorable IL28B genotype (if data are available). These pooled analyses should be conducted using data from the following completed and currently ongoing boceprevir clinical trials: P03523, P05216, P05101, P05411, P05685, and P06086. These analyses should be completed, and a study report submitted, within 9 months of collection of SVR outcome data from these clinical trials.**

**Merck Response (SDN 67/eCTD 65):**

Merck agrees to conduct these analyses. The proposed dates are as follows:

A summary of the study plan will be submitted by the end of August 2011.

The analyses will begin in 2011.

The results will be presented within 9 months of collection of SVR outcome data from the last clinical trial, PN05411.

The final report will be issued in April, 2013.

- 4. Conduct a study to analyze NS3/4A protease cleavage sites for the presence of boceprevir treatment-emergent substitutions for a selected subset of subjects (n~10) representative of the virologic failure responses and NS3 protease resistance patterns observed in Phase 3 trials. An additional subset of subjects (n~10) 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 boceprevir treatment emergent substitutions in NS3/4A protease cleavage sites.**

**Merck Response (SDN 67/eCTD 65):**

Merck agrees to conduct this study. The proposed dates are as follows:

A summary of the study plan will be submitted by the end of June 2011.

The studies will begin in 2011.

The expected time of completion of the study will be by end of March, 2012.

The final study report will be submitted by the end of July 2012.

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**VIROLOGY-RELATED PMCs**

- 1. Conduct a study to assess phenotypic susceptibility of baseline and treatment failure isolates from boceprevir-treated subjects (n~10) 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 (n~5) 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 vector for phenotypic characterization related to boceprevir susceptibility.**

**Merck Response (SDN 67/eCTD 65):**

Merck agrees to conduct this study. The proposed dates are as follows:  
A summary of the study plan will be submitted by the end of June 2011.  
The study will begin in 2011.  
The expected time for completion of the study is end of June, 2012.  
The final study report will be submitted by the end of July 2012.

- 2. Conduct analyses to identify potential mechanisms of persistence of viral populations harboring boceprevir treatment-emergent, resistance-associated substitutions, based on observations in clinical trial P05063. The potential role of compensatory amino acid substitutions or virologic failure category (e.g., breakthrough, non-response, relapse) on the long term persistence of boceprevir resistance-associated substitutions should be investigated. Also, a subset of subjects (n~20) 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 1 to 2 years of treatment-free follow-up.**

**Merck Response (SDN 67/eCTD 65):**

Merck agrees to conduct these analyses. The proposed dates are as follows:  
A summary of the study plan will be submitted by the end of June 2011.  
The study will begin in 2011.  
The expected time for completion is end of June, 2012.  
The final report will be submitted by end of September, 2012.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

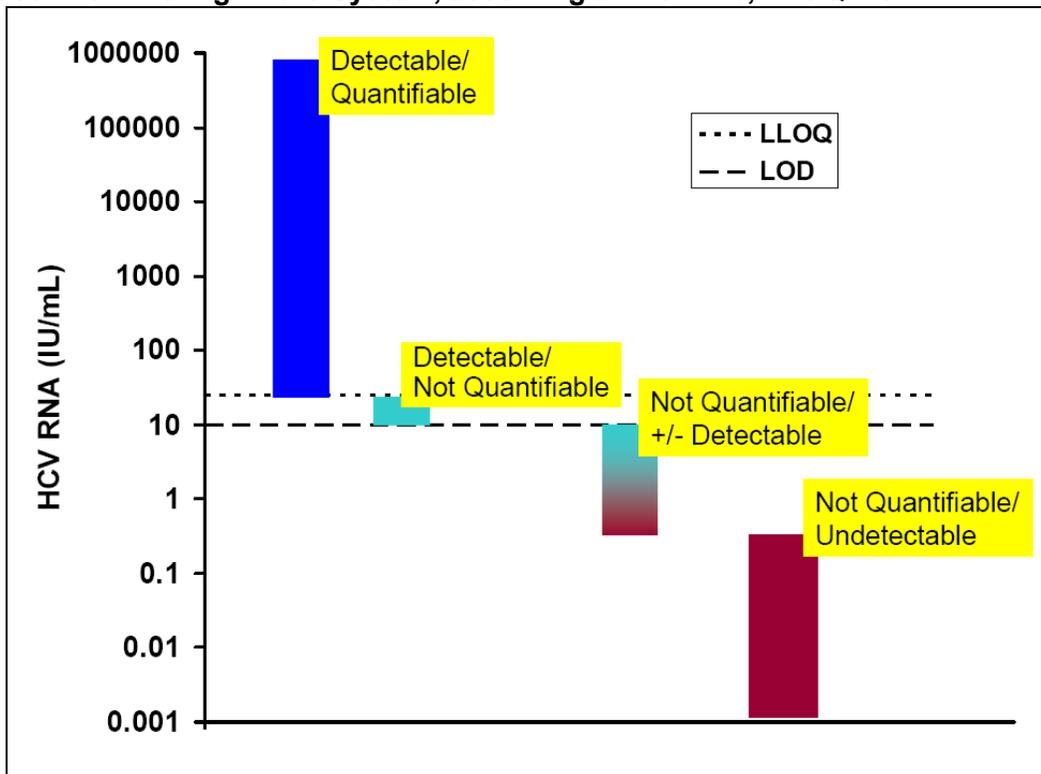
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(b) (4)

**ADDITIONAL EXPLORATORY ANALYSES OF HCV RNA LOD/LLOQ**

Since the finalization of the Virology review of the Original NDA for boceprevir (Victrelis™), additional exploratory analyses have been conducted to assess the clinical relevance of HCV RNA results that are detectable but below the limit of assay quantification. The following slides and annotations summarize these additional analyses:

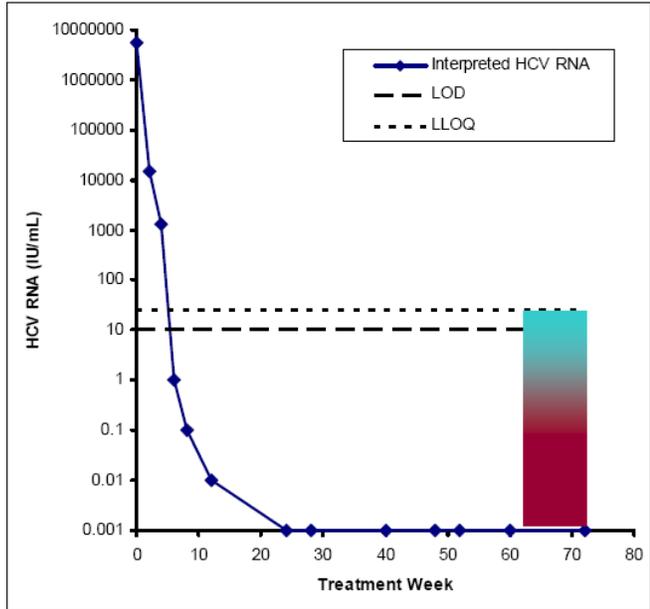
**Our interpretation of ‘qualitative’ HCV RNA results from Roche COBAS® TaqMan® HCV Test, v2.0 For Use With The High Pure System, assuming an LOD=10, LLOQ=25**



# Examples (from Boceprevir)

Subject 000047 (BOC48):Rapid and sustained HCV RNA decline

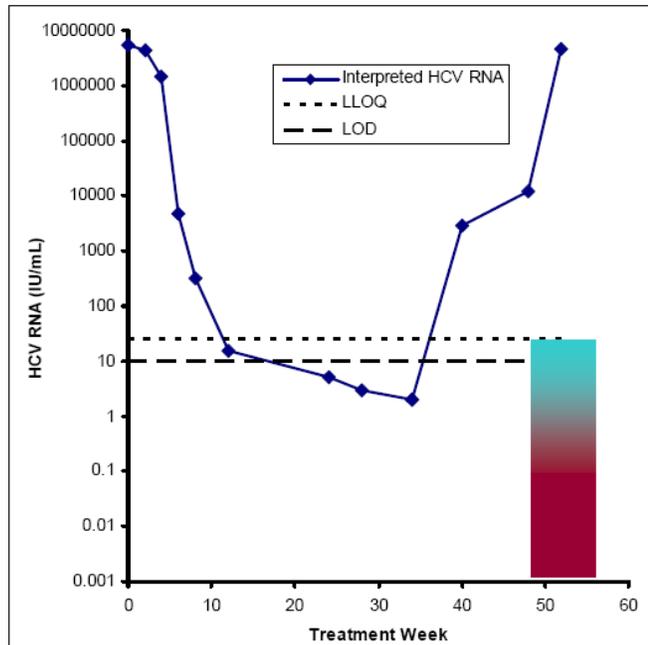
Timepoint	Reported HCV RNA (IU/mL)	Reported HCV RNA (Qualitative)
Baseline	5560000	Detectable
Week 2	15200	Detectable
Week 4 (add BOC)	1330	Detectable
Week 6	24	Undetectable
Week 8	24	Undetectable
Week 12	24	Undetectable
Week 24	24	Undetectable
Week 28	24	Undetectable
Week 40	24	Undetectable
Week 48	24	Undetectable
FU Wk 4	24	Undetectable
FU Wk 12	24	Undetectable
FU Wk 24	24	Undetectable



# Examples (from Boceprevir)

Subject 002009 (BOC48):Slower HCV RNA decline + breakthrough

Timepoint	Reported HCV RNA (IU/mL)	Reported HCV RNA (Qualitative)
Baseline	5410000	Detectable
Week 2	4450000	Detectable
Week 4 (add BOC)	1470000	Detectable
Week 6	4690	Detectable
Week 8	313	Detectable
<b>Week 12</b>	<b>24</b>	<b>Detectable</b>
Week 24	24	Undetectable
<b>Week 28</b>	<b>24</b>	<b>Detectable</b>
<b>Week 34</b>	<b>24</b>	<b>Detectable</b>
Week 34	24	Undetectable
Week 40	2900	Detectable
Week 48	12200	Detectable
FU Wk 4	4600000	Detectable

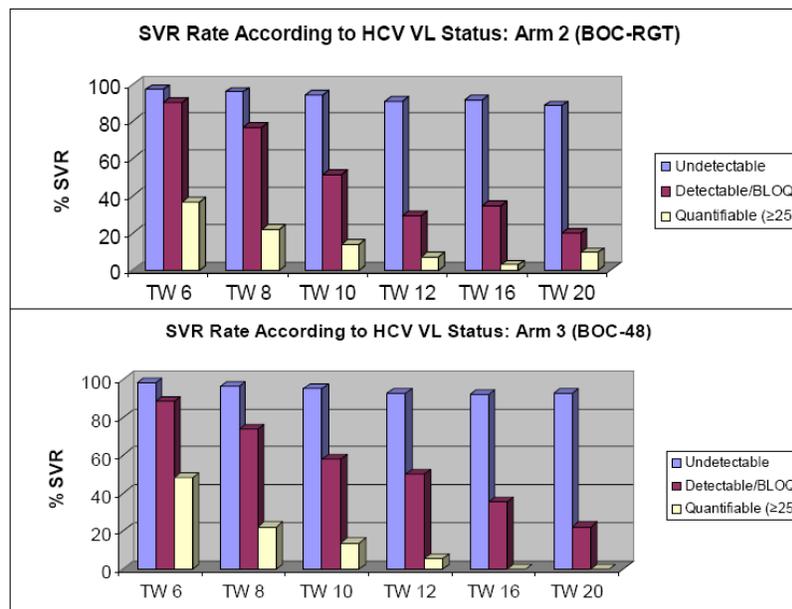


## Detectable/BLOQ Not Uncommon During Treatment (Phase 3 Boceprevir Trial P05216)

Timepoint	HCV VL Status On-Treatment (All Arms)		
	Undetectable	Detectable/BLOQ	Quantifiable ( $\geq 25$ )
TW 6	301/883 (34%)	123/883 (14%)	466/883 (53%)
TW 8	426/897 (47%)	147/897 (16%)	338/897 (38%)
TW 10	495/884 (56%)	134/884 (15%)	269/884 (30%)
TW 12	581/901 (64%)	106/901 (12%)	232/901 (26%)
TW 16	616/874 (70%)	78/874 (9%)	192/874 (22%)
TW 20	637/855 (75%)	69/855 (8%)	161/855 (19%)
TW 34	433/449 (96%)	11/449 (2%)	9/449 (2%)

Note that SVR rates determined in the following analyses of P05216 were based on a non-virologic-failure-censored dataset (i.e., censored subjects who failed treatment for reasons not necessarily attributable to virologic failure, such as early discontinuation while responding virologically). However, comparable results are expected regardless of whether a censored subject listing is used.

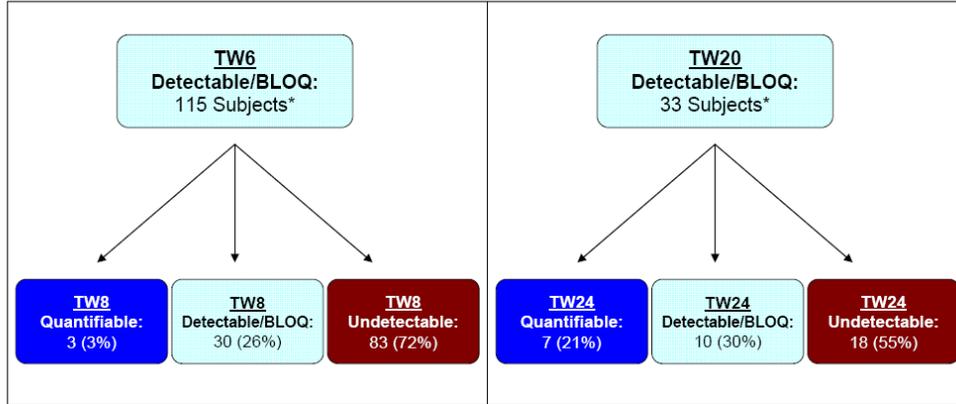
## Detectable/BLOQ During Treatment is Clinically Relevant



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## Detectable/BLOQ Viral Load is a Transition Phase

P05216 (BOC arms) VL Status

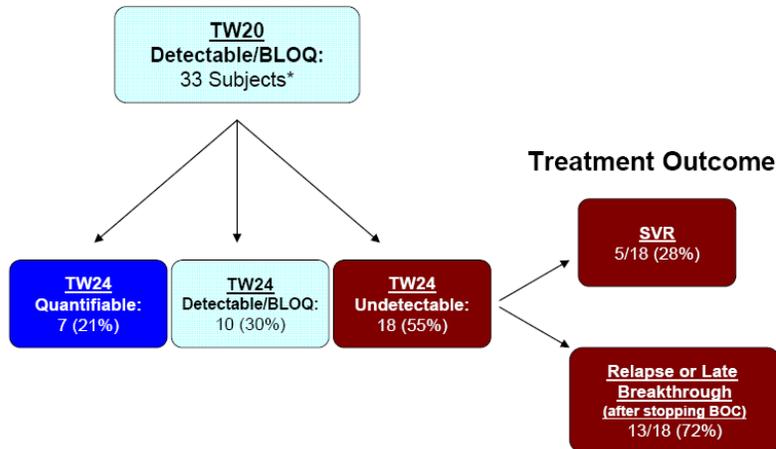


\*Subjects who also have VL data available at next timepoint

Note: 1 subject at TW8, and 2 subjects at TW24 with multiple, discordant results (included in numerator)

## Detectable/BLOQ at TW20, Followed by Undetectable at TW24, is a Late Response

P05216 (BOC arms) VL Status



\*Subjects who also have VL data available at next timepoint

Note: 1 subject at TW8, and 2 subjects at TW24 with multiple, discordant results (included in numerator)

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**False-positive detection rate likely  
very low in Boceprevir Phase 3 trials**

(Assay False-Positive Rate According to Label: 1.3%)

**Boceprevir Tx-naïve trial (P05216):**

- 2,578 follow-up samples from 610 subjects who achieved SVR (based on <25 IU/mL cutoff)
- 13 samples (0.5%) with detectable HCV RNA
  - 8 BLOQ, 5 in linear range
- All of these follow-up detectable HCV RNA results from SVR subjects could be interpreted as false-positives
- Estimates a 0.5% false-positive detection rate in Boceprevir Trials
- VL assessments conducted by [REDACTED] (b) (4)

**Summary points from these analyses**

- “Detectable/BLOQ” and “Undetectable” during treatment are two qualitatively different HCV RNA results; “Detectable/BLOQ” during treatment is generally indicative of having a reduced virologic response compared to “Undetectable” during treatment
- One cannot substitute “Detectable/BLOQ” for “Undetectable” for regimens that validated response-guided therapy based on a Detectable/Undetectable viral load cutoff
- The 0.5% rate of detectable HCV RNA during follow-up for P05216 trial subjects who apparently achieved SVR may represent the overall false-positive rate of detectable HCV RNA during the conduct of the trial (assays conducted by [REDACTED] (b) (4)).

**Additional information from Dr. Lisa Naeger’s analysis of the telaprevir NDA (please see Dr. Naeger’s review of these data for more details)**

- Based on similar preliminary analyses as those summarized above, in the telaprevir 216 trial (which also used [REDACTED] (b) (4) for HCV viral load testing) there was a 0.3% rate of detectable HCV RNA during follow-up for subjects who apparently achieved SVR based on a <25 IU/mL cutoff.
  - The trend of SVR rate according to HCV viral load status (Undetectable, Detectable/BLOQ, Quantifiable >25) was very similar to that of the boceprevir P05216 trial.
- For a second telaprevir trial, 108, [REDACTED] (b) (4) was used to conduct HCV viral load testing. In this trial, there was a 7% rate (~23-fold higher than in 216, preliminary analysis) of detectable HCV RNA during follow-up for subjects who apparently achieved SVR based on a <25 IU/mL cutoff.
  - Interestingly, there was still a trend of a reduced SVR rate for subjects with Detectable/BLOQ HCV RNA results versus those with Undetectable HCV RNA results at the same on-treatment timepoint. However, the overall SVR rate trend for subjects with Detectable/BLOQ HCV RNA results at any given on-treatment timepoint was much higher than what was observed for the 108 trial and the boceprevir P05216 trial, which may be due to a potentially higher rate of false-positive HCV RNA detection in the 108 trial.

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**ADMINISTRATIVE**

**Reviewer's Signature**

\_\_\_\_\_  
Patrick R. Harrington, Ph.D.  
Virology Reviewer, Division of Antiviral Products

**Concurrence**

\_\_\_\_\_  
Julian J. O'Rear, Ph.D.  
Virology Team Leader, Division of Antiviral Products

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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PATRICK R HARRINGTON  
05/12/2011

JULIAN J O'REAR  
05/12/2011

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)**  
**VIROLOGY REVIEW**  
**NDA: 202258 SDN: 003 DATE REVIEWED: 04/14/2011**  
**Virology Reviewer: Patrick R. Harrington, Ph.D.**

**NDA#:** 202285      **SDN:** 003      **eCTD:** 0001  
**Reviewer's Name(s):** Patrick R. Harrington, Ph.D.

**Sponsor's Name and Address:** Schering-Plough Corporation  
2000 Galloping Hill Road  
Kenilworth, NJ 07033-0530  
Thomas J. Chambers, M.D.  
Director, Global Regulatory Affairs  
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**Initial Submission Dates:**  
**Correspondence Date:** 11/10/2010  
**CDER Receipt Date:** 11/15/2010  
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**Review Complete Date:** 04/14/2011  
**PDUFA Date:** 5/23/2011

**Amendments:** none

**Related/Supporting Documents:**

- IND 69027
- NDA 202285 submissions: SDN 001 (eCTD 000), NDA presubmission; SDN 002 (eCTD 002), AIMS datasets; SDN 007 (eCTD 005), response to preNDA action items; SDN 010 (eCTD 008), response to Virology request; SDN 016 (eCTD 014), response to Virology request; SDN 023 (eCTD 021), response to Virology request; SDN 024 (eCTD 022), response to pharmacometrics request for data from select Phase 1/2 PK-PD studies; SDN 027 (eCTD 25), 3 month safety update report; SDN 28 (eCTD 26), response to Virology/Clinical/Statistics request; SDN 32 (eCTD 30), response to Virology request; SDN 34 (eCTD 32), response to Virology request; SDN 36 (eCTD 34), response to Virology request

**Product Name(s)**

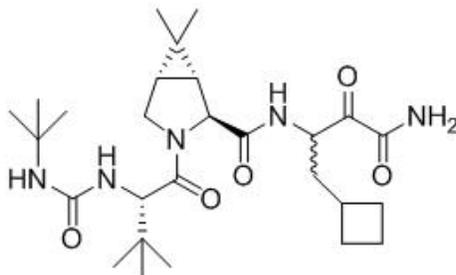
**Proprietary:** Victrelis™  
**Non-Proprietary/USAN:** boceprevir  
**Code Name/Number:** SCH 503034

**Chemical Name:** (1R,5S)-N-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(S)-[[[(1,1-dimethylethyl)amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2(S)-carboxamide

**Molecular Weight:** 519.7

**Molecular Formula:** C<sub>27</sub>H<sub>45</sub>N<sub>5</sub>O<sub>5</sub>

**Structural Formula:**



**SCH 503034 (boceprevir, Victrelis™)**

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)**  
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**Dosage Form/Route of Administration:** 200 mg capsule /Oral

**Dispensed:** Rx  OTC

**Proposed Indication(s):** "treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alpha and ribavirin, in adult patients (18 years and older) with compensated liver disease who are previously untreated or who have failed previous therapy"

**Abbreviations:** BLOQ, below limit of quantification; bp, base pair; BT, breakthrough; DAA, direct acting antiviral agent; EC, effective concentration; EOT, end of treatment; HCV, hepatitis C virus; HIV(-1), human immunodeficiency virus (type 1); IFN( $\alpha$ ), interferon (alfa); ITT, intent-to-teat; IVR, incomplete virologic response; LOCF, last observation carried forward; LLOQ, lower limit of quantification; LOD, limit of detect; NCR, non-coding region; Peg-IFN $\alpha$ , pegylated interferon alfa; RBV, ribavirin; RGT, response-guided therapy; RT-PCR, reverse transcription polymerase chain reaction; SEAP, secreted alkaline phosphatase; SNP, single nucleotide polymorphism; SOC, standard of care; SVR, sustained virologic response; VF, virologic failure

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**EXECUTIVE SUMMARY**

**1. RECOMMENDATIONS**

**1.1 Recommendation and Conclusion on Approvability**

This Original NDA is approvable from a Virology perspective for the treatment of chronic HCV genotype 1 infected patients who are either naïve to prior anti-HCV therapy, or who failed prior therapy with Peg-IFN $\alpha$ /RBV but achieved at least a partial virologic response to the prior therapy ( $>2$  log<sub>10</sub> IU/mL decline through 12 weeks, or equivalent).

**1.2 Recommendation on Phase IV (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.**

This reviewer recommends the following post-marketing commitments:

1. 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. A166T, with and without linked V170A, genotype 1b replicon
  - f. V36M, R155K and V36M+R155K, genotype 1a replicon
2. 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 vector for phenotypic characterization related to boceprevir susceptibility.
3. Report results from P05063 regarding the long term persistence ( $\geq 2$  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

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substitutions associated with persistence of resistance-associated substitutions should also be explored.

4. 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-IFN $\alpha$ /RBV treatment regimens among subjects who (1) respond relatively poorly to the Peg-IFN $\alpha$ /RBV 4-week lead-in (e.g.,  $<1 \log_{10}$  IU/mL decline,  $\geq 1 \log_{10}$  IU/mL to  $<2 \log_{10}$  IU/mL decline, etc.), or (2) have an unfavorable IL28B genotype.
5. 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.

## **2. SUMMARY OF OND VIROLOGY ASSESSMENTS**

### **2.1 Nonclinical Virology**

Boceprevir is a small molecule drug that binds to the active site of the hepatitis C virus (HCV) NS3/4A protease and inhibits its enzymatic activity that is necessary for processing the viral nonstructural polyprotein. Boceprevir inhibited the replication of an HCV genotype 1b (strain Con1) subgenomic replicon in Huh-7 cells with 50% and 90% effective concentration ( $EC_{50}$  and  $EC_{90}$ ) values of approximately 200 nM and 400 nM, respectively. An ~2-fold reduction in boceprevir antiviral activity was observed against the genotype 1a (H77) replicon relative to the genotype 1b (Con1) replicon. In the HCV genotype 1b replicon system, boceprevir and interferon  $\alpha$ -2b (IFN $\alpha$ -2b) had a non-antagonistic combination antiviral activity relationship. The anti-HCV activity of boceprevir in the genotype 1b HCV replicon system was not antagonized by the human immunodeficiency virus type 1 (HIV-1) protease inhibitors atazanavir (1-10  $\mu$ M), lopinavir (5-20  $\mu$ M), or ritonavir (0.3-10  $\mu$ M). Similarly, the anti-HIV-1 activities of atazanavir, lopinavir and ritonavir were not antagonized by the presence of boceprevir (0.5-5  $\mu$ M).

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

Cross-resistance between boceprevir and other NS3/4A protease inhibitors is expected. The key boceprevir resistance-associated substitutions observed in cell culture or in clinical studies are predicted to confer at least some degree of cross-resistance to other HCV NS3/4A protease inhibitors in development. Cross-resistance is not expected between boceprevir and Peg-IFN $\alpha$ -2a, Peg-IFN $\alpha$ -2b, ribavirin (RBV) or other classes of HCV DAAs currently in development.

### **2.2 Clinical Virology**

Boceprevir was studied in HCV-infected patient populations in several Phase 1, 2 and 3 trials. The two pivotal Phase 3 trials were P05216 (SPRINT-2) and P05101 (RESPOND-2). These trials

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compared the efficacy of two therapeutic regimens (with or without a response-guided therapy [RGT] approach) of boceprevir in combination with Peg-IFN $\alpha$ -2b/RBV versus standard of care Peg-IFN $\alpha$ -2b/RBV therapy in treatment-naïve subjects (P05216) or in prior Peg-IFN $\alpha$ /RBV treatment failure subjects (P05101; note that this trial excluded prior Peg-IFN $\alpha$ /RBV null responders). Subjects in both trials were chronically infected with HCV genotype 1. Boceprevir dosed in combination with Peg-IFN $\alpha$ -2b/RBV resulted in a significantly higher rate of sustained virologic response (SVR) compared to treatment with Peg-IFN $\alpha$ -2b/RBV alone. In both trials, SVR rates were numerically higher among subjects infected with HCV genotype 1b versus 1a. Please see the review of Dr. Wen Zeng, biostatistics reviewer, for the FDA analyses of boceprevir efficacy.

Among boceprevir-treated subjects in P05216 or P05101 who did not achieve SVR, and for whom samples were analyzed, 52% (153/292) had one or more of the following post-baseline, treatment-emergent NS3 amino acid substitutions detected: V36A, V36M, T54A, T54S, V55A, V107I, R155K, R155T, A156S, A156T, A156V, V158I, D168N, I/V170A and I/V170T. The most common treatment-emergent amino acid substitutions detected in HCV subtype 1a-infected subjects were, in decreasing order of occurrence, R155K, V36M and T54S. The most common treatment-emergent amino acid substitutions detected in HCV subtype 1b-infected subjects were T54A, T54S, I/V170A, A156S and V55A.

The D168N and V107I substitutions have not been previously reported to be associated with boceprevir resistance. D168N was detected in 11 post-baseline samples from 8 boceprevir-treated subjects. All 8 subjects were infected with HCV subtype 1a, and all 11 samples also had detectable R155T, indicating that the combination of R155T+D168N linked on the same HCV subtype 1a genome likely confers reduced HCV susceptibility to boceprevir. The V107I substitution emerged in 6 boceprevir-treated subjects and 0 control arm subjects, indicating its emergence is specific to boceprevir treatment.

The patterns of boceprevir treatment-emergent, resistance-associated substitutions were generally similar for both Phase 3 clinical trials, P05216 (treatment-naïve trial) and P05101 (treatment-experienced trial). However, there was a higher rate of detection of treatment-emergent substitutions in clinical trial P05216 versus P05101, which might be explained by the use of a Treatment Week 12 detectable HCV RNA treatment futility rule that was employed in P05101 but not P05216. The patterns of treatment-emergent substitutions were generally similar across treatment arms (RGT versus non-RGT) in the pooled analysis of both trials. Subjects who experienced virologic breakthrough or incomplete virologic response (as defined by the sponsor) were more likely to have the detection of one or more treatment-emergent, resistance-associated substitutions, relative to subjects who experienced virologic nonresponse or relapse. Subjects who had a poor virologic response during the Peg-IFN $\alpha$ -2b/RBV lead-in period were also more likely to have the detection of treatment-emergent substitutions following treatment failure.

An independent analysis was conducted to identify any NS3/4A amino acid substitutions that, when present/enriched as baseline polymorphisms, were associated with poor treatment outcomes in clinical trials P05216 and P05101. In general, there were no baseline amino acid substitutions anywhere in the NS3/4A coding sequence that were clearly associated with a poor treatment outcome, although in most cases the number of subjects with any single baseline NS3/4A substitution relative to a subtype-specific reference was inadequate for meaningful analysis. Polymorphisms at NS3 position Q80, which are common in HCV genotype 1a-infected patients and have been shown to reduce the anti-HCV activity of certain macrocyclic/non-linear NS3/4A protease inhibitors, did not appear to have a negative impact on boceprevir efficacy.

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In the pooled clinical trials P05216 and P05101, there were 40 subjects (<5% of boceprevir-treated subjects) who had 1 or more of the following major boceprevir treatment-emergent substitutions detected at baseline: V36M, T54A, T54S, V55A, or R155K. Despite the detection of these substitutions at baseline, 28/40 (70%) of the subjects achieved SVR. A possible impact of these baseline polymorphisms on boceprevir efficacy could be observed in subjects with a reduced response to the Peg-IFN $\alpha$ /RBV lead-in period. Among subjects with one or more of these polymorphisms detected at baseline, 0 of 7 (0%) who achieved a <1 log<sub>10</sub> IU/mL decline through Treatment Week 4, and 3 of 14 (21%) who achieved a <2 log<sub>10</sub> IU/mL decline, eventually achieved SVR on boceprevir/Peg-IFN $\alpha$ /RBV protocol therapy. In comparison, boceprevir-treated subjects in these same Peg-IFN $\alpha$ /RBV lead-in response strata, but without detectable boceprevir resistance-associated substitutions at baseline, had SVR rates of 38% and 55%, respectively.

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

This review also includes virology summaries of two supportive Phase 2 trials, P03523 (SPRINT-1) and P03659 (RESPOND-1), a recently completed Phase 3 trial (P05685) that studied the efficacy of boceprevir dosed in combination with Peg-IFN $\alpha$ -2a/RBV, and a Phase 1 PK/PD trial (P03648) that studied boceprevir monotherapy in subjects infected with HCV genotype 2 or 3.

### **3. ADMINISTRATIVE**

#### **3.1 Reviewer's Signature**

\_\_\_\_\_  
Patrick R. Harrington, Ph.D.  
Virology Reviewer, Division of Antiviral Products

#### **3.2 Concurrence**

\_\_\_\_\_  
Julian J. O'Rear, Ph.D.  
Virology Team Leader, Division of Antiviral Products

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***OND Virology Review***

**1. INTRODUCTION AND BACKGROUND**

**1.1 Important milestones in product development**

Boceprevir (SCH 503034, Victrelis™) is a hepatitis C virus (HCV) direct-acting antiviral agent (DAA) that has been developed for the treatment of chronic HCV infection. Pre-IND correspondence for boceprevir was submitted on 3/25/2005. The Original IND 69027 was submitted on 5/18/2005. Numerous non-clinical and clinical studies have been conducted under the IND. Clinical study reports for two supportive Phase 2 trials, P03659 (RESPOND-1) and P03523 (SPRINT-1), were submitted to the IND on 11/03/2008 and 6/29/2009, respectively (IND 69027 SDNs 237 and 322, respectively). Two Phase 3 trials, P05216 (SPRINT-2) and P05101 (RESPOND-2), have been completed to support this Original NDA. A pre-NDA face-to-face meeting with the sponsor was held on 9/29/2010.

**1.2 Methodology**

This section summarizes clinical virology procedures that were used for the Phase 3 boceprevir trials. Additional methodologies for other boceprevir non-clinical and clinical virology studies are summarized in Sections 2 and 4.

**HCV genotype/subtype determination**

HCV genotype/subtype assessments were originally determined by 2 approaches: TRUGENE™ HCV 5'NC assay (conducted by (b) (4)), and a combination of NS3/4A reverse-transcription polymerase chain reaction (RT-PCR) amplification and/or NS5B phylogenetic analysis (conducted by (b) (4)).

**TRUGENE™ HCV 5'NC assay**

The TRUGENE™ HCV 5'NC assay (subsequently referred to as "TRUGENE™ assay"), is a commercially available HCV genotyping assay. The assay method determines HCV genotype/subtype by sequence analysis of 183 base pairs in cDNA derived from the 5' non-coding region (5'NCR) of the HCV genome. Briefly, HCV viral RNA is extracted from an HCV-infected patient's plasma or serum sample, the HCV RNA is amplified by RT-PCR, the cDNA amplicon is sequenced, and the resulting sequences are analyzed in reference to a library of HCV sequences from various genotypes and subtypes.

**NS3/4A RT-PCR amplification/NS5B phylogenetic analysis**

This approach was used as a secondary analysis to determine HCV genotype/subtype:

- a. Samples identified as **subtype 1a by TRUGENE™ assay** were subjected to the following analysis:
  - Subtype-optimized primers for NS3/4A RT-PCR amplification were used for resistance assessments. If RT-PCR amplification using subtype 1a-optimized primers was successful, then the sample was considered subtype 1a. For these instances, NS3/4A RT-PCR amplifications using subtype 1b-optimized primers were not conducted.
  - If NS3/4A RT-PCR amplification with subtype 1a-optimized primers was unsuccessful, then subtype 1b-optimized primers were used; if amplification was successful then sample was considered subtype 1b.
  - NS5B RT-PCR, nucleotide sequencing, and phylogenetic analyses were not conducted for subjects identified as subtype 1a by TRUGENE™ assay.

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- b. Samples identified as **subtype 1b (or non-determined subtype) by TRUGENE™ assay** were subjected to the following analysis:
- NS5B RT-PCR, nucleotide sequencing, and phylogenetic analysis of a 329 base pair (bp) “subtype-predictive domain.” This analysis was conducted by (b) (4). Note that phylogenetic analysis of NS5B is generally considered the reference method for determination of HCV genotype/subtype ([Simmonds et al., 2005](#))

During the initial review of the boceprevir NDA we expressed concerns about the HCV genotype/subtype methodologies used in the Phase 3 boceprevir trials. It is now well accepted that analysis of 5’NCR only (i.e., TRUGENE™ assay) frequently does not identify an HCV genotype 1 subtype, and in some cases misclassifies HCV genotype 1 subtype, relative to the reference NS5B phylogenetic analysis method. In one study ([Chevaliez et al., 2009](#)), the TRUGENE™ assay failed to correctly identify HCV subtype 1a in 22.8% of cases, and HCV subtype 1b in 9.5% of cases.

The secondary HCV genotype/subtype analysis approach based on NS3/4A RT-PCR amplification or NS5B phylogenetic analysis, while potentially an improvement in performance over the TRUGENE™ assay, was also concerning to this reviewer. The algorithm used was unconventional and will not likely be used in clinical practice. Furthermore, ‘inferring’ HCV subtype indirectly based on successful RT-PCR amplification of the NS3/4A gene is concerning because RT-PCR primers can be promiscuous, and no performance data were provided to characterize the subtype-specificity of the subtype-optimized RT-PCR primers. Finally, a secondary HCV genotype/subtype analysis method ideally would have been applied to all study subjects regardless of the TRUGENE™ assay result.

These concerns about the HCV genotype/subtype analysis methods were communicated to the sponsor near the time of NDA filing, and we requested the sponsor conduct an additional HCV genotype/subtype analysis to address the concerns, with multiple acceptable approaches recommended (see 12/13/2010 request, documented in Appendix C).

#### NS3/4A phylogenetic analysis

In response to our request for a third HCV genotype/subtype assessment, the sponsor conducted phylogenetic analysis of all available baseline NS3 or NS3/4A nucleotide sequences that were generated from study subjects for genotypic resistance analysis purposes. Approximately 95% of study subjects from the two Phase 3 trials P05216 and P05101 had baseline NS3 or NS3/4A nucleotide sequence data available for phylogenetic analysis to determine HCV genotype 1 subtype. The sequences were aligned with HCV H77 and Con1 sequences (references for genotype 1a and 1b, respectively) and phylogenetic trees were constructed using PHYLIP Version 3.6 (<http://evolution.genetics.washington.edu/phylip.html>).

HCV genotype/subtype results of the NS3/4A phylogenetic analysis were 99.9% concordant (excluding missing data) with the results generated by the NS3/4A RT-PCR amplification/NS5B phylogenetic analysis algorithm described above (see sponsor’s reply to 12/13/2010 request, documented in Appendix C). Based on this result, HCV genotype/subtype results originally reported based on NS3/4A RT-PCR amplification/NS5B phylogenetic analysis (referred to as “(b) (4)” method in the NDA) were considered acceptable, and were used in this review for the purpose of exploring boceprevir efficacy according to HCV genotype 1 subtype, and also for characterizing boceprevir resistance pathways.

#### **HCV viral load assessments**

For the Phase 3 trials P05216 and P05101, HCV viral load was determined by (b) (4) using the Roche COBAS® TaqMan® HCV/HPS Test, Version 2.0. This assay

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measures HCV RNA levels by quantitative real-time RT-PCR. According to the assay manufacturer, the Roche COBAS® TaqMan® HCV/HPS v2.0 assay has a linear range from 25 to 391,000,000 IU/mL, with a lower limit of quantification of 25 IU/mL and a limit of detection of 9.3 IU/mL. The limit of detection of the assay represents the lowest concentration of HCV RNA that is detectable with a 95% positivity rate. The linear range and limit of detection were confirmed by (b) (4). Note that this assay is currently FDA-approved, with the label reporting a lower limit of quantification of 23 IU/mL, and a limit of detection of 15.1 IU/mL (EDTA Plasma, Genotype 1).

### **Resistance-related Assessments**

For the Phase 3 trials P05216 and P05101, study subject plasma samples were subjected to RNA extraction, RT-PCR amplification and population-based nucleotide sequence analysis to infer amino acid coding sequences in the viral population. These analyses were performed by (b) (4). The entire NS3/4A coding region of the HCV genome was targeted. According to assay validation documentation provided by (b) (4) the success rate of the assay was >90% for samples with an HCV RNA level of ≥10,000 IU/mL, and ~71% for samples with HCV RNA levels of 1,000-10,000 IU/mL. Amino acid coding data for the two Phase 3 trials were reported using subtype-specific reference sequences.

Note that population-based sequence analyses typically cannot detect minority populations that contribute <25% of the total population; therefore, the absence or lack of detection of a given substitution does not necessarily mean it does not exist in the subject. Rather, the substitution may be present but at a level below the limit of detection by population-based or other conventional nucleotide sequence analysis methods. For a detailed review of current HCV drug resistance analysis methods, see [Kwong et al., 2011](#).

### **1.3 Prior FDA Virology reviews**

A Pre-IND submission was reviewed by Dr. Jules O'Rear, Ph.D. The Original IND 69027 and subsequent IND submissions through SDN 219 (5/2008) were reviewed by Dr. Lisa Naeger, Ph.D. IND submissions after SDN 219 were reviewed by Dr. Patrick Harrington, Ph.D.

### **1.4 Major virology issues that arose during product development**

#### **HCV Drug Resistance**

During boceprevir development, it was revealed that HCV variants with reduced susceptibility to boceprevir, and cross-resistance to other HCV NS3/4A protease inhibitors in development, can become enriched rapidly in boceprevir-exposed patients. This issue is not unique to boceprevir or to the NS3/4A protease inhibitor class in general. HCV variants with reduced susceptibility to many other HCV DAAs in development across multiple classes can emerge rapidly during treatment, particularly when the agents are administered individually as monotherapy. For multiple HCV DAA classes, including NS3/4A protease inhibitors, outgrowth of drug-resistant variants during monotherapy can be observed within a few days of dosing.

Recently described mathematical models of HCV dynamics suggest that mixed HCV populations, with all possible single-nucleotide substitutions and all possible combinations of double-nucleotide substitutions represented in the total population, circulate in most HCV-infected patients and pre-exist before treatment with HCV antiviral agents ([Rong et al., 2010](#)). Because many HCV DAAs are affected by certain single amino acid substitutions in the viral drug target, many of which are coded by a single nucleotide change, it is assumed that HCV variants with reduced susceptibility to many HCV DAAs pre-exist, at least as minority populations, in most HCV-infected patients. Exposure of the

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mixed HCV population to a single HCV DAA with a low genetic barrier to resistance results in the suppression of “wild-type” susceptible viral populations, and the enrichment of pre-existing viral subpopulations with reduced susceptibility to the DAA.

The potential for persistence of HCV drug resistant variants raises concerns regarding the ability of patients previously exposed to a given HCV DAA to respond optimally when re-treated with the HCV DAA or another agent with an overlapping resistance pathway. Theoretically, prolonged drug exposure in a patient with an inadequate virologic response to the DAA will lead to the accumulation of additional HCV genome changes that increase the replicative fitness of drug-resistant HCV variants. As a result, after a patient stops treatment with the DAA the absolute and relative levels of drug resistant HCV variant(s) will not return, or will return slowly, to the minority levels that pre-existed in the mixed HCV population prior to drug exposure. Anecdotal reports have indicated that HCV variants harboring certain HCV DAA resistance-associated substitutions can persist at a high level in some infected patients for several months or even years following exposure to the DAA.

The concerns about HCV drug resistance that emerged during boceprevir development have changed the way HCV DAA clinical trials are typically designed and conducted. As experienced with drug development for human immunodeficiency virus type 1 (HIV-1), drug resistance has become a key consideration in the design of optimally effective HCV DAA-containing treatment regimens.

#### Role of Ribavirin

During boceprevir development it was discovered that ribavirin (RBV) is an important component of the combination anti-HCV regimen of boceprevir plus pegylated interferon alfa and RBV (Peg-IFN $\alpha$ /RBV). Not including RBV in the regimen, or using a reduced RBV dose, resulted in increased virologic breakthrough rates, increased relapse rates, and decreased sustained virologic response (SVR) rates. The important role of RBV was similarly demonstrated in clinical trials of telaprevir, another HCV NS3/4A protease inhibitor ([Hézode et al., 2009](#); [McHutchison et al., 2010](#)).

#### Impact of Peg-IFN $\alpha$ /RBV Treatment Response History

It has become apparent that for subjects who previously failed a Peg-IFN $\alpha$ /RBV treatment regimen, the efficacy of an NS3/4A protease inhibitor in combination with Peg-IFN $\alpha$ /RBV is related to the magnitude of virologic response during the previous Peg-IFN $\alpha$ /RBV treatment. This association was observed in clinical trials of boceprevir (summarized in this NDA), and also in clinical trials of telaprevir ([Berg et al., 2010](#); [McHutchison et al., 2010](#)), and likely applies to most if not all classes of HCV DAAs in development. In other words, not all previous Peg-IFN $\alpha$ /RBV treatment failure subjects respond equally when re-treated with a combination regimen of an HCV DAA plus Peg-IFN $\alpha$ /RBV.

These observations indicate that virologic responsiveness to the Peg-IFN $\alpha$ /RBV background therapy has a major impact on the ultimate efficacy (i.e., SVR) of a DAA/Peg-IFN $\alpha$ /RBV regimen. Further confirming the importance of responsiveness to Peg-IFN $\alpha$ /RBV background therapy, the efficacy of boceprevir/Peg-IFN $\alpha$ /RBV is associated with subjects' virologic responses to a 4-week Peg-IFN $\alpha$ /RBV lead-in period prior to the addition of boceprevir to the treatment regimen (see below, “Peg-IFN $\alpha$ /RBV Lead-in Phase”). One of the key functions of the Peg-IFN $\alpha$ /RBV components of the combination regimen is believed to be the prevention of the enrichment of HCV subpopulations with reduced susceptibility to the HCV DAA.

Based on these observations, it is important to understand the efficacy of a DAA/Peg-IFN $\alpha$ /RBV combination regimen, with the patients sub-grouped by the magnitude of virologic response to previous (or possibly lead-in) Peg-IFN $\alpha$ /RBV therapy. FDA currently recognizes the following definitions for defining treatment history and previous virologic response to Peg-IFN $\alpha$ /RBV for

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purposes of HCV DAA clinical trial enrollment and analysis (treatment-experienced populations ordered by response to re-treatment with DAA/Peg-IFN $\alpha$ /RBV):

- **Naïve:** received no prior therapy for HCV (including interferon or pegylated interferon monotherapy)
- **Responder Relapser:** HCV RNA undetectable at the end of treatment with Peg-IFN $\alpha$ /RBV, but HCV RNA detectable within 24 weeks of treatment follow-up
- **Partial Responder:**  $\geq 2 \log_{10}$  IU/mL reduction in HCV RNA at Week 12, but not achieving HCV RNA undetectable at end of treatment with Peg-IFN $\alpha$ /RBV (“Partial responders” are frequently referred to as “non-responders” by the sponsor. This reviewer prefers usage of “partial responders” to avoid confusion between “non-responders” and “null responders”.)
- **Null Responder:**  $< 2 \log_{10}$  IU/mL reduction in HCV RNA at Week 12 during treatment with Peg-IFN $\alpha$ /RBV

#### IL28B Genotype

Multiple independent research groups recently demonstrated that certain human genome single nucleotide polymorphisms (SNPs) near the IL28B gene, which encodes interferon lambda 3 (IFN $\lambda$ -3), significantly affect patients’ responses to Peg-IFN $\alpha$ /RBV treatment ([Ge et al., 2009](#); [Suppiah et al., 2009](#); [Tanaka et al., 2009](#)). The rs12979860 SNP near the IL28B gene is now recognized as one of the strongest baseline predictors of Peg-IFN $\alpha$ /RBV treatment efficacy, with the rs12979860 C allele being the favorable allele, and the T allele being unfavorable. Based on the seminal SNP analysis of the IDEAL trial, SVR rates in a selected population of >1,000 patients treated with Peg-IFN $\alpha$ /RBV were ~79% for patients with the CC homozygous genotype, ~38% for patients with the CT heterozygous genotype, and ~28% for patients with the TT homozygous genotype ([Ge et al., 2009](#)). Furthermore, the authors found that the TT genotype was more prevalent in Black/African American patients, which could account for ~50% of the Peg-IFN $\alpha$ /RBV treatment efficacy difference between Black/African Americans and individuals of European descent. Other SNPs near IL28B also reported to be associated with SVR rates include rs8099917 and rs12980275 ([Ge et al., 2009](#); [Suppiah et al., 2009](#); [Tanaka et al., 2009](#)). A higher rate of spontaneous clearance of acute HCV infection has also been reported for patients with the rs12979860 CC genotype, relative to those with the TT or CT genotypes ([Thomas et al., 2009](#))

The precise mechanism by which these SNPs influence the efficacy of Peg-IFN $\alpha$ /RBV is unclear, and is a subject of intense investigation. Despite the unknown mechanism, the dramatic impact of IL28B genotype on Peg-IFN $\alpha$ /RBV efficacy has made it a potentially important demographic consideration in making Peg-IFN $\alpha$ /RBV treatment decisions, and at least one commercial IL28B rs12979860 SNP assay is now available to care providers ([LabCorp](#)).

It is important to understand the relative efficacy of a boceprevir/Peg-IFN $\alpha$ /RBV treatment regimen in patients with or without the favorable IL28B genotype(s), as this knowledge may help guide treatment decisions. IL28B genotype may have relatively little direct influence on virologic response to HCV DAAs. However, given that initial HCV DAAs will need to be administered in combination with Peg-IFN $\alpha$ /RBV, and virologic responsiveness to Peg-IFN $\alpha$ /RBV background therapy affects the efficacy of a DAA/Peg-IFN $\alpha$ /RBV combination regimen (see above, “Impact of Peg-IFN $\alpha$ /RBV Treatment Response History”), IL28B genotype is anticipated to have at least an indirect influence on the efficacy of an HCV DAA. Unfortunately due to the timing of the IL28B SNP-related discoveries and lack of appropriate patient consent, the role of IL28B genotype could not be evaluated prospectively in the Phase 3 boceprevir clinical trials, and limited post-hoc analyses using patient de-identified IL28B genotype data could be conducted.

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Peg-IFN $\alpha$ /RBV Lead-in Phase

The sponsor designed and utilized a Peg-IFN $\alpha$ /RBV “lead-in” approach in an attempt to optimize the overall efficacy of a boceprevir/Peg-IFN $\alpha$ /RBV regimen. In the two Phase 3 boceprevir trials P05216 (SPRINT-2) and P05101 (RESPOND-2), and for some subjects in the Phase 2 trial P03523 (SPRINT-1), patients initially received 4 weeks of Peg-IFN $\alpha$ /RBV treatment prior to having boceprevir (or placebo) added to their treatment regimens.

There are theoretical advantages of utilizing a 4-week Peg-IFN $\alpha$ /RBV lead-in period for a boceprevir/Peg-IFN $\alpha$ /RBV treatment regimen. First, it may enhance the suppression of HCV variants resistant to boceprevir. The efficiency of selection and enrichment of drug resistant HCV relates partly to the antiviral activity of the background therapy and the size of the HCV quasispecies pool. Because the concentrations and anti-HCV activities of RBV (specifically, RBV-triphosphate) and Peg-IFN $\alpha$  may not achieve steady state until several weeks after the initiation of dosing, the lead-in period will allow these agents to be near steady state by the time boceprevir is added to the treatment regimen. In addition, the initial Peg-IFN $\alpha$ /RBV-driven decline in the HCV body burden may reduce the complexity and absolute quantity of pre-existing HCV variants with reduced susceptibility to boceprevir, prior to the addition of boceprevir drug pressure.

A second potential advantage of the Peg-IFN $\alpha$ /RBV lead-in period is that it may help guide treatment decisions. Both adherence and responsiveness to Peg-IFN $\alpha$ /RBV have major impacts on eventual boceprevir/Peg-IFN $\alpha$ /RBV treatment efficacy. Clinical assessments near the end of the 4-week Peg-IFN $\alpha$ /RBV lead-in period may provide some insight into a patient’s initial tolerability and virologic responsiveness to Peg-IFN $\alpha$ /RBV. This information may then be used to predict if it is advantageous for a patient to continue treatment with boceprevir added to the treatment regimen. For example, if a patient is not responding virologically to the initial Peg-IFN $\alpha$ /RBV treatment and is also unlikely to remain adherent to the treatment due to poor tolerability, then it may be futile to add boceprevir to the regimen and continue treatment. In this example, exposing the patient to boceprevir may enrich for drug resistant HCV without providing a clinical benefit, which may limit future treatment options.

A potential practical disadvantage of the Peg-IFN $\alpha$ /RBV lead-in phase is that it may unnecessarily complicate anti-HCV treatment. Ideally, this potential disadvantage would be balanced by a clearly established efficacy benefit of using the lead-in phase. Only one clinical trial, P03523 (SPRINT-1), compared the overall efficacy of a boceprevir/Peg-IFN $\alpha$ /RBV regimen administered with or without a Peg-IFN $\alpha$ /RBV lead-in phase. Although intent-to-treat SVR rates were numerically higher in the Peg-IFN $\alpha$ /RBV lead-in arms (two different total treatment durations, 28 weeks and 48 weeks), the trial was conducted open label and was not sufficiently powered to detect a statistically significant difference in efficacy. Furthermore, there were multiple lines of evidence of bias or randomization imbalance in this trial. For example, overall treatment adherence rates were higher in the Peg-IFN $\alpha$ /RBV lead-in arms relative to the non-lead-in arms, and SVR rates among subjects who were considered adherent to study treatment for the full duration were numerically higher in the non-lead-in arms. In this reviewer’s opinion, use of the Peg-IFN $\alpha$ /RBV lead-in is unlikely to make a boceprevir/Peg-IFN $\alpha$ /RBV treatment regimen less effective, but the sponsor has not proven that the lead-in makes the regimen more effective. See Section 4.5.1 for a more detailed review of P03523.

Use of Virologic Response during Peg-IFN $\alpha$ /RBV Lead-in as a Surrogate for Prior Treatment History  
Prior Peg-IFN $\alpha$ /RBV null responders (defined as having achieved a  $<2 \log_{10}$  IU/mL reduction in HCV RNA at Week 12 during prior treatment with Peg-IFN $\alpha$ /RBV) were not eligible for enrollment into either of the two pivotal boceprevir Phase 3 trials. Presumably this decision was made because of the poor and largely non-interpretable boceprevir efficacy observed in the Phase 2 trial P03659, which included both prior partial responders and prior null responders (see Section 4.5.2 for details). Despite the lack

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of inclusion of this significant patient population in the Phase 3 program, the sponsor has proposed a broad indication for boceprevir approval for the treatment of patients who have previously failed treatment with Peg-IFN $\alpha$ /RBV, regardless of virologic response during the prior therapy.

The sponsor argues that boceprevir efficacy among Peg-IFN $\alpha$ /RBV null responders has effectively been well characterized, based on the rationale that current responsiveness to Peg-IFN $\alpha$ /RBV can serve as a demographic variable that makes prior treatment history irrelevant. The sponsor has also suggested that during standard Peg-IFN $\alpha$ /RBV therapy, a  $<1 \log_{10}$  IU/mL decline in HCV RNA at Treatment Week 4 is highly concordant with a  $<2 \log_{10}$  IU/mL decline at Treatment Week 12, based on an analysis from the IDEAL trial (Table 1; P05101 Clinical Study Report, pg. 74). Based on these two points, the sponsor suggests that a  $<1 \log_{10}$  IU/mL decline in HCV RNA during a current 4-week Peg-IFN $\alpha$ /RBV lead-in period is representative of a Peg-IFN $\alpha$ /RBV null response, regardless of prior treatment history. Boceprevir efficacy has been well characterized in this population: in the two Phase 3 boceprevir trials, boceprevir-treated subjects who experienced a  $<1 \log_{10}$  IU/mL decline in HCV RNA during the 4-week Peg-IFN $\alpha$ /RBV lead-in period eventually had a 33-38% SVR rate.

**Table 1. Concordance analysis of HCV RNA declines at Treatment Week 4 ( $<1 \log_{10}$  IU/mL) and Treatment Week 12 ( $<2 \log_{10}$  IU/mL) during treatment with Peg-IFN $\alpha$ /RBV (IDEAL trial). Overall concordance of TW 4 and TW 12 results was 88.5%.**

	TW 4 Response	TW 12 Response	
		$<2.0 \log_{10}$ decline	$\geq 2.0 \log_{10}$ decline
PEG-IFN alfa-2b 1.5 / RBV	$<1.0 \log_{10}$ decline	150	56
	$\geq 1.0 \log_{10}$ decline	55	639
PEG-IFN alfa-2b 1.0 / RBV	$<1.0 \log_{10}$ decline	235	51
	$\geq 1.0 \log_{10}$ decline	69	577
PEG-IFN alfa-2a / RBV	$<1.0 \log_{10}$ decline	148	65
	$\geq 1.0 \log_{10}$ decline	22	710

PEG-IFN = peginterferon alfa; RBV = ribavirin; TW = Treatment Week.

Although it is clear that current Peg-IFN $\alpha$ /RBV responsiveness is associated with the efficacy of a Peg-IFN $\alpha$ /RBV/boceprevir treatment regimen, there are some weaknesses in the sponsor's argument that boceprevir efficacy has been sufficiently characterized to justify inclusion of prior Peg-IFN $\alpha$ /RBV null responders in the treatment indication. Both on treatment measures of poor virologic responsiveness during standard Peg-IFN $\alpha$ /RBV therapy ( $<1 \log_{10}$  IU/mL at Week 4,  $<2 \log_{10}$  IU/mL at Week 12) have a robust negative predictive value for SVR, but these patient populations are not necessarily the same. Based on the sponsor's analysis of virologic response data from the IDEAL trial, while 679 subjects had a  $<2 \log_{10}$  IU/mL decline in HCV RNA at Treatment Week 12, 146 (21.5%) of these subjects had a  $\geq 1 \log_{10}$  IU/mL decline in HCV RNA at Treatment Week 4. Similarly, 705 subjects met the sponsor's surrogate definition of a null responder ( $<1 \log_{10}$  IU/mL decline in HCV RNA at Treatment Week 4), but 172 (24.4%) of these subjects had a  $\geq 2 \log_{10}$  IU/mL decline at Treatment Week 12, meaning they did not meet the more commonly used definition of a null responder.

Analyses of Peg-IFN $\alpha$ /RBV lead-in responses in the Phase 3 treatment-experienced trial (P05101) also raise questions about using Peg-IFN $\alpha$ /RBV lead-in responsiveness as a surrogate for prior treatment history. Although this trial specifically excluded prior Peg-IFN $\alpha$ /RBV null responders ( $<2 \log_{10}$  IU/mL decline at Treatment Week 12), 25.3% (102/403) of all subjects enrolled achieved a  $<1 \log_{10}$  HCV RNA decline at Treatment Week 4 (end of Peg-IFN $\alpha$ /RBV lead-in). In other words, the sponsor's surrogate indicator of Peg-IFN $\alpha$ /RBV "null responder" applied to 25% of subjects who were

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considered partial responders or relapsers to prior Peg-IFN $\alpha$ /RBV therapy for the purposes of trial enrollment.

For subjects treated with a Peg-IFN $\alpha$ /RBV/boceprevir regimen, virologic responsiveness during a 4-week Peg-IFN $\alpha$ /RBV lead-in period might be more predictive of SVR outcome compared to prior Peg-IFN $\alpha$ /RBV treatment response history. Furthermore, boceprevir likely provides an efficacy benefit over placebo regardless of the null responder definition. However, to compare directly the predictive value of either variable, and to validate the use of the 4-week lead-in response as a surrogate for prior treatment history, all key subpopulations representative of prior Peg-IFN $\alpha$ /RBV treatment response history, including prior null responders, ideally would have been studied. In logical terms, to determine *directly* if variables D, E and F can be used in place of variables A, B and C, variable C cannot be excluded from the analysis.

An analysis of a telaprevir clinical trial ("REALIZE") demonstrated that while current responsiveness to Peg-IFN $\alpha$ /RBV lead-in is clearly related to the eventual SVR rate with a Peg-IFN $\alpha$ /RBV/telaprevir regimen, prior response history remains an important efficacy variable that cannot be substituted entirely with a measure of current Peg-IFN $\alpha$ /RBV lead-in responsiveness. This analysis was recently published in an abstract for presentation at the 2011 European Association for the Study of Liver Disease (EASL) meeting ([Foster et al., 2011](#)). The REALIZE trial evaluated telaprevir efficacy in previous treatment failure subjects, including Peg-IFN $\alpha$ /RBV null responders (<2 log<sub>10</sub> IU/mL HCV RNA decline at Treatment Week 12). Like the boceprevir Phase 3 trials, this trial included an arm that used a 4-week Peg-IFN $\alpha$ /RBV lead-in period prior to addition of telaprevir to the regimen. In this arm, 41/69 (59%) prior Peg-IFN $\alpha$ /RBV null responders had a <1 log<sub>10</sub> IU/mL decline in HCV RNA after the 4-week Peg-IFN $\alpha$ /RBV lead-in, while 28/69 (41%) had a  $\geq$ 1 log<sub>10</sub> IU/mL decline in HCV RNA after the 4-week Peg-IFN $\alpha$ /RBV lead-in. Furthermore, among all subjects with a <1 log<sub>10</sub> IU/mL decline in HCV RNA after the Peg-IFN $\alpha$ /RBV lead-in period, prior Peg-IFN $\alpha$ /RBV null responders ultimately had a 15% SVR rate, compared to SVR rates of 56% and 62% among prior Peg-IFN $\alpha$ /RBV partial responders and relapsers, respectively. Thus, even after accounting for Peg-IFN $\alpha$ /RBV lead-in responsiveness, prior Peg-IFN $\alpha$ /RBV response history remained an important efficacy variable in this trial.

### **1.5 State of Antivirals Used for the Indication(s) Sought**

According to the [U.S. Centers for Disease Control and Prevention](#) (CDC), an estimated 3.2 million people in the U.S. have chronic HCV infection. The virus is transmitted primarily by the use of contaminated needles, but may also be transmitted by exposure to contaminated blood in healthcare settings, by mother-to-child transmission, or less commonly through sexual contact. Prior to the implementation of screening of the blood supply in the 1990s, HCV was commonly transmitted through blood transfusions and organ transplants. Approximately 15-30% of acute HCV infections are resolved without treatment, while the infection becomes chronic in ~70-85% of cases. Most patients with chronic HCV develop chronic liver disease, ~5-25% of patients eventually develop cirrhosis over a period of ~20-30 years, and a subset of these patients will eventually die due to liver cancer or other complications. Chronic HCV infection is the leading indication for liver transplantation in the U.S., and the CDC estimates that 8,000-10,000 people die each year due to the disease.

Hepatitis C viruses that circulate in the general population are extremely diverse. There are at least 6 genotypes and 50 subtypes of HCV (NS5B gene phylogenetic analysis is the reference method for determination of HCV genotype/subtype). The most common HCV genotype in the U.S. is genotype 1, with subtype 1a being relatively more common than subtype 1b. To put the extensive HCV genetic

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diversity in perspective, the genetic diversity just within HCV genotype 1 is comparable to the genetic diversity among all known HIV-1 clades.

The current standard of care (SOC) for treatment of chronic HCV infection is pegylated interferon alfa plus ribavirin for a duration of 24-48 weeks depending on HCV genotype. The goal of treatment is to obtain a sustained virologic response (SVR), which is defined as having undetectable circulating HCV RNA 24 weeks following the cessation of therapy. One of two different FDA-approved Peg-IFN $\alpha$  products is typically used for SOC, either Peg-IFN $\alpha$ -2a (PEGASYS<sup>®</sup>) or Peg-IFN $\alpha$ -2b (PEGINTRON<sup>®</sup>). A recently completed clinical trial has demonstrated similar efficacy (based on SVR rate) when either agent is administered in combination with RBV ([McHutchison et al., 2009](#)).

There is a major public health need for chronic HCV therapies that are more effective, better tolerated, and can be effectively dosed for shorter durations. For treatment of chronic HCV genotype 1 infection, the recommended duration of SOC therapy is 48 weeks ([Ghany et al., 2009](#)). This treatment results in an SVR rate of ~40% for previously untreated, HCV genotype 1 infected subjects. Peg-IFN $\alpha$ /RBV therapy is relatively more effective for the treatment of chronic HCV genotypes 2 or 3, with SVR rates of 70-80% after 24 weeks of dosing ([Ghany et al., 2009](#)). Both Peg-IFN $\alpha$  and RBV are poorly tolerated in many subjects who receive treatment. Use of one or both agents is also contraindicated in many HCV infected patients, for example patients with autoimmune disorders, depression, organ transplant, or one of several other concurrent medical diseases, and also for women who are pregnant or unwilling to use contraception.

A major shift in HCV drug discovery and development in recent years has been in the area HCV direct acting antivirals (DAAs), which target specific steps in the HCV replication cycle catalyzed by viral encoded functions. Safe and effective HCV DAAs may play an important role in addressing the need for better HCV therapies. Due to the inability of single HCV DAA agents (to date) to demonstrate durable suppression of HCV replication in such a manner that will typically result in SVR (see section 1.4), the first available HCV DAAs will primarily be dosed in combination with Peg-IFN $\alpha$ /RBV. In the future, after additional HCV DAAs with non-overlapping resistance pathways or more durable antiviral activity advance through clinical development, treating patients effectively with DAA regimens lacking Peg-IFN $\alpha$  or RBV may be possible. Ideally such regimens will be more tolerable, may be effective with shorter durations of treatment, and will address the need for treatments in chronic HCV patients in whom Peg-IFN $\alpha$  or RBV are contraindicated.

## **2. NONCLINICAL VIROLOGY**

### **2.1 Mechanism of Action**

The HCV RNA genome is translated inside an infected cell to generate a single polyprotein. A host cell signal peptidase processes the N-terminal region of the polyprotein to generate mature structural (Core, E1, E2) and p7 proteins. Two protease complexes encoded in the HCV genome, NS2/3 and NS3/4A, co- and post-translationally process the C-terminal two-thirds of the HCV polyprotein to generate the mature forms of the nonstructural proteins (Figure 1; from [Moradpour et al., 2007](#)). The NS2/3 protease is an autoprotease that mediates a *cis* cleavage reaction at the NS2-NS3 junction. The NS3/4A protease is responsible for processing the HCV polyprotein at the junctions of NS3-NS4A, NS4A-NS4B, NS4B-NS5A and NS5A-NS5B.

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**Figure 1. HCV genome organization, translation and polyprotein processing ([Moradpour et al., 2007](#)).**

Boceprevir is a small molecule that binds to the active site of the HCV NS3/4A protease and inhibits its activity. Because the activity of the HCV NS3/4A protease is essential for viral replication, boceprevir inhibition of NS3/4A protease results in inhibition of HCV replication.

In a biochemical assay, boceprevir inhibited the activity of an HCV genotype 1b NS3/4A protease, with a  $K_i$  of 14 nM. Similar boceprevir activity was observed against an HCV genotype 1a NS3/4A protease, also with a  $K_i$  of 14 nM. Approximately 2- to 3-fold reduced boceprevir activity was observed for NS3/4A proteases from HCV genotypes 2 and 3a, with  $K_i$  values of 39 nM and 25 nM, respectively.

The activity of boceprevir is reasonably specific for the HCV NS3/4A protease, although there is potential for off target anti-protease activity. Weak cross-reactivity was observed for human neutrophil elastase ( $K_i = 26 \pm 5 \mu\text{M}$ ) and human plasma thrombin ( $K_i = 27 \pm 3 \mu\text{M}$ ). Additional studies screening for off target activity found that boceprevir can inhibit human cathepsin B ( $\text{IC}_{50}$  value =  $10.2 \pm 0.3 \mu\text{M}$ ), human cathepsin G ( $\text{IC}_{50}$  value =  $2.2 \pm 1.1 \mu\text{M}$ ), human cathepsin L ( $\text{IC}_{50}$  value =  $9.6 \pm 0.8 \mu\text{M}$ ), and rat hepatic acyl CoA-cholesterol acyltransferase ( $\text{IC}_{50}$  value =  $1.7 \pm 0.5 \mu\text{M}$ ). The sponsor conducted additional internal studies of boceprevir activity against cathepsins G, H, and L, and reported  $K_i$  values of 520 nM, >135  $\mu\text{M}$ , and 80 nM, and, respectively. Boceprevir had an  $\text{IC}_{50}$  value of >20  $\mu\text{M}$  against human adrenal acyl Co-A-cholesterol acyltransferase.

## **2.2 Cell Culture Studies**

### **Antiviral Activity in Cell Culture**

Boceprevir inhibited the replication of an HCV genotype 1b (strain Con1) subgenomic replicon in Huh-7 cells with 50% and 90% effective concentration ( $\text{EC}_{50}$  and  $\text{EC}_{90}$ ) values of approximately 200 nM and 400 nM, respectively (n=25 replicates). In these studies, the HCV replicon-harboring cells were exposed to boceprevir for 72 hours, and replicon RNA levels were measured by real-time RT-PCR. According to the sponsor (data not provided), Western analyses showed that boceprevir inhibited HCV polyprotein processing, consistent with its mechanism of action.

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Boceprevir also inhibited a genotype 1a (strain H77) HCV replicon with EC<sub>50</sub> and EC<sub>90</sub> values of 900 and 1400 nM, respectively. In the same experiment the boceprevir EC<sub>50</sub> values for three different genotype 1b (Con1) replicon cell lines were 300 nM, 400 nM and 600 nM, and the EC<sub>90</sub> values were 500 nM, 900 nM and 900nM. These data indicate an ~2-fold reduction in boceprevir antiviral activity against the genotype 1a (H77) replicon relative to the genotype 1b (Con1) replicon. In these studies HCV replicon-harboring cells were exposed to boceprevir for 3 days and replicon RNA levels were measured by real-time RT-PCR.

No data have been provided to characterize boceprevir activity against HCV replicons derived from a panel of clinical isolates. Such data are necessary to understand the range of boceprevir activity against HCV variants circulating in the clinical setting.

Antiviral Activity in Cell Culture in the Presence of Serum and Serum Proteins

The presence of 50% human serum decreased the antiviral activity of boceprevir by ~3-fold relative to a 0% human serum control in the HCV replicon system (presumably genotype 1b/Con1).

Cytotoxicity/Therapeutic Index

Minimal cytotoxicity was observed in Huh-7 cells or Huh-7/clone 16 (replicon harboring) cells exposed to boceprevir concentrations up to 50 µM, representing a therapeutic index of >250. Cells were exposed to boceprevir for 72 hours, and cytotoxicity was measured using MTS dye to assess cell viability. Over a 21-day exposure period, boceprevir concentrations up to 4 µM had no significant effect on the doubling time of Huh-7 cells or phytohemagglutinin-stimulated peripheral blood mononuclear cells. Boceprevir concentrations up to 4 µM also had no effect on apoB secretion (marker of liver function) by primary baboon hepatocytes.

In another set of experiments, boceprevir tested at concentrations up to 100 µM had minimal measurable cytotoxicity over 3 days against a panel of human cell lines and primary cells, which included multiple replicon cell lines, human melanoma, pancreatic cancer, colon cancer and mammary epithelial cell lines, and primary human hepatocytes and peripheral blood mononuclear cells from two different donors each. A boceprevir 50% cytotoxicity concentration value of 80 µM was calculated for a PM-1 human T cell line. The culturing conditions and cytotoxicity analysis methods used for each cell type in these studies are unclear.

Combination Antiviral Activity in Cell Culture

In the HCV genotype 1b replicon system, boceprevir and IFNα-2b had a non-antagonistic combination antiviral activity relationship. HCV replicon-harboring cells were exposed to IFNα-2b and boceprevir for 72 hours, and replicon RNA levels were measured by real-time RT-PCR. The range of IFNα-2b and boceprevir concentrations evaluated in this study spanned the EC<sub>50</sub> and EC<sub>90</sub> values of each agent.

The anti-HCV activity of boceprevir in the genotype 1b HCV replicon system was not antagonized by the HIV-1 protease inhibitors atazanavir (1-10 µM), lopinavir (5-20 µM), or ritonavir (0.3-10 µM). The HIV-1 protease inhibitor concentration ranges used in these assays are similar to the range of plasma concentrations expected in treated patients, according to the individual drug labels. No significant cytotoxicity was observed in the replicon cells by MTS dye assay for any of the boceprevir and HIV-1 protease inhibitor combinations.

Similarly, the anti-HIV-1 activities of atazanavir, lopinavir and ritonavir were not antagonized by the presence of boceprevir (0.5-5 µM). Of note, the EC<sub>50</sub> value of lopinavir against HIV-1 may be slightly lower in the presence of higher concentrations of boceprevir (2.5-5 µM), although the clinical

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relevance of this observation is unknown. These experiments utilized U87-CD4-CCR5 cells and HIV-1 strain RU<sub>570</sub> (subtype G, CCR5-tropic), and HIV-1 replication was assessed by p24 production. The concentration range of boceprevir used in these assays is similar to the plasma concentration range expected in treated subjects (Investigator's Brochure dated 6/23/2010, pg. 67; 800 mg TID dose). No significant cytotoxicity was observed by MTS dye assay for any of the boceprevir and HIV-1 protease inhibitor combinations.

### **2.3 Animal Studies**

No virology-related animal studies were reported.

### **2.4 Resistance Studies**

#### **Resistance Development in Cell Culture**

Passage of HCV genotype 1b replicon-harboring cells in the presence of boceprevir (6x EC<sub>90</sub> value) resulted in the emergence of replicons with reduced susceptibility to boceprevir. Exposure to higher levels of boceprevir (25x EC<sub>90</sub> value) selected for HCV replicons with higher levels of resistance, with 100- to 150-fold increases in EC<sub>90</sub> values observed for certain clones.

Consistent with the known mechanism of action of boceprevir, substitutions in the NS3 protease coding region of the HCV genome were detected in the boceprevir-selected replicons. The NS3 substitutions most commonly observed were T54A, Q86R, A156S, A156T, V170A, and E176G. The A156T substitution was identified in 100% of analyzed replicons from the 25x EC<sub>90</sub> value selections, indicating that it confers a high level of resistance to boceprevir. The Q86R and E176G substitutions may not be directly involved in boceprevir resistance, as they have been reported to represent HCV replicon cell culture adaptations ([Blight et al., 2000](#); [Krieger et al., 2001](#)).

The sponsor did not report any information on the selection of HCV genotype 1a replicons with reduced susceptibility to boceprevir. This absence is important to consider in the interpretation of the HCV genotype 1b replicon selection studies, as patterns of HCV DAA resistance-associated substitutions can vary depending on the HCV replicon genotype/subtype used. For example, the well described NS3 R155K substitution is preferentially enriched in HCV genotype 1a replicons selected for reduced susceptibility to telaprevir ([McCown et al., 2009](#)). Subtype-associated resistance pathways have also been observed in patients exposed to telaprevir or boceprevir (e.g., [Sarrazin et al., 2007](#); [Susser et al., 2009](#); also see boceprevir resistance analyses in Section 4.3). A single nucleotide change is required to produce the R155K amino acid substitution in HCV genotype 1a, whereas two nucleotide changes are required for genotype 1b, which may explain why R155K is detected more frequently in the context of genotype 1a.

#### **Effect of Individual Amino Acid Substitutions on Boceprevir Anti-HCV Activity**

Specific NS3 amino acid substitutions, individually or in certain combinations, were engineered into the HCV genotype 1b replicon to assess their impact on HCV susceptibility to boceprevir. Protease biochemical assays and cell-based secreted alkaline phosphatase (SEAP) reporter assays were also conducted to evaluate the effect of NS3 amino acid substitutions on boceprevir activity. The NS3 substitutions evaluated include those identified by the sponsor and others as potentially being associated with HCV resistance to various NS3/4A protease inhibitors in non-clinical or clinical studies.

The results of these studies are compiled in Table 2. Note that most of these data were generated from biochemical and SEAP assays. The only replicon studies were conducted using an HCV

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genotype 1b replicon background, and the effect of certain substitutions on boceprevir anti-HCV activity may vary depending on HCV subtype. Certain individual amino acid substitutions at NS3 positions T54, R155, A156 and V170 conferred  $\geq 10$ -fold reductions in boceprevir anti-HCV activity (biochemical, replicon, or SEAP assay). Individual substitutions at NS3 positions V36, Q41, F43, V55 and V158 conferred  $\geq 2.5$  to  $< 10$ -fold reductions in boceprevir anti-HCV activity. A D168V substitution did not reduce boceprevir anti-HCV activity in the biochemical or replicon assay. The presence of V36M or T54S in combination with R155K further reduced boceprevir anti-HCV activity relative to R155K alone.

Results from the SEAP assay may underestimate the overall reduction in boceprevir anti-HCV activity conferred by individual NS3 amino acid substitutions. For the 14 substitutions characterized by SEAP and at least 1 additional assay (replicon or biochemical) in the HCV genotype 1b background, the reduction in boceprevir anti-HCV activity was smallest when estimated by SEAP assay in 11/14 (79%) of cases. For certain substitutions (e.g., A156S/T, V170A) the fold-reduction in boceprevir anti-HCV activity was 3- to 5-fold greater based on the HCV genotype 1b replicon assay relative to the SEAP assay.

The clinical relevance of the reported reductions in boceprevir anti-HCV activity conferred by specific amino acid substitutions may vary based on the biochemical or cell culture assay used to generate the data. As summarized in Section 4.3.1, the most common treatment-emergent NS3 amino acid substitutions associated with boceprevir treatment failure in HCV subtype 1a-infected subjects in the phase 3 trials P05216 and P05101 were V36M, T54S and R155K. In many subjects V36M and R155K were detected in the same sample. The high frequency of boceprevir treatment-emergent V36M, T54S, R155K, and V36M+R155K observed in HCV subtype 1a-infected subjects does not seem to correlate with the modest effects of these substitutions on boceprevir anti-HCV NS3/4A protease activity based on SEAP assay: 1.8- to 2.1-fold for V36M, T54S or R155K, 4.3-fold for V36M+R155K. This reviewer hypothesizes that the SEAP assay underestimates the overall reduction in boceprevir anti-HCV activity conferred by these substitutions when they emerge in boceprevir-treated subjects. In support of this hypothesis, the most common treatment-emergent NS3 amino acid substitutions associated with boceprevir treatment failure in HCV subtype 1b-infected subjects in the phase 3 trials (T54A, T54S, V55A, A156S and I/V170A) conferred 6- to 16-fold reductions in boceprevir anti-HCV activity in the genotype 1b replicon system, but only 2.7- to 4.4-fold reductions in boceprevir anti-HCV activity based on SEAP assay. The sponsor should evaluate the effect of V36M, R155K, and V36M+R155K on boceprevir anti-HCV activity using the HCV genotype 1a replicon system. The HCV replicon system is assumed by this reviewer to be the most relevant system to characterize the anti-HCV activity of boceprevir, and the effect of NS3 amino acid substitutions on boceprevir anti-HCV activity, as it models additional biological steps that are not captured in the biochemical assay (cellular penetration of drug, viral genome replication, viral replicative fitness, virus-host interactions) or the SEAP assay (viral genome replication, viral replicative fitness, virus-host interactions).

Some boceprevir resistance-associated substitutions affected the replicative fitness of HCV replicons, based on efficiency of stable replicon cell colony formation and wild-type/mutant replicon competition assays. The V36M-, R155K-, A156T- and V36M+R155K-harboring replicons had reduced colony formation efficiency relative to the wild-type parental genotype 1b replicon. The F43S, T54A, A156S and V170A substitutions did not significantly affect replicon colony formation efficiency. The Q41R substitution conferred a 10-fold higher colony formation efficiency. In replicon competition assays, V170A conferred no growth disadvantage, A156S conferred a slight growth disadvantage, and A156T conferred a relatively large growth disadvantage relative to the wild-type parental replicon. Additional studies suggested that the A156T replicon had decreased NS3 protease activity.

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**Table 2. Effect of specific NS3 amino acid substitutions on boceprevir anti-HCV activity in replicon, biochemical, and cellular secreted alkaline phosphatase (SEAP) assays. \*Most common treatment-emergent NS3 amino acid substitutions associated with boceprevir treatment failure in the phase 3 trials P05216 and P05101.**

<b>Substitution(s)</b>	<b>HCV Replicon (EC<sub>50</sub> value fold-increase)</b>	<b>Biochemical Assay (K<sub>i</sub> value fold-increase)</b>	<b>SEAP Assay (EC<sub>50</sub> value fold-increase)</b>
<b><i>HCV Genotype 1a Background</i></b>			
V36A	not available	not available	2.9
V36M*	not available	not available	1.9
Q41R	not available	not available	0.5
F43S	not available	not available	5.4
T54A	not available	not available	3.9
T54S*	not available	not available	1.8
V55A	not available	not available	2.7
R155K*	not available	not available	2.1
R155T	not available	not available	5.1
A156S	not available	not available	3.4
A156T	not available	not available	13.7
A156V	not available	not available	20.0
I170A	not available	not available	2.6
I170T	not available	not available	2.2
V36A+R155K	not available	not available	8.6
V36M+R155K*	not available	not available	4.3
T54S+R155K	not available	not available	7.0
V36A+T54S+R155K	not available	not available	12.3
<b><i>HCV Genotype 1b Background</i></b>			
V36A	not available	2.5	2.1
V36I	not available	3	not available
V36L	not available	1.4	not available
V36M	3	2	1.5
Q41R	3	2	0.6
F43C	not available	7	not available
F43S	5	not available	3.6
T54A*	6	4	2.7
T54C	not available	32	not available
T54S*	6	2.5	3.2
V55A*	6.9	4.2	4.4
V55I	not available	7	not available
R155G	not available	18	not available
R155I	not available	45	not available
R155K	4	3.5	2.6
R155M	not available	8	not available
R155Q	not available	3	not available
R155T	not available	20	8.6
A156S*	16	17	3.5
A156T	85	300	16.7
A156V	not available	not available	21.5

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Substitution(s)	HCV Replicon (EC <sub>50</sub> value fold-increase)	Biochemical Assay (K <sub>i</sub> value fold-increase)	SEAP Assay (IC <sub>50</sub> value fold-increase)
<b>HCV Genotype 1b Background (cont.)</b>			
<b>V158I</b>	3.3	2.5	not available
<b>V158M</b>	not available	1.5	not available
<b>D168V</b>	1	0.6	not available
<b>V170A*</b>	12	10	3.8
<b>V170I</b>	not available	not available	1.2
<b>V170T</b>	not available	2	2.4
<b>M175L</b>	2	3.5	not available
<b>V36M+R155K</b>	10	14	4.5
<b>T54S+R155K</b>	not available	12	9.0
<b>T54S+A156S</b>	not available	not available	14.0

The clinical relevance of the replicon fitness assessments is not entirely clear, as selective pressures may differ in cell culture and in infected patients. Furthermore, boceprevir resistance-associated substitutions that emerge in treated patients will do so in the context of numerous other amino acid changes relative to standard HCV cell culture reference strains.

Cross-Resistance Assessment

Cross-resistance between boceprevir and other HCV NS3/4A protease inhibitors in clinical development is expected. Any of the key boceprevir resistance-associated substitutions is predicted to confer at least some degree of cross-resistance to nearly every HCV NS3/4A protease inhibitor currently being studied under FDA IND, including telaprevir (VX-950, IND 71832), (b) (4)

(b) (4)  
 In particular, the R155K substitution is associated with virologic failure and confers large reductions in anti-HCV activity for many of these agents. Other boceprevir resistance-associated substitutions at positions V36, T54, R155, A156 and V170 also reduce the anti-HCV activity of most HCV NS3/4A protease inhibitors in development.

Substitutions at NS3 D168 can confer large reductions in anti-HCV activity for the macrocyclic/non-linear subclass of NS3/4A protease inhibitors (e.g., (b) (4)), but substitutions at D168 generally are not associated with resistance to boceprevir or other linear NS3/4A protease inhibitors (e.g., telaprevir, (b) (4)). Theoretically, if a patient who fails therapy with a macrocyclic/non-linear NS3/4A protease inhibitor has enrichment of HCV viral populations with D168 substitution(s), but no enrichment of variants with substitutions at other key positions such as R155 or A156, then the HCV population in this subject could still be susceptible to boceprevir. However, such a scenario will likely be infrequent, as substitutions at R155 remain the predominant resistance pathway for most macrocyclic/non-linear NS3/4A protease inhibitors. Furthermore, independent analyses of resistance data from the two boceprevir Phase 3 trials P05216 and P05101 revealed that a D168N substitution (in combination with R155T) emerged in some boceprevir-treated, HCV subtype 1a-infected subjects (see Section 4.3.1), indicating that boceprevir selection of HCV variants with substitutions at D168 is indeed possible.

For a patient who fails boceprevir treatment, and this treatment is associated with the enrichment of drug resistant HCV, the clinical impact of NS3/4A protease inhibitor cross-resistance depends on the extent to which boceprevir-resistant HCV variants persist following the cessation of treatment. In the

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absence of continued drug selection pressure, the relative and absolute quantity of drug-resistant HCV variants within the patient's viral population could eventually decline to low or even pre-treatment levels, such that successful re-treatment with an NS3/4A protease inhibitor-containing regimen may be possible. The overall extent of persistence of drug resistant variants in a given patient likely depends on many factors, including the specific treatment-emergent resistance-associated substitutions. The sponsor has conducted observational studies to characterize the persistence of boceprevir resistance-associated substitutions in subjects who failed treatment with boceprevir-containing regimens during clinical development (see Section 4.4.3). Prospective clinical studies would be needed to assess more directly the relationship between the levels of existing boceprevir-resistant HCV populations and virologic responsiveness to re-treatment with a regimen that includes boceprevir or another NS3/4A protease inhibitor.

Cross-resistance is not expected between boceprevir and Peg-IFN $\alpha$ -2a, Peg-IFN $\alpha$ -2b, RBV or other classes of HCV DAAs. In cell culture, the presence of IFN $\alpha$  (presumably IFN $\alpha$ -2b based on its use in other cell culture studies) reduced the selection efficiency of HCV genotype 1b replicons resistant to boceprevir. Furthermore, HCV genotype 1b replicon cells selected to be resistant to boceprevir remained sensitive to IFN $\alpha$ .

### **3. RELEVANT FINDINGS FROM OTHER DISCIPLINES**

#### **3.1 Summary of Efficacy in Phase 3 Boceprevir Trials**

##### Phase 3 Program Overview

The two Phase 3 boceprevir clinical trials were: 1) P05216, conducted in a treatment-naïve population; and 2) P05101, conducted in a previous Peg-IFN $\alpha$ /RBV treatment failure population. Both trials studied boceprevir dosed in combination with Peg-IFN $\alpha$ -2b/RBV. In both trials, the primary endpoint was SVR, defined as undetectable HCV RNA measured 24 weeks after the end of therapy. During the NDA review, DAVP modified the Follow-up Week 24 HCV RNA cutoff for determination of SVR from undetectable to <25 IU/mL (lower limit of assay quantification, LLOQ) for defining SVR.

##### Treatment-Naïve Subjects (P05216)

Clinical trial P05216 was a randomized, double-blind, placebo-controlled Phase 3 trial of treatment-naïve subjects with chronic hepatitis C virus infection (HCV genotype 1). Two separate population cohorts were enrolled: Cohort 1 (non-black subjects), and Cohort 2 (black subjects). For the primary endpoint analysis, Cohorts 1 and 2 were combined. All subjects received the 4-week lead-in treatment period with Peg-IFN $\alpha$ -2b/RBV prior to addition of boceprevir or placebo. The three treatment arms were:

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

The same dose of boceprevir, 800 mg administered orally three times a day, was used in both boceprevir treatment arms. PegIntron<sup>®</sup> was dosed at 1.5  $\mu$ g/kg subcutaneously weekly, and Rebetol<sup>®</sup> was administered as (600 to 1400 mg/day orally) on the basis of weight. In Arm 2 (RGT), all subjects received 24 weeks of boceprevir in combination with Peg-IFN $\alpha$ -2b/RBV (after the 4 week Peg-IFN $\alpha$ -2b/RBV 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

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undetectable at Week 24, boceprevir was stopped and subjects received an additional 20 weeks of Peg-IFN $\alpha$ -2b/RBV and placebo. For subjects in each of the treatment arms, all treatment was discontinued for futility if HCV RNA was detectable at Week 24.

For both boceprevir arms, SVR rates were significantly higher compared to the Peg-IFN $\alpha$ -2b/RBV control arm (Arm 1). SVR rates for Arms 1, 2 and 3 were 38%, 63% and 66%, respectively. 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 Peg-IFN $\alpha$ -2b/RBV control; however, within each cohort SVR was higher in both boceprevir treatment arms than in the Peg-IFN $\alpha$ -2b/RBV control arm. Within the boceprevir treatment arms no differences in SVR rates were observed for gender, age, or location (US vs. non-US sites). SVR rates were higher for subjects with baseline HCV RNA  $\leq$ 800,000 IU/mL compared to those with baseline HCV RNA  $>$ 800,000 IU/mL, in subjects infected with HCV subtype 1b compared to subjects infected with subtype 1a, in subjects with a baseline platelet count  $\geq$ 150,000/ $\mu$ L than those with platelet count  $<$ 150,000/ $\mu$ L, 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).

Previous Treatment-Failure Subjects (P05101)

In P5101, chronic HCV (genotype 1) infected subjects who had previously failed treatment with Peg-IFN $\alpha$ /RBV were enrolled. This study enrolled subjects who would generally be classified as previous partial responders ( $\geq$ 2 log<sub>10</sub> IU/mL decline in HCV 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<sub>10</sub> IU/mL 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<sup>®</sup>) plus ribavirin (Rebetol<sup>®</sup>) 48 weeks control (PR48)
- Arm 2: Boceprevir plus PegIntron<sup>®</sup>/Rebetol<sup>®</sup> response-guided therapy (RGT) (described below)
- Arm 3: Boceprevir plus PegIntron<sup>®</sup>/Rebetol<sup>®</sup> (Boc/PR48)

All subjects received a 4-week lead-in treatment phase with Peg-IFN $\alpha$ -2b/RBV 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 Peg-IFN $\alpha$ -2b/RBV 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, Peg-IFN $\alpha$ -2b, and RBV dosing regimens were the same as those evaluated in P05216.

SVR rates for Arms 1, 2 and 3 were 22.5%, 59.3% and 66.5%, respectively. SVR rates were numerically higher (difference not statistically significant) in Arm 3 than in the RGT arm. The sponsor reported that the difference in response rates between the two boceprevir arms was observed while subjects in each arm were receiving identical therapy prior to Week 36. SVR rates were somewhat lower in blacks than in non-black subjects in the Boc/PR48 arm. Within the boceprevir treatment arms, subjects 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 with higher baseline HCV RNA ( $>$ 800,000 IU/mL), higher Metavir scores (F3 and F4 combined), and HCV subtype 1a, respectively. Arm 1, 2 and 3 SVR rates were 31.4%, 69.5% and 74.8% for prior Peg-IFN $\alpha$ /RBV relapsers, and 6.9%, 40.4% and 51.7 % for prior partial responders, respectively.

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Null Responders and Interferon Responsiveness

The sponsor has proposed that prior Peg-IFN $\alpha$ /RBV null responders not be excluded from the indication even though they were not eligible for enrollment in either phase 3 trial. The sponsor's rationale for this proposal is based on the use of virologic response data during the Peg-IFN $\alpha$ /RBV lead-in period as a surrogate for prior treatment history. Specifically, the sponsor considers a  $<1 \log_{10}$  IU/mL at Treatment Week 4 (end of lead-in period) an indicator of a Peg-IFN $\alpha$ /RBV "null" response. In both Phase 3 trials, the overall SVR rate was lower for subjects who met this criterion of poor virologic response compared to subjects who had a  $>1 \log_{10}$  IU/mL virologic response during the Peg-IFN $\alpha$ /RBV lead-in period. Boceprevir still provided a treatment benefit over placebo (28-38% versus 4% in P05216; 33-34% versus 0% in P05101) for subjects with a  $<1 \log_{10}$  IU/mL HCV RNA decline during the Peg-IFN $\alpha$ /RBV lead-in period.

Note that a formal decision regarding the specific patient populations (with respect to prior treatment history) to be included in the treatment indication for boceprevir had not yet been made at the time of finalization of this review. See Section 1.4 of this review for a more detailed summary of the Virology perspective on this issue.

Further Analyses of Response-guided Therapy

In P05216 the SVR rate was numerically higher in the Boc/PR48 arm (Arm 3) compared to the RGT arm (Arm 2). For early virologic responders, there did not appear to be a difference between shorter (Arm 2) and longer (Arm 3) duration of treatment, indicating that an additional 20 weeks of 3-drug therapy did not increase efficacy in early responders.

In contrast to early virologic responders, there appeared to be a difference in SVR rates for late virologic responders in Arm 2 versus Arm 3. Among late responder subjects in Arm 2, who stopped boceprevir at Week 28 and continued on treatment with Peg-IFN $\alpha$ -2b/RBV to Week 48, SVR rates were numerically ~9% lower than late responders in Arm 3, who remained on boceprevir to Week 48. This difference was not statistically significant, but the trial was not designed to detect differences in this subgroup. The lower SVR rate for late responders in Arm 2 versus Arm 3 appears to be attributed largely to virologic breakthrough while on Peg-IFN $\alpha$ -2b/RBV after stopping boceprevir. Taken together, these results indicate that late virologic responders may benefit from continued boceprevir treatment (in combination with Peg-IFN $\alpha$ -2b/RBV) beyond Week 28. Interestingly, bridging data from P05216 (treatment-naïve trial) with that from P05101 (treatment-experienced trial) indicate that continued dosing of boceprevir plus Peg-IFN $\alpha$ -2b/RBV to Week 36, followed by Peg-IFN $\alpha$ -2b/RBV alone to Week 48, may be an appropriate response-guided therapy approach for both treatment-naïve and treatment-experienced patients who are considered late responders to boceprevir plus Peg-IFN $\alpha$ -2b/RBV.

Note that analyses regarding to the utility and optimal design of a response-guided therapy approach for boceprevir were ongoing at the time of finalization of this review.

For more detailed FDA reviews of boceprevir efficacy please see the reviews by Dr. Wen Zeng, biostatistics reviewer, and Dr. Jeffrey Florian pharmacometrics reviewer.

**3.2 Summary of Safety in Boceprevir Trials**

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. Overall, most of the adverse events reported in these trials have been well-described for Peg-IFN $\alpha$ /RBV therapy.

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The most important safety concern during the clinical development of boceprevir has been the decrease in hemoglobin above and beyond that observed with Peg-IFN $\alpha$ /RBV alone. 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 Peg-IFN $\alpha$ /RBV in a larger population. Dysgeusia (alteration of taste) was a common adverse event reported at an increased frequency in boceprevir-treated subjects as compared to control; however, the majority of dysgeusia events were mild-moderate in intensity and were not treatment-limiting. Gastrointestinal symptoms such as nausea, diarrhea, and vomiting also occurred at a slightly increased frequency in boceprevir-treated subjects compared to control arm subjects.

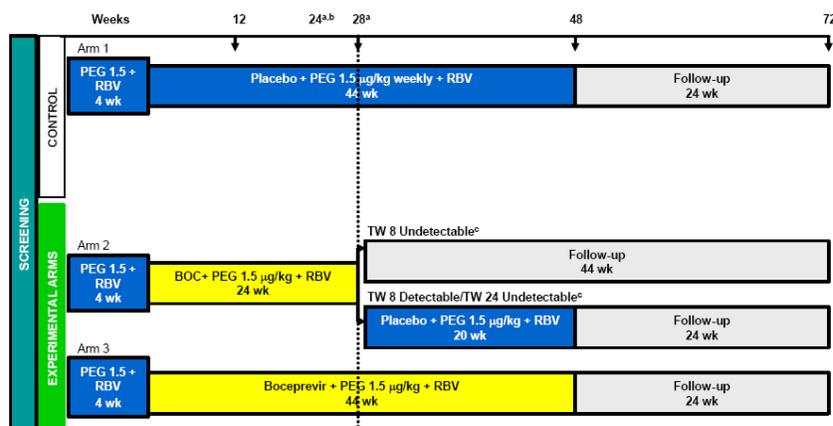
For more detailed FDA reviews of boceprevir safety please see the medical officer reviews of Dr. Poonam Mishra and Dr. Sarah Connelly.

#### 4. CLINICAL VIROLOGY

##### 4.1 Overview of Phase 3 Trial P05216 (SPRINT-2)

##### 4.1.1 Summary of Trial Design and Inclusion Criteria

A schematic of the design for P05216 is shown in Figure 2 (CSR pg. 95). The primary objective of this trial was to compare the efficacy of two therapeutic regimens of boceprevir in combination with Peg-IFN $\alpha$ -2b/RBV versus SOC Peg-IFN $\alpha$ -2b/RBV therapy in treatment-naïve subjects. Eligible subjects were adults, chronically infected with HCV genotype 1, treatment-naïve, and with HCV RNA levels  $\geq 10,000$  IU/mL prior to treatment. Subjects with evidence of co-infection with HIV or hepatitis B virus were excluded from the trial.



PEG + RBV=PEG2b + ribavirin (weight-based dosing [WBD]); BOC=boceprevir 800 mg TID; TW=Treatment Week; wk=weeks.

- <sup>a</sup> Subjects in any arm with detectable HCV-RNA at TW 24 were to be considered treatment failures and were to discontinue treatment and advance to Follow-up no later than the TW 28 visit.
- <sup>b</sup> Subjects in Arm 1 with detectable HCV-RNA at TW 24 were to be eligible to participate in an access trial (P05514) and receive boceprevir + PEG2b 1.5 µg/kg/week +RBV for up to 44 weeks. If they did not participate in the access study, they were to proceed to the follow-up phase of this study.
- <sup>c</sup> See Section 9.4.1 for a complete description of the TW 8 undetectable and TW 8 detectable/TW 24 undetectable rule for Arm 2.

**Figure 2. Study design schematic for clinical trial P05216.**

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The trial enrolled 1,097 study subjects who were randomized 1:1:1 across the three treatment arms illustrated in Figure 2. Study subjects were enrolled as two cohorts: Cohort 1 was comprised of non-black subjects; Cohort 2 was comprised of black subjects. Randomized treatment assignment was stratified based on baseline viral load ( $>400,000$  IU/mL versus  $\leq 400,000$  IU/mL) and on HCV genotype 1 subtype at screening (based on TRUGENE™ assay results). Subjects with HCV genotype 1 infection that could not be classified as subtype 1a or 1b were to be randomly assigned to a treatment arm within their HCV RNA strata.

A Treatment Week 24 detectable HCV RNA futility rule was followed for all arms. Also, subjects with identified virologic breakthrough or incomplete virologic response were to discontinue treatment. During the conduct of the trial, virologic breakthrough was defined as having achieved undetectable HCV RNA and subsequently having an HCV RNA level  $>1,000$  IU/mL while on study treatment. Incomplete virologic response was defined as having a  $\geq 1$   $\log_{10}$  IU/mL increase in HCV RNA from nadir with an HCV RNA level  $>1,000$  IU/mL; however, if the time interval from Peg-IFN $\alpha$ -2b injection to HCV RNA sampling was different for two samples, a  $\geq 2$   $\log_{10}$  IU/mL HCV RNA increase was required to meet the criteria for incomplete virologic response. Note that the  $\geq 2$   $\log_{10}$  IU/mL and  $>1,000$  IU/mL requirements were not used in the sponsor's efficacy analyses related to incomplete virologic response rates. Rather, an "Expert Review" analysis of the data was conducted, defining incomplete virologic response simply as a  $\geq 1$   $\log_{10}$  IU/mL HCR RNA increase from nadir.

The primary efficacy endpoint was SVR, defined as undetectable HCV RNA at Follow-up Week 24. Subjects who failed treatment in Arm 1 (Peg-IFN $\alpha$ -2b/RBV control arm) were offered re-treatment with boceprevir plus Peg-IFN $\alpha$ -2b/RBV in a treatment access protocol (P05514).

#### **4.1.2 Sponsor's Efficacy Summary**

The sponsor's efficacy analysis is shown in Table 3 (CSR pgs. 145-147). According to the sponsor's analysis, subjects who received boceprevir in addition to Peg-IFN $\alpha$ -2b/RBV had an approximately 20-30% improvement in SVR rates over Peg-IFN $\alpha$ -2b/RBV alone, across all cohorts and treatment arms. Please see the review of Dr. Wen Zeng, biostatistics reviewer, for the FDA analysis of efficacy.

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**Table 3. Sponsor's efficacy analysis of Clinical trial P05216.**

	FAS <sup>a</sup>			mITT <sup>a</sup>		
	Control	Experimental		Control	Experimental	
	Arm 1 PR48 <sup>b</sup>	Arm 2 RGT <sup>b</sup>	Arm 3 BOC/PR48 <sup>b</sup>	Arm 1 PR48 <sup>b</sup>	Arm 2 RGT <sup>b</sup>	Arm 3 BOC/PR48 <sup>b</sup>
<b>Cohort 1</b>	n=311	n=316	n=311	n=297	n=303	n=299
<b>Overall Response</b>						
EOT <sup>c</sup> (Undetectable HCV-RNA), n (%)	176 (56.6)	235 (74.4)	241 (77.5)	176 (59.3)	235 (77.6)	241 (80.6)
<b>SVR<sup>d</sup></b> n (%)	125 (40.2)	211 (66.8)	213 (68.5)	125 (42.1)	211 (69.6)	213 (71.2)
Δ SVR	--	26.6	28.3	--	27.5	29.1
95% CI for Δ	--	19.1, 34.1	20.8, 35.8	--	19.9, 35.2	21.5, 36.8
P value <sup>e</sup>	--	<.0001	<.0001	--	<.0001	<.0001
Relapse <sup>f</sup> n/N (%)	37/162 (22.8)	21/232 (9.1)	18/230 (7.8)	37/162 (22.8)	21/232 (9.1)	18/230 (7.8)
<b>SVR by TW 4 Response<sup>g</sup>, n/N (%)</b>						
<1.0-log <sub>10</sub> Decline <sup>h</sup>	3/62 (4.8)	21/73 (28.8)	31/79 (39.2)	3/62 (4.8)	21/72 (29.2)	31/78 (39.7)
≥1.0-log <sub>10</sub> Decline <sup>i</sup>	121/234 (51.7)	187/228 (82.0)	178/218 (81.7)	121/233 (51.9)	187/227 (82.4)	178/215 (82.8)
Missing HCV-RNA	1/15 (6.7)	3/15 (20.0)	4/14 (28.6)	1/2 (50.0)	3/4 (75.0)	4/6 (66.7)
<b>Cohort 2</b>	n=52	n=52	n=55	n=47	n=47	n=55
<b>Overall Response</b>						
EOT <sup>c</sup> (Undetectable HCV-RNA) n (%)	15 (28.8)	26 (50.0)	36 (65.5)	15 (31.9)	26 (55.3)	36 (65.5)
<b>SVR<sup>d</sup></b> n (%)	12 (23.1)	22 (42.3)	29 (52.7)	12 (25.5)	22 (46.8)	29 (52.7)
Δ SVR	--	19.2	29.7	--	21.3	27.2
95% CI for Δ	--	1.6, 36.9	12.2, 47.1	--	2.3, 40.2	9.0, 45.3
P value <sup>e</sup>	--	0.0440	0.0035	--	0.0366	0.0107
Relapse <sup>f</sup> n/N (%)	2/14 (14.3)	3/25 (12.0)	6/35 (17.1)	2/14 (14.3)	3/25 (12.0)	6/35 (17.1)
<b>SVR by TW 4 Response<sup>g</sup>, n/N (%)</b>						
<1.0-log <sub>10</sub> Decline <sup>h</sup>	0/21 (0.0)	6/24 (25.0)	5/16 (31.3)	0/21 (0.0)	6/23 (26.1)	5/16 (31.3)
≥1.0-log <sub>10</sub> Decline <sup>i</sup>	12/26 (46.2)	16/24 (66.7)	22/36 (61.1)	12/26 (46.2)	16/24 (66.7)	22/36 (61.1)
Missing HCV-RNA	0/5 (0.0)	0/4 (0.0)	2/3 (66.7)	0/0	0/0	2/3 (66.7)
<b>Cohort 1 Plus Cohort 2</b>	n=363	n=368	n=366	n=344	n=350	n=354
<b>Overall Response</b>						
EOT <sup>c</sup> (Undetectable HCV-RNA) n (%)	191 (52.6)	261 (70.9)	277 (75.7)	191 (55.5)	261 (74.6)	277 (78.2)
<b>SVR<sup>d</sup></b> n (%)	137 (37.7)	233 (63.3)	242 (66.1)	137 (39.8)	233 (66.6)	242 (68.4)
Δ SVR	--	25.6	28.4	--	26.7	28.5
95% CI for Δ	--	18.6, 32.6	21.4, 35.3	--	19.6, 33.9	21.4, 35.6
P value <sup>e</sup>	--	<.0001	<.0001	--	<.0001	<.0001
Relapse <sup>f</sup> n/N (%)	39/176 (22.2)	24/257 (9.3)	24/265 (9.1)	39/176 (22.2)	24/257 (9.3)	24/265 (9.1)
<b>SVR by TW 4 Response<sup>g</sup>, n/N (%)</b>						
<1.0-log <sub>10</sub> Decline <sup>h</sup>	3/83 (3.6)	27/97 (27.8)	36/95 (37.9)	3/83 (3.6)	27/95 (28.4)	36/94 (38.3)
≥1.0-log <sub>10</sub> Decline <sup>i</sup>	133/260 (51.2)	203/252 (80.6)	200/254 (78.7)	133/259 (51.4)	203/251 (80.9)	200/251 (79.7)
Missing HCV-RNA	1/20 (5.0)	3/19 (15.8)	6/17 (35.3)	1/2 (50.0)	3/4 (75.0)	6/9 (66.7)

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(Footnotes to Table 3)

BOC=boceprevir 800 mg TID; CI=confidence interval; HCV-RNA=hepatitis C virus-ribonucleic acid; NA=not applicable; PEG2b, P=peginterferon alfa-2b 1.5 µg/kg QW; QW=once weekly; RBV, R=ribavirin 800 to 1400 mg/day; RGT=response-guided therapy; SVR=sustained virologic response; TW=Treatment Week.

- <sup>a</sup> Full Analysis Set (FAS)=all randomized subjects who received at least one dose of any study medication (PEG2b, RBV, or boceprevir). Modified Intent-to-Treat Set (mITT)=all randomized subjects who received at least one dose of boceprevir (experimental arms) or placebo (control arm).
- <sup>b</sup> Arm 1 (PR48) = PEG2b + RBV for 48 weeks.  
Arm 2 (RGT) = PR lead-in for 4 weeks, then BOC/PR for 24 weeks (subjects with undetectable HCV-RNA at Treatment Week [TW] 8 and all subsequent assays through TW 24) or BOC/PR for 24 weeks followed by placebo/PR for 20 weeks (subjects with detectable HCV-RNA at TW 8 or any subsequent assay up to TW 24).  
Arm 3 (BOC/PR48) = PR lead-in for 4 weeks, then BOC/PR for 44 weeks.
- <sup>c</sup> Undetectable HCV-RNA at End of Treatment (EOT) regardless of treatment duration.
- <sup>d</sup> SVR: The last available value in the period at or after Follow-up (FW) 24. If there is no such value, the FW 12 value is carried forward. SVR<sub>24</sub> rates (SVR with "missing=failure" approach) were nearly identical. FAS Cohort 1: 39% Control, 66% RGT, 68% BOC/PR48. mITT Cohort 1: 41% Control, 68% RGT, 71% BOC/PR48. FAS Cohort 2: 21% Control, 42% RGT, 51% BOC/PR48. mITT Cohort 2: 23% Control, 47% RGT, 51% BOC/PR48. FAS Cohort 1+Cohort 2: 37% Control, 62% RGT, 65% BOC/PR48. mITT Cohort 1+Cohort 2: 39% Control, 65% RGT, 68% BOC/PR48. Subjects who were missing FW 24 results and had undetectable HCV-RNA at FW 12 included 3, 4, and 3 subjects in the PR48 control, RGT, and BOC/PR48 arms, respectively, in Cohort 1 and 1, 0, and 1 subject, respectively, in Cohort 2. [Section 14.2.1.1.1](#), [Section 14.2.2.1.1](#), [Section 14.2.3.1.1](#).
- <sup>e</sup> vs PR48 control arm. Using the Cochran-Mantel Haenszel Chi-square test adjusted for baseline stratification factors: viral load (>400,000 vs. ≤400,000 IU/mL) and Genotype (1a vs 1b). In addition, cohort (race: Black vs. Non-Black) was also adjusted in the test for combined cohorts. See [Section 14.2.1.1.4](#), [Section 14.2.2.1.4](#), and [Section 14.2.3.1.4](#) for stratum-adjusted differences.
- <sup>f</sup> Relapse rate was the proportion of subjects with undetectable HCV-RNA at End of Treatment (EOT) and detectable HCV-RNA at End of Follow-up (EOF) among subjects who were undetectable at EOT and not missing EOF data.
- <sup>g</sup> After 4-week PR lead-in (lead-in response).
- <sup>h</sup> Poorly interferon responsive: <1.0-log<sub>10</sub> decline in HCV-RNA at TW 4 from baseline.
- <sup>i</sup> Interferon responsive: ≥1.0-log<sub>10</sub> decline in HCV-RNA at TW 4 from baseline. Subjects with undetectable HCV-RNA at TW 4 are also included.

#### **4.1.3 Overview of Non-Virologic-Failure-Censored Population**

##### P05216 Clinical Virology and Resistance Datasets Analyzed

Two resistance datasets for clinical trial P05216 were included in the NDA: one for HCV genotype 1a-infected subjects, and one for HCV genotype 1b-infected subjects. For the purposes of organizing the resistance datasets, HCV genotype 1 subtype was based on the secondary NS3/4A RT-PCR amplification/NS5B phylogenetic analysis approach (see Section 1.2). The datasets included full-length NS3/4A amino acid sequence data for baseline/pre-treatment and numerous on-treatment and follow-up samples. The NS3/4A amino acid sequence data were reported using subtype-specific reference HCV strains: H77 for subtype 1a, and Con1 for subtype 1b.

Of the 1,097 subjects included in the sponsor's intent-to-treat (ITT) population, data from a total of 725 subjects were included in the genotype 1a resistance dataset, and data from 362 enrolled subjects were included in the genotype 1b dataset.

Data for 10 subjects in the ITT population were not included in either dataset (listing in Appendix A). Four of the 10 subjects not included in the P05216 resistance datasets were determined to be infected with HCV genotype 6 based on NS5B phylogenetic analysis, and all 4 subjects achieved SVR (see Summary of SVR Outcome Data below). The other 6 subjects did not have available HCV genotype/subtype data based on the secondary NS3/4A RT-PCR amplification/NS5B phylogenetic analysis approach, and only 1 subject (002244) had available post-baseline samples with HCV RNA levels that were considered adequate (>1,000 IU/mL) for RT-PCR amplification. According to the sponsor, nucleotide sequence data for all tested samples from these 6 subjects did not meet <sup>(b) (4)</sup> quality control standards, and therefore could not be analyzed and were not included in the resistance datasets.

##### Creation of Non-Virologic-Failure-Censored Resistance Datasets

An as-treated, non-virologic-failure-censored (non-VF-censored) dataset was constructed from each of the two subtype-specific resistance datasets. The primary purpose of creating the non-VF-censored datasets was to enhance the sensitivity of detecting baseline or treatment-emergent amino

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acid substitutions associated with boceprevir treatment failure by not including subjects who failed in an ITT SVR analysis apparently for reasons other than virologic failure. Examples of non-VF reasons for failing an ITT SVR analysis include treatment discontinuation due to an adverse event, subject withdrawal from study, and loss of follow-up. To construct the non-VF-censored datasets, individual subject virologic responses and sponsor-defined reasons for treatment discontinuation or non-response were analyzed to identify ITT SVR failure subjects who were clearly responding virologically to treatment, and thus were considered to have failed in the ITT SVR analysis for reasons other than true virologic failure.

Specifically, subjects were censored from the resistance datasets based on the following criteria:

- Discontinued treatment early, with <6 weeks total treatment duration (i.e., <2 weeks of boceprevir)
- Discontinued treatment early for reasons other than poor virologic response, with undetectable HCV RNA at last on-treatment timepoint closest to time of treatment discontinuation
- Discontinued treatment early for reasons other than poor virologic response, had not yet achieved undetectable HCV RNA, but viral RNA levels clearly on a downward trend for all available sample time points through time of treatment discontinuation
- Undetectable HCV viral RNA at end-of-treatment (EOT), but inadequate follow-up data available to determine whether a subject achieved SVR or experienced virologic relapse

Appendix B includes a complete listing of subjects removed from the sponsor’s original datasets to assemble the non-VF-censored datasets, along with brief summaries of virologic responses for each censored subject.

Summary of Non-Virologic-Failure-Censored Resistance Datasets

For the genotype 1a and 1b datasets, 16.6% (120/725) and 14.1% (51/362) were censored, respectively. Among boceprevir-treated subjects in the non-VF-censored datasets, 3.2% of subjects did not have appropriate data available to analyze the relationship between baseline HCV NS3/4A sequence and treatment outcome, and 3.9% of non-SVR subjects did not have appropriate data available for a treatment-emergent resistance analysis (Table 4). The lack of adequate data for this small number of subjects is unlikely to influence the overall conclusions of the resistance analyses.

**Table 4. Subjects in P05216 non-VF-censored resistance datasets without appropriate data to conduct baseline or treatment-emergent resistance analyses, boceprevir arms only.**

	<b>Data Not Available for Baseline Analysis</b>	<b>Data Not Available for Treatment-Emergent Analysis</b>
<b>Genotype 1a</b>	4.4% (18/410)	5.1% (6/117)
<b>Genotype 1b</b>	1.0% (2/208)	0% (0/37)
<b>All Subjects</b>	3.2% (20/618)	3.9% (6/154)

To identify treatment-emergent NS3/4A amino acid substitutions associated with boceprevir/Peg-IFN $\alpha$ -2b/RBV treatment failure, post-baseline clinical specimens used in these analyses ideally would have been obtained during drug treatment or within a few days after stopping treatment. An extended period of time after removal of drug pressure theoretically could result in the outgrowth of “wild-type” HCV variants that are relatively more fit than drug-resistant variants. Because population-based nucleotide sequence analyses typically cannot detect viral populations that comprise <25% of the total population, sequence analyses of samples obtained at later treatment-free follow-up timepoints may fail to detect drug-resistant variants that may have predominated at times of drug pressure.

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Importantly, such variants may still exist in the mixed viral population at an abundance that is orders of magnitude above that which existed prior to treatment, despite not being detected by population-based sequence analyses.

As an initial step in conducting an independent analysis of boceprevir treatment-emergent NS3/4A amino acid substitutions, resistance datasets from boceprevir-treated subjects who did not achieve SVR were constructed such that each subject had a single NS3/4A sequence from a baseline or other pre-treatment timepoint, and a single NS3/4A sequence at a post-baseline timepoint. For subjects who had multiple available post-baseline NS3/4A sequences, the following order of precedence was used to select the single post-baseline sample timepoint for initial comparison with the baseline sample data: (1) sample obtained within 1 week of stopping treatment due to virologic failure, (2) last available on-treatment sample obtained on or after Week 8 (Note that Week 8 analysis was specified in the protocol for subjects with HCV RNA levels >1,000 IU/mL), and (3) first available post-treatment follow-up sample. This approach in choosing a single post-baseline sample for analysis was designed for optimal sensitivity in detecting amino acid substitutions associated with boceprevir treatment failure. Subsequent treatment-emergent resistance analyses were conducted considering all available post-baseline NS3/4A sequence data.

In this reviewer's opinion, the timing of samples analyzed by the sponsor in clinical trial P05216 for the purposes of identifying boceprevir treatment-emergent NS3/4A amino acid substitutions was adequate. Table 5 summarizes the timing of post-baseline samples used by this reviewer for initial identification of boceprevir treatment-emergent substitutions. For 32% (48/148) of subjects, the 'optimal' post-baseline sample for analysis was obtained at least 4 weeks after the end-of treatment, a timepoint which may not be ideal for detection of treatment-emergent substitutions. However, for 41/48 (85%) of the subjects this sample timing could be explained by the fact that subjects were either treatment relapsers, or were non-relapse virologic failures but their on-treatment (Week ≥8) HCV RNA levels were not adequate for analysis.

**Table 5. Timing of clinical trial P05216 post-baseline samples used for initial identification of boceprevir treatment-emergent NS3/4A amino acid substitutions.**

Subjects in boceprevir arms only. Note that for simplicity EOT (end-of-treatment) was based on all protocol treatment; i.e., a subset of subjects in the response-guided therapy arm was only being treated with Peg-IFNα-2b/RBV at the time of EOT per protocol.

	n	≥4 Weeks prior to EOT	<4 Weeks prior to EOT	EOT to <4 Weeks post-EOT	≥4 Weeks post-EOT
<b>Genotype 1a</b>	111	34	22	22	33
<b>Genotype 1b</b>	37	11	6	5	15
<b>All Subjects</b>	148	45	28	27	48

Summary of SVR Outcome Data for Non-VF-Censored Population

Rates of SVR, defined as undetectable HCV RNA at Follow-up Week 24, are summarized in Table 6. Pooled subjects in boceprevir-containing arms had an ~30% higher SVR rate compared to the Peg-IFNα-2b/RBV control arm. Also, SVR rates were ~10% higher in HCV genotype 1b-infected subjects relative to HCV genotype 1a-infected subjects. Note that SVR data presented here are based on the sponsor's SVR determination. For the FDA analysis of efficacy, please see the review by Dr. Wen Zeng, Biostatistics Reviewer.

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**Table 6. Summary of SVR rates for subjects included in P05216 non-VF-censored resistance datasets.** P/R, Peg-IFN $\alpha$ -2b/RBV (Arm 1); B/P/R-RGT, Boceprevir + Peg-IFN $\alpha$ -2b/RBV response-guided therapy (Arm 2); B/P/R-48, Boceprevir + Peg-IFN $\alpha$ -2b/RBV for 48 Weeks (Arm 3).

	P/R	B/P/R-RGT	B/P/R-48	Boceprevir Arms
<b>Genotype 1a</b>	42.1% (82/195)	69.5% (141/203)	73.4% (152/207)	71.5% (293/410)
<b>Genotype 1b</b>	45.6% (47/103)	81.9% (86/105)	82.5% (85/103)	82.2% (171/208)
<b>All Subjects</b>	43.3% (129/298)	73.7% (227/308)	76.5% (237/310)	75.1% (464/618)

Four of the 10 subjects not included in the P05216 resistance datasets were determined to be infected with HCV genotype 6 based on NS5B phylogenetic analysis. Two (2) of the genotype 6-infected subjects were in the Peg-IFN $\alpha$ -2b/RBV control arm, 2 were in boceprevir arms, and all 4 achieved SVR. For the 2 subjects in the boceprevir arms, HCV RNA declines at the end of the Peg-IFN $\alpha$ -2b/RBV lead-in phase (i.e., Week 4) were 3.06 log<sub>10</sub> IU/mL and 5.9 log<sub>10</sub> IU/mL, indicating that these 2 subjects were also responding favorably to Peg-IFN $\alpha$ -2b/RBV alone. Therefore, a boceprevir efficacy benefit for subjects infected with HCV genotype 6 cannot be inferred based on these limited data.

Analysis of follow-up period viral load ‘blips’

In the telaprevir NDA it was observed that a significant proportion of subjects who were apparently treated successfully in one or more telaprevir clinical trials had measurements of detectable, low level HCV RNA in plasma samples obtained at post-treatment follow-up timepoints, followed by measurements of undetectable HCV RNA. In most cases the levels of detectable HCV RNA were so low they were below the lower limit of assay quantification. For some subjects these viral load ‘blips’, despite having no apparent clinical relevance, could lead to the conclusion that SVR was not achieved based on the standard SVR definition: *undetectable* HCV RNA 24 weeks following therapy. Conceptually, one would expect that in the absence of any drug pressure to inhibit viral replication, an observed low level of detectable HCV RNA would be followed by a further increase in HCV RNA levels over time, up to a given set point that is several orders of magnitude above the viral load assay detection limit. Therefore, these transient viral load ‘blips’ during the follow-up period could represent false positive results, the circulation of non-infectious HCV RNA, or the circulation of infectious HCV that is subsequently controlled by the patient.

An analysis was conducted to explore the frequency of follow-up viral load ‘blips’ in P05216. For this analysis, a subject was classified as having a follow-up viral load ‘blip’ if there was at least 1 measurement of detectable HCV RNA during the treatment-free follow-up period, which was followed by a measurement of undetectable HCV RNA at a subsequent follow-up timepoint. Twelve (12) such subjects were identified in P05216, out of a total of 427 subjects (2.8%) with detectable HCV RNA at any follow-up timepoint, or 12 out of 1,041 subjects (1.2%) with any available follow-up HCV RNA data. Of these 12 subjects, only 3 had the transient detectable HCV RNA measurement at the Follow-up Week 24 timepoint that was used to assess SVR. Also, for 10 of the 12 subjects, the viral load ‘blip’ sample timepoint was analyzed in triplicate, with two of the measurements demonstrating undetectable HCV RNA, and only one measurement of detectable HCV RNA that was below or near the lower limit of assay quantification.

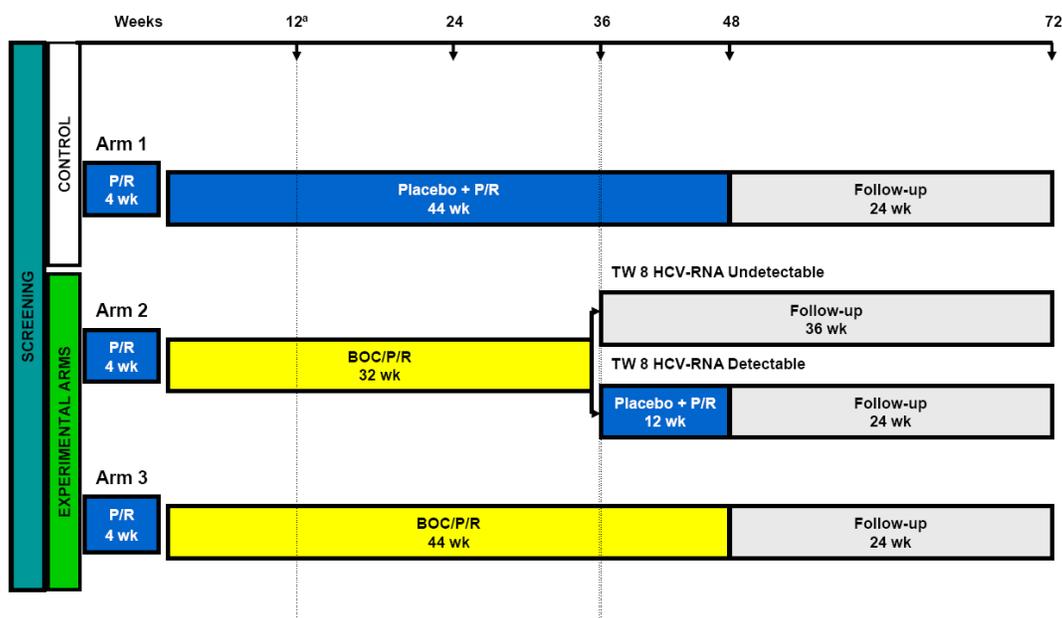
Taken together, follow-up viral load ‘blips’ in P05216 were rare, and in all but 2 cases could be ruled out by reanalysis of the ‘blip’ timepoint sample. Note that follow-up viral load ‘blips’ in clinical trial P05101 were similarly rare (data not shown).

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**4.2 Overview of Phase 3 Trial P05101 (RESPOND-2)**

**4.2.1 Summary of Trial Design and Inclusion Criteria**

A schematic of the design for P05101 is shown in Figure 3 (CSR pg. 81). The primary objective of this trial was to compare the efficacy of two therapeutic regimens of boceprevir in combination with Peg-IFN $\alpha$ -2b/RBV versus SOC Peg-IFN $\alpha$ -2b/RBV therapy, in subjects who previously failed treatment with Peg-IFN $\alpha$ /RBV. Eligible subjects were adults, chronically infected with HCV genotype 1, and failed to achieve SVR with a previous Peg-IFN $\alpha$ /RBV regimen. Subjects must have demonstrated interferon responsiveness to prior therapy based on having a  $\geq 2 \log_{10}$  IU/mL HCV RNA decrease by Week 12 (i.e., partial responders), or undetectable HCV RNA at the end of treatment (i.e., relapsers). Prior Peg-IFN $\alpha$ /RBV null responders, defined as having achieved a  $< 2 \log_{10}$  IU/mL HCV RNA decrease by Week 12 of prior Peg-IFN $\alpha$ /RBV therapy, were not eligible for enrollment into this trial. Subjects with evidence of co-infection with HIV or hepatitis B virus were excluded from the trial.



<sup>a</sup> Subjects in any treatment arm with detectable HCV-RNA at TW 12 were to be considered treatment failures. Subjects in Arm 1 with detectable HCV-RNA at TW 12 were eligible to participate in study P05514 and receive BOC/PR for up to 44 weeks. If they did not participate in study P05514, they were to proceed to the follow-up phase of this study. Subjects in Arms 2 and 3 were to proceed directly to the follow-up phase of this study. Sites and subjects were to remain blinded as to whether subjects had been in Arms 2 or 3.

**Figure 3. Study design schematic for clinical trial P05101.**

The trial enrolled 404 study subjects, of whom 403 received at least one dose of study medication. Subjects were randomized 1:2:2 across the three treatment arms illustrated in Figure 3. Randomized treatment assignment was stratified based on HCV genotype 1 subtype at screening (based on TRUGENE™ assay results), and also based on response to previous qualifying treatment regimen: relapser versus “nonresponder” (the sponsor’s use of “nonresponder” is more accurately described as “partial responder”).

A Treatment Week 12 detectable HCV RNA futility rule was followed for all arms. Also, subjects with identified virologic breakthrough or incomplete virologic response were to discontinue treatment. As in P05216, during the conduct of P05101 virologic breakthrough was defined as having achieved

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undetectable HCV RNA and subsequently having an HCV RNA level >1,000 IU/mL while on study treatment. Incomplete virologic response was defined as having a  $\geq 1 \log_{10}$  IU/mL increase in HCV RNA from nadir with an HCV RNA level >1,000 IU/mL; however, if the time interval from Peg-IFN $\alpha$ -2b injection to HCV RNA sampling was different for two samples, a  $\geq 2 \log_{10}$  IU/mL HCV RNA increase was required to meet the criteria for incomplete virologic response. Note that this  $\geq 2 \log_{10}$  IU/mL and >1,000 IU/mL requirements were not used in the sponsor's efficacy analyses related to incomplete virologic response rates. Rather, an "Expert Review" analysis of the data was conducted, defining incomplete response simply as a  $\geq 1 \log_{10}$  IU/mL HCV RNA increase from nadir.

The primary efficacy endpoint was SVR, defined as undetectable HCV RNA at Follow-up Week 24. Subjects who failed treatment in Arm 1 (Peg-IFN $\alpha$ -2b/RBV control arm) were offered re-treatment with boceprevir plus Peg-IFN $\alpha$ -2b/RBV in a treatment access protocol (P05514).

**4.2.2 Sponsor's Efficacy Summary**

The sponsor's efficacy analysis is shown in Table 7 (CSR pgs. 121-123). According to the sponsor's analysis, subjects who received boceprevir in addition to Peg-IFN $\alpha$ -2b/RBV had an approximately 35-45% improvement in SVR rates over Peg-IFN $\alpha$ -2b/RBV alone, across both boceprevir treatment arms. Please see the review of Dr. Wen Zeng, Biostatistics Reviewer, for the FDA analysis of efficacy.

**Table 7. Sponsor's efficacy analysis of clinical trial P05101.**

	FAS <sup>a</sup>			mITT <sup>a</sup>		
	Control	Experimental		Control	Experimental	
	Arm 1 PR48 <sup>b</sup> n=80	Arm 2 RG1 <sup>b</sup> n=162	Arm 3 BOC/PR48 <sup>b</sup> n=161	Arm 1 PR48 <sup>b</sup> n=78	Arm 2 RG1 <sup>b</sup> n=156	Arm 3 BOC/PR48 <sup>b</sup> n=160
<b>Overall Response</b>						
EOT (Undetectable HCV-RNA), n (%)	25 (31.3)	114 (70.4)	124 (77.0)	25 (32.1)	114 (73.1)	124 (77.5)
SVR <sup>c</sup> , n (%)	17 (21.3)	95 (58.6)	107 (66.5)	17 (21.8)	95 (60.9)	107 (66.9)
$\Delta$ SVR <sup>d, e</sup>	--	37.4	45.2	--	39.1	45.1
95% CI for $\Delta$	--	(25.7, 49.1)	(33.7, 56.8)	--	(27.2, 51.0)	(33.4, 56.8)
P value <sup>d</sup>	--	<0.0001	<0.0001	--	<0.0001	<0.0001
Relapse <sup>f</sup> , n/N (%)	8/25 (32.0)	17/111 (15.3)	14/121 (11.6)	8/25 (32.0)	17/111 (15.3)	14/121 (11.6)
<b>EOT, SVR, and Relapse by Previous Treatment Response, n/N (%)</b>						
EOT (Undetectable HCV-RNA)						
Previous Nonresponder	3/29 (10.3)	31/57 (54.4)	35/58 (60.3)	3/29 (10.3)	31/54 (57.4)	35/57 (61.4)
Previous Relapser <sup>g</sup>	22/51 (43.1)	83/105 (79.0)	89/103 (86.4)	22/49 (44.9)	83/102 (81.4)	89/103 (86.4)
SVR						
Previous Nonresponder	2/29 (6.9)	23/57 (40.4)	30/58 (51.7)	2/29 (6.9)	23/54 (42.6)	30/57 (52.6)
Previous Relapser <sup>g</sup>	15/51 (29.4)	72/105 (68.6)	77/103 (74.8)	15/49 (30.6)	72/102 (70.6)	77/103 (74.8)
Relapse <sup>f</sup>						
Previous Nonresponder	1/3 (33.3)	5/28 (17.9)	5/35 (14.3)	1/3 (33.3)	5/28 (17.9)	5/35 (14.3)
Previous Relapser <sup>g</sup>	7/22 (31.8)	12/83 (14.5)	9/86 (10.5)	7/22 (31.8)	12/83 (14.5)	9/86 (10.5)
<b>SVR by TW 4 Response, n/N (%)</b>						
SVR <sup>h</sup>						
<1.0 $\log_{10}$ Decline <sup>i</sup>	0/12 (0.0)	15/46 (32.6)	15/44 (34.1)	0/12 (0.0)	15/46 (32.6)	15/44 (34.1)
$\geq 1.0 \log_{10}$ Decline <sup>j</sup>	17/67 (25.4)	80/110 (72.7)	90/114 (78.9)	17/66 (25.8)	80/110 (72.7)	90/114 (78.9)
Missing	0/1 (0.0)	0/6 (0.0)	2/3 (66.7)	0/0	0/0	2/2 (100.0)
<b>SVR by TW 8 Response, n/N (%)</b>						
SVR <sup>k</sup>						
Undetectable HCV-RNA	7/7 (100)	64/74 (86.5)	74/84 (88.1)	7/7 (100)	64/74 (86.5)	74/84 (88.1)
Detectable HCV-RNA	8/65 (12.3)	29/72 (40.3)	30/70 (42.9)	8/65 (12.3)	29/72 (40.3)	30/70 (42.9)
Missing	2/8 (25.0)	2/16 (12.5)	3/7 (42.9)	2/6 (33.3)	2/10 (20.0)	3/6 (50.0)

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**(Footnotes to Table 7)**

BOC = boceprevir 800 mg TID; BOC/PR = boceprevir + PEG2b + RBV; CI = confidence interval; FAS = Full Analysis Set; HCV-RNA = hepatitis C virus-ribonucleic acid; mITT = Modified Intent to Treat data set; PEG2b = peginterferon alfa-2b 1.5 µg/kg QW; PR = PEG2b + RBV; QW = once weekly; RBV = ribavirin 600 mg to 1400 mg/day; RGT = response-guided therapy; SVR = sustained virologic response; TID = three times daily.

- <sup>a</sup> FAS = all randomized subjects who received at least one dose of any study medication (PEG2b, RBV, or boceprevir/placebo). mITT = all randomized subjects who received at least one dose of boceprevir (experimental arms) or placebo (control arm).
- <sup>b</sup> Arm 1 (PR48) = PEG2b + RBV for 48 weeks.  
Arm 2 (RGT) = PR lead-in for 4 weeks, then BOC/PR for 32 weeks (if undetectable HCV-RNA at TW 8) or BOC/PR for 32 weeks followed by placebo/PR for 12 weeks (if detectable HCV-RNA at TW 8).  
Arm 3 (BOC/PR48) = PR lead-in for 4 weeks, then BOC/PR for 44 weeks.
- <sup>c</sup> SVR: The last available value in the period at or after FW 24. If there is no such value, the FW 12 value was carried forward. SVR<sub>24</sub> rates (SVR with "missing=failure" approach) were nearly identical (FAS: 17/80 [21.3%] Control, 94/162 [58.0%] RGT, 106/161 [65.8%] BOC/PR48, and mITT: 17/78 [21.8%] Control, 94/156 [60.3%] RGT, and 106/160 [66.3%] BOC/PR48) (Section 14.2.1.1).
- <sup>d</sup> Versus PR control arm. P values were calculated using the two-sided Cochran-Mantel Haenszel (CMH) Chi-square test adjusted for the baseline stratification factors: previous treatment response (nonresponder vs relapser) and genotype (1a vs 1b).
- <sup>e</sup> Adjusted treatment differences (95% CI) in Mantel-Haenszel proportions adjusted for baseline stratification factors (previous treatment response [nonresponder vs relapser] and genotype [1a vs 1b]) were: 37.3 (25.5, 49.0) for RGT vs Control, and 44.7 (33.0, 56.4) for BOC/PR48 vs Control, which were nearly identical to the unadjusted ΔSVR values presented in the table. (See Section 14.2.1.5).
- <sup>f</sup> Relapse rate was the proportion of subjects with undetectable HCV-RNA at End of Treatment (EOT) and detectable HCV-RNA at End of Follow-up (EOF) among subjects with undetectable HCV-RNA at EOT and not missing EOF data.
- <sup>g</sup> After 4-week PR lead-in (lead-in response).
- <sup>h</sup> EOT in subjects with <1.0 log<sub>10</sub> decrease in HCV-RNA at TW 4 (FAS): 0% (0/12) Control, 41% (19/46) RGT, 48% (21/44) BOC/PR48 (same results in mITT); EOT in subjects with ≥1.0 log<sub>10</sub> decrease in HCV-RNA at TW 4 (FAS): 37% (25/67) Control, 86% (95/110) RGT, 89% (101/114) BOC/PR48 (mITT: 38% [25/66] Control, 86% [95/110] RGT, 89% [101/114] BOC/PR48); EOT in subjects missing TW 4 response (FAS): 0% (0/1) Control, 0% (0/6) RGT, 67% (2/3) BOC/PR48 (mITT: 0% [0/0] Control, 0% [0/0] RGT, 100% [2/2] BOC/PR48) (Section 14.2.8.37). Relapse in subjects with <1.0 log<sub>10</sub> decrease in HCV-RNA at TW 4 (FAS and mITT): 0% (0/0) Control, 12% (2/17) RGT, 25% (5/20) BOC/PR48; relapse in subjects with ≥1.0 log<sub>10</sub> decrease in HCV-RNA at TW 4 (FAS and mITT): 32% (8/25) Control, 16% (15/94) RGT, 9% (9/99) BOC/PR48. Two subjects in the BOC/PR48 arm were missing relapse by TW 4 response data (Section 14.2.8.38).
- <sup>i</sup> Poorly interferon responsive: <1.0 log<sub>10</sub> decline in HCV-RNA at TW 4 from baseline.
- <sup>j</sup> Interferon responsive: ≥1.0 log<sub>10</sub> decline in HCV-RNA at TW 4 from baseline. Subjects with undetectable HCV-RNA at TW 4 are also included.
- <sup>k</sup> After 4 weeks of BOC/placebo added to PR backbone.
- Source Data: Section 14.2.1.1, Section 14.2.1.3, Section 14.2.6.1, Section 14.2.4.1, Section 14.2.8.21, Section 14.2.8.22, Section 14.2.8.15, and Section 14.2.4.2.

### **4.2.3 Overview of Non-Virologic-Failure-Censored Population**

#### **P05101 Clinical Virology and Resistance Datasets Analyzed**

As in the case of P05216, two resistance datasets for clinical trial P05101 were included in the NDA: one for HCV genotype 1a-infected subjects, and one for HCV genotype 1b-infected subjects. For the purposes of organizing the resistance datasets, HCV genotype 1 subtype was based on the secondary NS3/4A RT-PCR amplification/NS5B phylogenetic analysis approach (see Section 1.2). The datasets included full-length NS3/4A amino acid sequence data for baseline/pre-treatment and numerous on-treatment and follow-up samples. The NS3/4A amino acid sequence data were reported using subtype-specific reference HCV strains: H77 for subtype 1a, and Con1 for subtype 1b.

Of the 403 subjects included in the ITT population, data from a total of 241 subjects were included in the genotype 1a resistance dataset, and data from 161 enrolled subjects were included in the genotype 1b dataset. One subject not included in the datasets (011052) was determined to be infected with HCV genotype 6 (Appendix A).

#### **Creation of Non-Virologic-Failure-Censored Resistance Datasets**

As described above for clinical trial P051216, an as-treated, non-VF-censored dataset was constructed from each of the two subtype-specific resistance datasets. The primary purpose of creating the non-VF-censored datasets was to enhance the sensitivity of detecting baseline or treatment-emergent amino acid substitutions associated with boceprevir treatment failure, by not including subjects who failed in an ITT SVR analysis apparently for reasons other than virologic failure. Examples of non-VF reasons for failing an ITT SVR analysis include treatment discontinuation due to an adverse event, subject withdrawal from study, and loss of follow-up. To construct the non-VF-censored datasets, individual subject virologic responses and sponsor-defined reasons for treatment discontinuation or non-response were analyzed to identify ITT SVR failure subjects who were clearly responding virologically to treatment, and thus were considered to have failed in the ITT SVR analysis for reasons other than true virologic failure.

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Specifically, subjects were censored from the resistance datasets based on the following criteria:

- Discontinued treatment early, with <6 weeks total treatment duration (i.e., <2 weeks of boceprevir)
- Discontinued treatment early for reasons other than poor virologic response, with undetectable HCV RNA at last on-treatment timepoint closest to time of treatment discontinuation
- Discontinued treatment early for reasons other than poor virologic response, had not yet achieved undetectable HCV RNA, but viral RNA levels clearly on a downward trend for all available sample time points through time of treatment discontinuation
- Undetectable HCV viral RNA at EOT, but inadequate follow-up data available to determine whether a subject achieved SVR or experienced virologic relapse

Appendix B includes a complete listing of subjects removed from the sponsor’s original datasets to assemble the non-VF-censored datasets, along with brief summaries of virologic responses for each censored subject.

Summary of Non-Virologic-Failure-Censored Resistance Datasets

For the genotype 1a and 1b datasets, 9.5% (23/241) and 10% (16/161) were censored, respectively. Among boceprevir-treated subjects in the non-VF-censored datasets, 2.4% of subjects did not have appropriate data available to analyze the relationship between baseline HCV NS3/4A sequence and treatment outcome, and 9.8% of non-SVR subjects did not have appropriate data available for a treatment-emergent resistance analysis (Table 8). The lack of adequate data for this small number of subjects is unlikely to influence the overall conclusions of the resistance analyses.

**Table 8. Subjects in P05101 non-VF-censored resistance datasets without appropriate data to conduct baseline or treatment-emergent resistance analyses, boceprevir arms.**

	<b>Data Not Available for Baseline Analysis</b>	<b>Data Not Available for Treatment-Emergent Analysis</b>
<b>Genotype 1a</b>	4.0% (7/176)	11.1% (7/63)
<b>Genotype 1b</b>	0% (0/115)	6.9% (2/29)
<b>All Subjects</b>	2.4% (7/291)	9.8% (9/92)

As an initial step in conducting an independent analysis of boceprevir treatment-emergent NS3/4A amino acid substitutions, resistance datasets from boceprevir-treated subjects who did not achieve SVR were constructed such that each subject had a single NS3/4A sequence from a baseline or other pre-treatment timepoint, and a single NS3/4A sequence at a post-baseline timepoint (as conducted for P05216). For subjects who had multiple available post-baseline NS3/4A sequences, the following order of precedence was used to select the single post-baseline sample timepoint for initial comparison with the baseline sample data: (1) sample obtained within 1 week of stopping treatment due to virologic failure, (2) last available on-treatment sample obtained on or after Week 8 (Note that Week 8 analysis was specified in the protocol for subjects with HCV RNA levels >1,000 IU/mL), and (3) first available post-treatment follow-up sample. This approach in choosing a single post-baseline sample for analysis was designed for optimal sensitivity in detecting amino acid substitutions associated with boceprevir treatment failure. Subsequent treatment-emergent resistance analyses were conducted considering all available post-baseline NS3/4A sequence data.

In this reviewer’s opinion, the timing of samples analyzed by the sponsor in clinical trial P05101 for the purposes of identifying boceprevir treatment-emergent NS3/4A amino acid substitutions was adequate. Table 9 summarizes the timing of post-baseline samples used by this reviewer for initial

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identification of boceprevir treatment-emergent substitutions. For 49% (41/83) of subjects, the ‘optimal’ post-baseline sample for analysis was obtained at least 4 weeks after the end-of treatment, a timepoint which may not be ideal for detection of treatment-emergent substitutions. However, for all but 1 of the subjects this sample timing could be explained by the fact that subjects were either treatment relapsers, or were non-relapse virologic failures but their on-treatment (Week ≥8) HCV RNA levels were not adequate for analysis.

**Table 9. Timing of clinical trial P05101 post-baseline samples used for identification of boceprevir treatment-emergent NS3/4A amino acid substitutions.** Subjects in boceprevir arms only. Note that for simplicity EOT (end-of-treatment) was based on all protocol treatment; i.e., a subset of subjects in the response-guided therapy arm was only being treated with Peg-IFNα-2b/RBV at the time of EOT per protocol.

	n	≥4 Weeks prior to EOT	<4 Weeks prior to EOT	EOT to <4 Weeks post-EOT	≥4 Weeks post-EOT
<b>Genotype 1a</b>	56	10	8	12	26
<b>Genotype 1b</b>	27	4	4	4	15
<b>All Subjects</b>	83	14	12	16	41

Summary of SVR Outcome Data for Non-VF-Censored Population

Rates of SVR, defined as undetectable HCV RNA at Follow-up Week 24, are summarized in Table 10. Pooled subjects in boceprevir-containing arms had a ~45% higher SVR rate compared to the Peg-IFNα-2b/RBV control arm. Also, SVR rates were ~10% higher in HCV genotype 1b-infected subjects relative to HCV genotype 1a-infected subjects. Note that SVR data presented here are based on the sponsor’s SVR determination. For the FDA analysis of efficacy, see the review by Dr. Wen Zeng, Biostatistics Reviewer.

**Table 10. Summary of SVR rates for P05101 non-VF-censored subjects in resistance datasets.** P/R, Peg-IFNα-2b/RBV (Arm 1); B/P/R-RGT, Boceprevir + Peg-IFNα-2b/RBV response-guided therapy (Arm 2); B/P/R-48, Boceprevir + Peg-IFNα-2b/RBV for 48 Weeks (Arm 3).

	P/R	B/P/R-RGT	B/P/R-48	Boceprevir Arms
<b>Genotype 1a</b>	26.2% (11/42)	58.8% (50/85)	69.2% (63/91)	64.2% (113/176)
<b>Genotype 1b</b>	20% (6/30)	73.3% (44/60)	76.4% (42/55)	74.8% (86/115)
<b>All Subjects</b>	23.6% (17/72)	64.8% (94/145)	71.9% (105/146)	68.4% (199/291)

**4.3 Pooled Resistance Analysis of Boceprevir Phase 3 Trials**

When reading the following summaries of resistance analyses it is important to be aware that mathematical modeling studies of HCV population dynamics predict that viral subpopulations harboring nearly all combinations of single- and double-nucleotide substitutions are generated everyday in HCV-infected subjects (as described above in Section 1.4). Based on these predictions, it should be assumed that nearly every amino acid substitution possible in the HCV genome is present in at least a small minority of circulating HCV variants within a given subject, even prior to any drug exposure. Therefore, for the purposes of this review, the “presence” or “detection” of an HCV amino acid substitution in a clinical specimen by population nucleotide sequence analysis implies that the substitution was highly enriched in the patient’s mixed HCV population. Conversely, because population-based sequence analyses typically cannot detect minority populations that contribute <25% of the total population, the absence or lack of detection of a given substitution does not

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necessarily mean it does not exist in the subject. Rather, the substitution may be present but at a level below the limit of detection by population-based nucleotide sequence analysis methods.

**4.3.1 Treatment-Emergent Resistance Analysis**

Independent analysis of paired baseline/post-baseline samples

Paired baseline and post-baseline sample NS3/4A amino acid sequence data from non-VF-censored, subjects in boceprevir arms who failed to achieve SVR were analyzed to identify patterns of boceprevir treatment-emergent NS3/4A substitutions. Each subtype-specific dataset (2 for each Phase 3 trial) was analyzed independently in an unbiased fashion to identify any specific NS3/4A amino acid substitution that was enriched by  $\geq 2$  subjects in post-baseline samples relative to baseline samples. Results from each of the 4 analyses were then compiled to identify amino acid substitutions that were consistently enriched in post-baseline enrichment across multiple datasets. Table 11 summarizes the amino acid substitutions that were enriched in post-baseline samples across multiple datasets in paired baseline/post-baseline analyses from boceprevir treatment failure subjects.

**Table 11. NS3/4A amino acid coding substitutions enriched in paired baseline/post-baseline sequence analyses from boceprevir treatment-failure subjects in Phase 3 trials.** Analysis was conducted using subtype-specific, non-VF-censored datasets, with 1 baseline and 1 post-baseline sequence analyzed per subject. "Known position" indicates an amino acid position where substitution(s) have been shown to be associated with HCV resistance to boceprevir or other NS3/4A protease inhibitors in development. The most common substitutions enriched in post-baseline samples within an HCV subtype are indicated in bold type. Abbreviations: BL, baseline; n/a, not applicable due to substitution not detected in any baseline or post-baseline sample.

Position	Substitutions Enriched	P05216-1a (n=111)		P05216-1b (n=37)		P05101-1a (n=56)		P05101-1b (n=27)		Known position
		# Subjects BL	# Subjects Post-BL	# Subjects BL	# Subjects Post-BL	# Subjects BL	# Subjects Post-BL	# Subjects BL	# Subjects Post-BL	
NS3 V36	V36A	0	1	n/a	n/a	0	2	n/a	n/a	X
	<b>V36M</b>	<b>0</b>	<b>41</b>	<b>0</b>	<b>1</b>	<b>1</b>	<b>15</b>	<b>n/a</b>	<b>n/a</b>	X
NS3 T54	<b>T54A</b>	<b>0</b>	<b>4</b>	<b>0</b>	<b>7</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>4</b>	X
	T54A/S	n/a	n/a	0	2	n/a	n/a	0	1	X
	<b>T54S</b>	<b>2</b>	<b>13</b>	<b>1</b>	<b>7</b>	<b>1</b>	<b>3</b>	<b>1</b>	<b>4</b>	X
NS3 V55	V55A	5	6	0	3	1	3	0	3	X
NS3 V107	V107I	0	2	0	2	1	2	n/a	n/a	
NS3 P146	P146S	1	2	n/a	n/a	0	2	n/a	n/a	
NS3 R155	<b>R155K</b>	<b>0</b>	<b>52</b>	<b>n/a</b>	<b>n/a</b>	<b>1</b>	<b>14</b>	<b>n/a</b>	<b>n/a</b>	X
	R155K/T	0	1	n/a	n/a	0	1	n/a	n/a	X
	R155T	0	5	n/a	n/a	0	1	n/a	n/a	X
NS3 A156	<b>A156S</b>	<b>0</b>	<b>4</b>	<b>0</b>	<b>7</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>2</b>	X
NS3 V158	V158I	0	6	0	1	0	2	n/a	n/a	X
NS3 A166	A166T	0	1	0	2	n/a	n/a	n/a	n/a	
NS3 D168	D168N	0	5	n/a	n/a	0	2	n/a	n/a	X
NS3 I/V170	I170V (1a)	10	11	n/a	n/a	2	5	n/a	n/a	X
	<b>I/V170A</b>	<b>n/a</b>	<b>n/a</b>	<b>0</b>	<b>8</b>	<b>n/a</b>	<b>n/a</b>	<b>0</b>	<b>4</b>	X
NS3 S189	S189T	2	4	1	0	3	5	1	2	
NS3 S/T196	S196C (1a)	0	3	n/a	n/a	1	0	n/a	n/a	
NS3 K360	K360R	1	2	n/a	n/a	1	1	1	3	
NS3 A379	A379T	1	3	1	1	1	3	n/a	n/a	
NS3 P574	P574L	1	4	n/a	n/a	1	2	n/a	n/a	

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Overall, the most common substitutions enriched in post-baseline samples were V36M, T54A or S, R155K, A156S, and V170A. There are clear patterns of post-baseline enrichment of NS3/4A amino acid substitutions according to HCV subtype, with V36M and R155K detected almost exclusively in subjects infected with HCV subtype 1a, A156S detected preferentially in subjects infected with HCV subtype 1b, and I/V170A detected exclusively in subjects infected with HCV subtype 1b. In at least some cases, the subtype-specific patterns of treatment-emergent substitutions can be explained by differences in the numbers of nucleotide changes needed to generate a particular amino acid codon substitution, as previously described ([McCown et al., 2009](#)).

Despite meeting the criteria of being consistently enriched in post-baseline enrichment across multiple datasets, several of the NS3 substitutions indicated in Table 11 have not been previously described as being associated with HCV resistance to boceprevir or other NS3/4A protease inhibitors, and were either polymorphic or were detected only in a small number of subjects. Additional analyses were conducted for these substitutions, also in some cases multiple substitutions at the same position, to assess the strength of evidence in supporting these substitutions as being preferentially enriched in subjects who failed treatment with a boceprevir-containing regimen.

As shown in Table 12, considering the totality of available data from clinical trial P05216 and P05101, V107I appears to be a specific substitution that emerges in subjects who failed treatment with a boceprevir-containing regimen. Data regarding substitutions P146S, A166T, and I170V (in genotype 1a) are generally inconclusive; these substitutions should be monitored in future clinical trials, and it may be informative to characterize the effect of these substitutions on HCV susceptibility to boceprevir in cell culture. Further analyses (Table 12) do not support S189A/T, S196N, K360R, A379T or P574L as substitutions that emerge specifically in subjects who failed treatment with a boceprevir-containing regimen.

**Table 12. Summary of additional analyses of NS3 substitutions possibly enriched in subjects who failed a boceprevir-containing treatment regimen.** These additional analyses were conducted using non-VF-censored resistance datasets, including control arm subjects and all available resistance data (i.e., not just a single post-baseline sample per subject).

<b>Substitution</b>	<b>Summary of Additional Analyses</b>	<b>Conclusion</b>
<b>NS3 V107I</b>	<ul style="list-style-type: none"> <li>Detected pre-treatment in 7 subjects (2 in control arms; 5 in boceprevir arms-4 of 5 achieved SVR)</li> <li>Detected treatment-emergent in 6 boceprevir-treated subjects and 0 control arm subjects</li> <li>5 of 6 boceprevir-treated subjects with treatment-emergent V107I had at least 1 detected treatment-emergent boceprevir resistance-associated substitution: V36M, T54A, R155K, V170A</li> </ul>	Boceprevir treatment-emergent substitution, in combination with other substitutions
<b>NS3 P146S</b>	<ul style="list-style-type: none"> <li>Detected pre-treatment in 7 subjects (2 in control arms; 5 in boceprevir arms-4 of 5 achieved SVR)</li> <li>Detected treatment-emergent in 4 boceprevir-treated subjects and 1 control arm subject</li> <li>3 of 4 boceprevir-treated subjects with treatment-emergent P146S had at least 1 detected treatment-emergent boceprevir resistance-associated substitution: V36M, T54S, R155K/T, A156S/T, D168N</li> </ul>	Inconclusive-continue to monitor in other trials, and assess impact in cell culture
<b>NS3 A166T</b>	<ul style="list-style-type: none"> <li>Not detected pre-treatment in any subjects</li> <li>Detected treatment-emergent in 3 boceprevir-treated subjects and 0 control arm subjects</li> <li>All 3 subjects with treatment-emergent A166T had 2 or more detected treatment-emergent boceprevir resistance-associated substitutions: T54A, V55A, R155K, V170A</li> </ul>	Inconclusive-continue to monitor in other trials, and assess impact in cell culture
<b>NS3 I170V</b>	<ul style="list-style-type: none"> <li>Genotype 1a-specific substitution</li> <li>V is reference amino acid in genotype 1b</li> <li>Highly polymorphic position</li> </ul>	Inconclusive-continue to monitor in other trials, and assess impact in cell culture

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**Table 12 cont.**

<b>Substitution</b>	<b>Summary of Additional Analyses</b>	<b>Conclusion</b>
<b>NS3 S189A/T</b>	<ul style="list-style-type: none"> <li>Polymorphic position</li> <li>Emerged both in boceprevir-treated and control arm subjects</li> <li>No clear evidence of association with reduced boceprevir efficacy when substitution present at baseline</li> </ul>	Not considered a boceprevir treatment-emergent substitution
<b>NS3 S196C</b>	<ul style="list-style-type: none"> <li>Detected only in genotype 1a-infected subjects</li> <li>Detected pre-treatment in 5 subjects (2 in control arms; 3 in boceprevir arms-2 of 3 achieved SVR).</li> <li>Detected treatment-emergent in 3 boceprevir-treated subjects and 3 control arm subjects.</li> <li>2 of 3 boceprevir-treated subjects with treatment-emergent S196C had at least 1 detected treatment-emergent boceprevir resistance-associated substitution: V55A, R155K, V158I</li> </ul>	Not considered a boceprevir treatment-emergent substitution
<b>NS3 S196N</b>	<ul style="list-style-type: none"> <li>Detected only in genotype 1a-infected subjects</li> <li>Detected pre-treatment in 1 subject (boceprevir-treated, achieved SVR)</li> <li>Detected treatment emergent in 1 boceprevir-treated subject and 0 control arm subjects.</li> <li>Subject with treatment-emergent S196N also had treatment-emergent R155T and D168N</li> </ul>	Not considered a boceprevir treatment-emergent substitution
<b>NS3 K360R</b>	<ul style="list-style-type: none"> <li>Polymorphic position</li> <li>Emerged both in boceprevir-treated and control arm subjects</li> <li>No clear evidence of association with reduced boceprevir efficacy when substitution present at baseline</li> </ul>	Not considered a boceprevir treatment-emergent substitution
<b>NS3 A379T</b>	<ul style="list-style-type: none"> <li>Polymorphic position</li> <li>Emerged both in boceprevir-treated and control arm subjects</li> <li>No clear evidence of association with reduced boceprevir efficacy when substitution present at baseline</li> </ul>	Not considered a boceprevir treatment-emergent substitution
<b>NS3 P574L</b>	<ul style="list-style-type: none"> <li>Polymorphic position</li> <li>Emerged both in boceprevir-treated and control arm subjects</li> <li>No clear evidence of association with reduced boceprevir efficacy when substitution present at baseline</li> </ul>	Not considered a boceprevir treatment-emergent substitution

In addition to the “Known positions” indicated in Table 11, multiple other amino acid substitutions in NS3/4A have been reported by the sponsor or others as being associated with reduced HCV susceptibility to NS3/4A protease inhibitors. However, there is little evidence that boceprevir treatment failure is associated with the emergence of substitutions at these other “known positions”: NS3 Q41, NS3 F43, NS3 Q80, or NS4A V23 (Table 13).

**Table 13. Analysis of substitutions in other “known positions” (i.e., amino acid positions where substitutions have been shown to be associated with resistance or reduced HCV susceptibility to boceprevir or other NS3/4A protease inhibitors in development). Analysis was conducted using subtype-specific, non-VF-censored datasets, with 1 baseline and 1 post-baseline sequence analyzed per subject; boceprevir-treated patients only. BL, baseline.**

Position	Substitution of Interest	P05216-1a		P05216-1b		P05101-1a		P05101-1b	
		# Subjects BL	# Subjects Post-BL						
NS3 Q41	Q41H	n/a	n/a	1	1	n/a	n/a	n/a	n/a
NS3 F43	None obs.	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
NS3 Q80	Q80K	43	42	1	0	27	27	n/a	n/a
	Q80K/N	1	0	n/a	n/a	n/a	n/a	n/a	n/a
	Q80L	3	2	1	1	1	1	n/a	n/a
	Q80N	1	2	n/a	n/a	n/a	n/a	n/a	n/a
	Q80R	1	1	n/a	n/a	n/a	n/a	n/a	n/a
NS4A V23	V23A	1	1	n/a	n/a	0	1	n/a	n/a

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In summary, unbiased analyses of paired baseline/post-baseline NS3/4A coding sequence data have identified the following amino acid substitutions as being enriched among subjects who failed boceprevir treatment in clinical trials P05216 and P05101: NS3 V36A/M, T54A/S, V55A, V107I, R155K/T, A156S, V158I, D168N, and I/V170A. Further treatment-emergent resistance analyses were conducted focusing specifically on these substitutions and others at these positions, as described in the following sections.

Of practical value, all amino acid substitutions that were enriched among boceprevir treatment failure subjects were localized to the NS3 protease domain (amino acids 1-181). There was no clear evidence of significant enrichment of amino acid substitutions either in the NS3 helicase or in the NS4A protease cofactor protein. Based on this observation, for future boceprevir trials it may be reasonable to conduct genotypic resistance analyses focusing primarily only on the NS3 protease domain. The sponsor should analyze NS3/4A protease cleavage sites, as substitutions in these protease cleavage sites have been shown to reduce HIV-1 susceptibility to HIV-1 protease inhibitors in the absence of resistance-associated substitution in the protease enzyme itself ([Nijhuis et al., 2007](#)).

Pooled analyses of specific boceprevir treatment-emergent, resistance-associated substitutions

Table 14 summarizes the frequency of detection for 15 amino substitutions, across 9 different NS3 positions, among subjects who failed treatment with a boceprevir-containing regimen in the phase 3 boceprevir clinical trials P05216 and P05101. Shown are data from both non-VF-censored subjects as well as uncensored subjects. Unlike the analysis described above, all available post-baseline sample data from subjects who had appropriate comparator baseline data were used. Note that subjects who were randomized to boceprevir but discontinued during the Peg-IFN $\alpha$ -2b/RBV lead-in period (i.e., never received boceprevir) were excluded from the analysis.

As shown in Table 14, among boceprevir-treated subjects who did not achieve SVR, and for whom samples were analyzed, 52% (153/292, uncensored analysis) had one or more of the following post-baseline, treatment-emergent NS3 amino acid substitutions detected: V36A, V36M, T54A, T54S, V55A, V107I, R155K, R155T, A156S, A156T, A156V, V158I, D168N, I/V170A and I/V170T. There were clear subtype-specific patterns of treatment-emergent, resistance-associated substitutions, with a slight trend of more HCV subtype 1a-infected subjects having detectable treatment-emergent substitutions. The most common treatment-emergent amino acid substitutions detected in HCV subtype 1a-infected subjects were R155K, V36M and T54S. The most common treatment-emergent amino acid substitutions detected in HCV subtype 1b-infected subjects were T54A, T54S, I/V170A, V55A, and A156S. The following amino acid substitutions were detected in <1-10% of HCV subtype 1a-infected subjects: V36A, T54A, V55A, V107I, R155T, A156S, A156T, V158I, D168N, and I/V170T. The following amino acid substitutions were detected in 1-10% of HCV subtype 1b-infected subjects: V36A, V36M, V107I, R155K, A156T, A156V, V158I, I/V170T.

In a majority of cases, subjects with treatment-emergent, detectable resistance-associated substitutions had more than 1 such substitution detected post-baseline. The most common combination of substitutions observed was V36M+R155K, which was detected exclusively in subjects infected with HCV subtype 1a. The most common treatment-emergent resistance-associated substitutions observed in subjects in the absence of any other detectable post-baseline resistance-associated substitutions were V36M and R155K for HCV subtype 1a-infected subjects, and T54A, V55A and I/V170A for HCV subtype 1b-infected subjects.

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**Table 14. Pooled numbers of treatment-failure subjects with specific boceprevir treatment-emergent NS3 amino acid substitutions in clinical trials P05216 and P05101.** The numbers of substitutions was quantified from the list of 15 single substitutions indicated in the table. All post-baseline sequence data from boceprevir-treated patients were used to quantify the number of treatment-emergent substitutions (i.e., 2 specific treatment-emergent substitutions detected in 1 subject did not have to be detected in the same sample).

<b>Genotype 1a-Infected Subjects</b>			<b>Genotype 1b-Infected Subjects</b>		
<b>Substitution</b>	<b>Non-VF-Censored (n=167)</b>	<b>All Subjects (n=211)</b>	<b>Substitution</b>	<b>Non-VF-Censored (n=64)</b>	<b>All Subjects (n=81)</b>
R155K	75 (45%)	77 (36%)	T54A	16 (25%)	16 (20%)
V36M	66 (40%)	70 (33%)	T54S	14 (22%)	14 (17%)
T54S	21 (13%)	22 (10%)	I/V170A	12 (19%)	12 (15%)
R155T <sup>1</sup>	8 (5%)	8 (4%)	A156S	10 (16%)	10 (12%)
V158I	8 (5%)	8 (4%)	V55A	8 (13%)	9 (11%)
T54A	7 (4%)	7 (3%)	V107I	2 (3%)	2 (2%)
D168N <sup>1</sup>	7 (4%)	7 (3%)	A156V	2 (3%)	2 (2%)
A156S	6 (4%)	6 (3%)	V158I	2 (3%)	2 (2%)
A156T	5 (3%)	5 (2%)	V36M	1 (2%)	1 (1%)
V55A	4 (2%)	4 (2%)	R155K	1 (2%)	1 (1%)
V107I	4 (2%)	4 (2%)	A156T	1 (2%)	1 (1%)
V36A	3 (2%)	3 (1%)	I/V170T	1 (2%)	1 (1%)
I/V170T	1 (1%)	1 (<1%)	V36A	0	1 (1%)
A156V	0	0	R155T <sup>1</sup>	0	0
I/V170A	0	0	D168N <sup>1</sup>	0	0
V36M + R155K	47 (28%)	48 (23%)	V36M + R155K	0	0
1 substitution	31 (19%)	36 (17%)	1 substitution	17 (27%)	19 (23%)
2 substitutions	57 (34%)	58 (27%)	2 substitutions	12 (19%)	12 (15%)
3+ substitutions	20 (12%)	20 (9%)	3+ substitutions	8 (13%)	8 (10%)
<b>Any substitution</b>	<b>108 (65%)</b>	<b>114 (54%)</b>	<b>Any substitution</b>	<b>37 (58%)</b>	<b>39 (48%)</b>
<b>No substitutions</b>	<b>59 (35%)</b>	<b>97 (46%)</b>	<b>No substitutions</b>	<b>27 (42%)</b>	<b>42 (52%)</b>

<sup>1</sup>D168N and R155T detected almost exclusively in combination together. See text for details.

The detection of treatment-emergent D168N in 7 subjects was unexpected. Certain amino acid substitutions at NS3 D168 have been shown to confer large reductions in HCV susceptibility to several agents in the ‘macrocyclic/non-linear’ class of HCV NS3/4A protease inhibitors. However, this reviewer is not aware of any prior reports of substitutions at D168 emerging in subjects treated with ‘linear peptidomimetic’ NS3/4A protease inhibitors such as boceprevir or telaprevir, nor have such substitutions been reported as being associated with reduced HCV susceptibility to boceprevir or telaprevir in cell culture. To this reviewer’s knowledge, the sponsor made no mention of D168N in Clinical Virology-related study reports in the present NDA.

Interestingly, D168N was detected only in subjects infected with HCV subtype 1a, and emerged exclusively with R155T. In addition to the 7 subjects indicated in Table 14, 1 boceprevir-treated subject had detectable D168N in two post-baseline samples, but because the subject did not have reportable baseline sequence data it cannot be confirmed that D168N emerged as a result of boceprevir treatment. However, given the fact that D168N was not detected in any baseline/pre-treatment samples, it seems likely it also emerged in this subject. Considering all available data from

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clinical trials P05216 and P05101, D168N was detected in 11 post-baseline samples from 8 boceprevir-treated subjects. All 8 subjects were infected with HCV subtype 1a, and all 11 samples also had detectable R155T. Similarly, R155T was detected in 13 post-baseline samples (0 baseline samples) from 9 boceprevir-treated subjects; 11 of 13 samples also had detectable D168N. Although population nucleotide sequence analyses cannot prove linkage of two amino acid codon substitutions on the same viral genome, this strong association indicates that the combination of R155T+D168N linked on the same HCV subtype 1a genome likely confers reduced HCV susceptibility to boceprevir.

As can be implied from the results presented in Table 14, a relatively smaller proportion of subjects who were censored in the treatment-emergent resistance analysis had 1 or more detectable boceprevir treatment-emergent, resistance-associated substitutions. This result is not unexpected, as such subjects either appeared to be responding virologically to treatment, or were treated only for a short duration. Among the censored, intent-to-treat failure, non-virologic failure subjects who were treated with boceprevir for any duration and had available post-baseline NS3/4A sequence data, 13% (8/61) had one or more detectable boceprevir treatment-emergent, resistance-associated substitutions. The following treatment-emergent substitutions were observed in these subjects: V36A, T54S, V55A, R155K and V36M+R155K (1 subject each), and V36M (3 subjects).

Analysis of treatment-emergent substitutions by trial: potential effect of Week 12 futility rule

The patterns of boceprevir treatment-emergent, resistance-associated substitutions were generally similar for both Phase 3 clinical trials, P05216 (treatment-naïve trial) and P05101 (treatment-experienced trial) (Table 15). For both trials, among treatment failure subjects with available baseline and post-baseline NS3/4A amino acid coding sequence data, approximately half had 1 or more of the resistance-associated substitutions listed above in Table 14. For both trials, the most common treatment-emergent substitutions varied by HCV subtype: R155K and V36M were most common in subtype 1a-infected subjects; T54A and T54S were most common in subtype 1b-infected subjects.

**Table 15. Number of non-SVR subjects (uncensored analysis) with specific boceprevir treatment-emergent NS3 amino acid substitutions in P05216 and P05101.** Analysis excludes subjects who discontinued during Peg-IFN $\alpha$ -2b/RBV lead-in phase. Only the most common treatment-emergent substitutions from the listing in Table 14 are shown in this table. Calculations of numbers of substitutions are based on the complete listing in Table 14.

Genotype 1a-Infected Subjects			Genotype 1b-Infected Subjects		
Substitution	P05216 (n=147)	P05101 (n=64)	Substitution	P05216 (n=48)	P05101 (n=33)
R155K	60 (41%)	17 (27%)	T54A	10 (21%)	6 (18%)
V36M	50 (34%)	20 (31%)	T54S	9 (19%)	5 (15%)
T54S	18 (12%)	4 (6%)	I/V170A	8 (17%)	4 (12%)
R155T	6 (4%)	2 (3%)	A156S	7 (15%)	3 (9%)
V158I	6 (4%)	2 (3%)	V55A	5 (10%)	4 (12%)
T54A	6 (4%)	1 (2%)			
D168N	5 (3%)	2 (3%)			
V36M + R155K	37 (25%)	11 (17%)			
1 substitution	22 (15%)	14 (22%)	1 substitution	11 (23%)	8 (24%)
2 substitutions	47 (32%)	11 (17%)	2 substitutions	10 (21%)	2 (6%)
3+ substitutions	15 (10%)	5 (8%)	3+ substitutions	4 (8%)	4 (12%)
<b>Any substitution</b>	<b>84 (57%)</b>	<b>30 (47%)</b>	<b>Any substitution</b>	<b>25 (52%)</b>	<b>14 (42%)</b>
<b>No substitutions</b>	<b>63 (43%)</b>	<b>34 (53%)</b>	<b>No substitutions</b>	<b>23 (48%)</b>	<b>19 (58%)</b>

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Although the patterns of treatment-emergent substitutions were generally similar in the two trials, there was a consistent (across HCV subtype) 10% higher rate of detection of treatment-emergent substitutions in clinical trial P05216 versus P05101 for treatment failure subjects with available baseline and post-baseline NS3/4A coding sequence data (Table 15). This difference was even greater based on analyses of non-VF-censored subject datasets (Table 16), further strengthening the trend. There is no obvious explanation for this observation, although this reviewer speculates that one potential contributing factor could be the Week 12 detectable HCV RNA treatment futility rule that was employed in P05101 but not P05216. This futility rule theoretically would have reduced the selection or enrichment of HCV variants harboring boceprevir resistance-associated substitutions in subjects who had a low probability of achieving SVR had they continued with their protocol treatment.

**Table 16. Number of treatment-failure subjects (non-VF-censored analysis) with boceprevir treatment-emergent NS3 amino acid substitutions in Phase 3 clinical trials P05216 and P05101.** Substitutions considered in this analysis are those listed in Table 14.

Genotype 1a-Infected Subjects			Genotype 1b-Infected Subjects		
	P05216 (n=111)	P05101 (n=56)		P05216 (n=37)	P05101 (n=27)
<b>Any substitution</b>	81 (73%)	27 (48%)	<b>Any substitution</b>	24 (65%)	13 (48%)
<b>No substitutions</b>	30 (27%)	29 (52%)	<b>No substitutions</b>	13 (35%)	14 (52%)

An additional exploratory analysis was conducted to test the hypothesis that the lack of a Week 12 futility rule in P05216 may have contributed towards a higher rate of detection of boceprevir treatment-emergent, resistance-associated substitutions. In this analysis, the rates of detection of treatment-emergent substitutions among subjects with or without detectable HCV RNA at Treatment Week 12 were compared for the two trials. As shown in Table 17, there was an imbalance in the detection of treatment-emergent substitutions according to HCV RNA status at Treatment Week 12 for the two trials. In P05216, 74-75% of virologic failure subjects who had detectable HCV RNA at Week 12 ultimately had 1 or more detected boceprevir treatment-emergent, resistance-associated substitutions. In contrast, in P05101, 42-47% of virologic failure subjects who had detectable HCV RNA at Week 12 had 1 or more detected boceprevir treatment-emergent, resistance-associated substitutions. Note that these data should be interpreted with caution as some subjects in P05101 with detectable HCV RNA at Week 12 did not necessarily stop treatment immediately, presumably in most cases due to additional HCV RNA data indicative of virologic responsiveness (e.g., subsequent or confirmatory Week 12 HCV RNA measurement). Nevertheless, these data indicate that a Week 12 treatment futility rule may reduce the overall rate of selection or enrichment of boceprevir resistance-associated substitutions among treatment failure subjects.

**Table 17. Number of treatment-failure subjects with 1 or more boceprevir treatment-emergent NS3 amino acid substitutions in Phase 3 clinical trials P05216 and P05101, according to Treatment Week 12 (TW12) HCV RNA status.** Substitutions considered in this analysis are those listed in Table 14. Note that discontinuation prior to Week 12 is one primary reason for missing Treatment Week 12 HCV RNA data. Uncensored analysis.

HCV RNA Status at TW12	Genotype 1a-Infected Subjects		Genotype 1b-Infected Subjects	
	P05216	P05101	P05216	P05101
HCV RNA detectable	64/87 (74%)	18/43 (42%)	21/28 (75%)	8/17 (47%)
HCV RNA undetectable, or data missing	20/60 (33%)	12/21 (57%)	4/20 (20%)	6/16 (38%)

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Although a Week 12 treatment futility rule may reduce the overall rate of selection or enrichment of boceprevir resistance-associated substitutions among treatment failure subjects, the rationale for its use in practice must consider the response rates for subjects who might meet the futility criterion but continue treatment. Because such a futility rule was not included in the P05216 protocol, SVR rates could be determined for subjects with detectable HCV RNA at the Week 12 visit. Depending on how the data are analyzed, boceprevir arm subjects in P05216 with detectable HCV RNA at Treatment Week 12 ultimately had SVR rates of ~10-20% (see Section 4.6.2).

Analysis of treatment-emergent substitutions by boceprevir treatment arm

The patterns of treatment-emergent substitutions were generally similar across treatment arms (Table 18), which was expected. The percentage of treatment failure subjects who had one or more detectable treatment-emergent substitutions varied somewhat by treatment-arm, but the trends were discordant by HCV subtype. Presumably this is not a real finding, as there is no plausible or direct explanation for discordant subtype-specific trends in the rate of detection of treatment-emergent substitutions according to treatment arm.

**Table 18. Pooled numbers of treatment-failure subjects with specific boceprevir treatment-emergent NS3 amino acid substitutions in Phase 3 clinical trials P05216 and P05101, according to boceprevir treatment arm.** Analysis was conducted using uncensored subject datasets, but excluding subjects who discontinued during Peg-IFN $\alpha$ -2b/RBV lead-in phase (i.e., never received boceprevir). Only the most common treatment-emergent substitutions from the listing in Table 14 are shown in this table. B/P/R-RGT, Boceprevir + Peg-IFN $\alpha$ -2b/RBV response-guided therapy (Arm 2 for both trials); B/P/R-48, Boceprevir + Peg-IFN $\alpha$ -2b/RBV for 48 Weeks (Arm 3 for both trials).

Genotype 1a-Infected Subjects			Genotype 1b-Infected Subjects		
Substitution	B/P/R-RGT (n=109)	B/P/R-48 (n=102)	Substitution	B/P/R-RGT (n=43)	B/P/R-48 (n=38)
R155K	36 (33%)	41 (40%)	T54A	9 (21%)	7 (18%)
V36M	34 (31%)	36 (35%)	T54S	8 (19%)	6 (16%)
T54S	10 (9%)	12 (12%)	I/V170A	7 (16%)	5 (13%)
R155T	3 (3%)	5 (5%)	A156S	5 (12%)	5 (13%)
V158I	4 (4%)	4 (4%)	V55A	6 (14%)	3 (8%)
T54A	6 (6%)	1 (1%)			
D168N	2 (2%)	5 (5%)			
V36M + R155K	23 (21%)	25 (25%)			
1 substitution	17 (16%)	19 (19%)	1 substitution	15 (35%)	4 (11%)
2 substitutions	32 (29%)	26 (25%)	2 substitutions	5 (12%)	7 (18%)
3+ substitutions	6 (6%)	14 (14%)	3+ substitutions	5 (12%)	3 (8%)
<b>Any substitution</b>	<b>55 (50%)</b>	<b>59 (58%)</b>	<b>Any substitution</b>	<b>25 (58%)</b>	<b>14 (37%)</b>
<b>No substitutions</b>	<b>54 (50%)</b>	<b>43 (42%)</b>	<b>No substitutions</b>	<b>18 (42%)</b>	<b>24 (63%)</b>

Analysis of treatment-emergent substitutions by virologic failure category

Among boceprevir treated subjects who failed to achieve SVR, those who experienced virologic breakthrough were more likely to have the detection of one or more treatment-emergent, resistance-associated substitutions relative to those subjects who experienced virologic nonresponse or relapse (Table 19). Most virologic breakthrough subjects had more than 1 resistance-associated substitution detected. Approximately 40% of treatment failure subjects who experienced virologic nonresponse or relapse had at least one detectable treatment-emergent, resistance-associated substitution. For the

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purpose of this analysis, ‘virologic breakthrough’ subjects were pooled to include those who experienced sponsor-defined virologic breakthrough or incomplete virologic response: undetectable HCV RNA on treatment and a subsequent detectable value >1,000 IU/mL, or an on treatment increase in HCV RNA of  $\geq 1 \log_{10}$  IU/mL from nadir, respectively.

**Table 19. Pooled numbers of treatment-failure subjects with specific boceprevir treatment-emergent NS3 amino acid substitutions in Phase 3 clinical trials P05216 and P05101, according to virologic failure category.** Analysis was conducted using uncensored subject datasets, but excluding subjects who discontinued during Peg-IFN $\alpha$ -2b/RBV lead-in phase (i.e., never received boceprevir). Only the most common treatment-emergent substitutions from the listing in Table 14 are shown in this table. Virologic non-response category is based on sponsor’s definitions (“Incomplete Virologic Response” and “Virologic Breakthrough” pooled as “Virologic Breakthrough”; see Section 4.1.1 for definitions). “Nonresponse” represents any treatment failure that does not meet the sponsor’s criteria for virologic breakthrough, incomplete virologic response, or relapse.

<b>Genotype 1a-Infected Subjects</b>			
<b>Substitution</b>	<b>Nonresponse (n=105)</b>	<b>Breakthrough (n=58)</b>	<b>Relapse (n=48)</b>
R155K	29 (28%)	42 (72%)	6 (13%)
V36M	29 (28%)	31 (53%)	10 (21%)
T54S	9 (9%)	10 (17%)	3 (6%)
R155T	4 (4%)	4 (7%)	0 (0%)
V158I	3 (3%)	4 (7%)	1 (2%)
T54A	2 (2%)	3 (5%)	2 (4%)
D168N	3 (3%)	4 (7%)	0 (0%)
V36M + R155K	19 (18%)	28 (48%)	1 (2%)
1 substitution	12 (11%)	8 (14%)	16 (33%)
2 substitutions	23 (22%)	30 (52%)	5 (10%)
3+ substitutions	8 (8%)	11 (19%)	1 (2%)
<b>Any substitution</b>	<b>43 (41%)</b>	<b>49 (84%)</b>	<b>22 (46%)</b>
<b>No substitutions</b>	<b>62 (59%)</b>	<b>9 (16%)</b>	<b>26 (54%)</b>
<b>Genotype 1b-Infected Subjects</b>			
<b>Substitution</b>	<b>Nonresponse (n=29)</b>	<b>Breakthrough (n=24)</b>	<b>Relapse (n=28)</b>
T54A	4 (14%)	12 (50%)	0 (0%)
T54S	3 (10%)	11 (46%)	0 (0%)
I/V170A	2 (7%)	6 (25%)	4 (14%)
A156S	1 (3%)	9 (38%)	0 (0%)
V55A	1 (3%)	5 (21%)	3 (11%)
1 substitution	5 (17%)	6 (25%)	8 (29%)
2 substitutions	2 (7%)	9 (38%)	1 (4%)
3+ substitutions	1 (3%)	7 (29%)	0 (0%)
<b>Any substitution</b>	<b>8 (28%)</b>	<b>22 (92%)</b>	<b>9 (32%)</b>
<b>No substitutions</b>	<b>21 (72%)</b>	<b>2 (8%)</b>	<b>19 (68%)</b>

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Analysis of treatment-emergent substitutions according to Peg-IFN $\alpha$ -2b/RBV lead-in response  
Among boceprevir treated subjects who failed to achieve SVR, those who had a poor virologic response during the Peg-IFN $\alpha$ -2b/RBV lead-in period, defined as a  $<1 \log_{10}$  IU/mL HCV RNA decline at Treatment Week 4, were more likely to have the detection of one or more treatment-emergent, resistance-associated substitutions relative to those subjects with a  $>1 \log_{10}$  IU/mL HCV RNA decline at Treatment Week 4 (Table 20).

**Table 20. Pooled numbers of treatment-failure subjects with specific boceprevir treatment-emergent NS3 amino acid substitutions in Phase 3 clinical trials P05216 and P05101, according to virologic response through Treatment Week 4 (TW4, end of Peg-IFN $\alpha$ -2b/RBV lead-in).** Analysis was conducted using uncensored subject datasets, but excluding subjects who discontinued during Peg-IFN $\alpha$ -2b/RBV lead-in phase (i.e., never received boceprevir). Only the most common treatment-emergent substitutions from the listing in Table 14 are shown in this table.

Genotype 1a-Infected Subjects			Genotype 1b-Infected Subjects		
Substitution	$<1 \log_{10}$ IU/mL decline at TW4 (n=121)	$\geq 1 \log_{10}$ IU/mL decline at TW4 (n=90)	Substitution	$<1 \log_{10}$ IU/mL decline at TW4 (n=44)	$\geq 1 \log_{10}$ IU/mL decline at TW4 (n=37)
R155K	66 (55%)	11 (12%)	T54A	14 (32%)	2 (5%)
V36M	55 (45%)	15 (17%)	T54S	14 (32%)	0 (0%)
T54S	18 (15%)	4 (4%)	I/V170A	7 (16%)	5 (14%)
R155T	7 (6%)	1 (1%)	A156S	10 (23%)	0 (0%)
V158I	5 (4%)	3 (3%)	V55A	8 (18%)	1 (3%)
T54A	3 (2%)	4 (4%)			
D168N	7 (6%)	0 (0%)			
V36M + R155K	43 (36%)	5 (6%)			
1 substitution	15 (12%)	21 (23%)	1 substitution	12 (27%)	7 (19%)
2 substitutions	51 (42%)	7 (8%)	2 substitutions	9 (20%)	3 (8%)
3+ substitutions	18 (15%)	2 (2%)	3+ substitutions	8 (18%)	0 (0%)
<b>Any substitution</b>	<b>84 (69%)</b>	<b>30 (33%)</b>	<b>Any substitution</b>	<b>29 (66%)</b>	<b>10 (27%)</b>
<b>No substitutions</b>	<b>37 (31%)</b>	<b>60 (67%)</b>	<b>No substitutions</b>	<b>15 (34%)</b>	<b>27 (73%)</b>

Possible reasons for lack of detection of treatment-emergent substitutions in virologic failure subjects  
Of all non-VF-censored subjects in clinical trial P05216 or P05101 who had appropriate baseline and post-baseline nucleotide sequence data, boceprevir treatment failure was associated with the detected emergence of one or more of the NS3 substitutions listed in Table 14 in 63% (145/231) of subjects. Conversely, 37% (86/231) of such subjects did not have one of the treatment-emergent substitutions detected. Additional exploratory analyses were conducted for these 86 subjects to identify other potential resistance pathways or factors that might explain the lack of detection of treatment-emergent, resistance-associated substitutions.

An imbalance in treatment arm assignment does not explain the lack of detection of boceprevir treatment-emergent, resistance-associated substitutions. Of the boceprevir treatment-failure subjects with evidence of treatment-emergent, resistance-associated substitutions, 53% (77/145) were in response-guided therapy arms (Arm 2 in either trial) and 47% (68/145) were in non-response-guided therapy arms (Arm 3 in either trial). Of those subjects without treatment-emergent, resistance-

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associated substitutions, 55% (47/86) were in response-guided therapy arms and 45% (39/86) were in non-response-guided therapy arms.

Of the 86 non-VF-censored, boceprevir treatment failure subjects without evidence of treatment-emergent, resistance-associated substitutions, 8 (~10%) subjects had one or more of the resistance-associated substitutions detected at the baseline and all analyzed post-baseline visits. Therefore, it could not be concluded that these substitutions ‘emerged’ as a result of boceprevir exposure, although they are predicted to have had a negative impact on the potency of boceprevir anti-HCV activity.

Other potentially ‘novel’ resistance pathways do not seem to explain the lack of evidence of treatment-emergent, resistance-associated substitutions for the remaining 78 subjects. To address this question, additional analyses were conducted in an attempt to identify patterns of treatment-emergent substitutions in NS3/4A that are distinct from those indicated above in Table 14. In general, these analyses identified specific treatment-emergent substitutions only in 1 or 2 subjects, or at highly polymorphic positions that do not clearly influence boceprevir anti-HCV activity.

Differences in the frequencies of detection of boceprevir treatment-emergent, resistance-associated substitutions according to virologic failure category (e.g., as indicated above by Table 19) may partly explain the lack of detection of boceprevir treatment-emergent, resistance-associated substitutions. As shown in Table 21, nearly half of subjects with evidence of boceprevir treatment-emergent, resistance-associated substitutions experienced virologic breakthrough, whereas subjects without such substitutions were more likely to have experienced virologic nonresponse or relapse.

**Table 21. Virologic failure category for boceprevir arm subjects with or without detectable boceprevir treatment-emergent, resistance-associated substitutions.** Pooled analysis of clinical trial P05216 and P05101, non-VF-censored datasets. Virologic failure category indicated below is based on sponsor’s definitions (“Incomplete Virologic Response” and “Virologic Breakthrough” pooled as “Virologic Breakthrough”; see Section 4.1.1 for definitions).

	<b>Nonresponse</b>	<b>Breakthrough</b>	<b>Relapse</b>
<b>Subjects with Tx-emergent Substitutions</b>	49/145 (34%)	71/145 (49%)	25/145 (17%)
<b>Subjects without Tx-emergent Substitutions</b>	58/86 (67%)	11/86 (13%)	17/86 (20%)
<b>Subjects without Tx-emergent Substitutions (excluding subjects with substitutions at baseline)</b>	52/78 (67%)	10/78 (13%)	16/78 (21%)

Suboptimal timing of post-baseline samples analyzed to generate NS3/4A sequence data could result in the lack of detection of boceprevir treatment-emergent, resistance-associated substitutions. Theoretically, the ability to detect treatment-emergent, resistance-associated substitutions by population nucleotide sequence analysis after stopping treatment will decline over time, as ‘wild-type susceptible’ viral variants may outgrow treatment-emergent ‘drug resistant’ variants in the absence of drug pressure (investigated in detail in Section 4.4.3), and population-based sequence analysis is generally not sufficiently sensitive to detect minority variants that represent <25% of the total viral population. Similarly, NS3/4A sequence analyses for study visits that occurred prior to a subject experiencing virologic failure may fail to reveal resistance-associated substitutions that emerged at times during or following virologic failure.

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To determine if differences in the timing of post-baseline samples analyzed could explain differences in the frequencies of detecting resistance-associated substitutions, an analysis was first conducted for the 145 subjects with evidence of treatment-emergent substitutions. Data from these subjects were analyzed to calculate the timing, relative to the timing of stopping treatment, of post-baseline visits for which resistance-associated substitutions were detected. These results were then compared to the timing of visits from the same subjects for which no resistance-associated substitutions were detected (Table 22). As predicted, sample visits with detectable resistance-associated substitutions generally occurred at times much closer to times of stopping treatment, relative to sample visits without detectable resistance-associated substitutions (median of 12 days versus 324 days following treatment cessation, respectively). Furthermore, despite the high median value for timing from treatment cessation for visits without detectable substitutions, the 25% quartile for these visits was earlier than that for visits with detectable substitutions, indicating that the lack of detection of substitutions for some visits may also be explained by sample timing that occurred prior to virologic failure.

**Table 22. Relationship between timing of post-baseline visits and detection of treatment-emergent, resistance-associated substitutions.** Note that these calculations underestimate the median time following *boceprevir* exposure, as many subjects in response-guided therapy arms received a ‘tail’ treatment of Peg-IFN $\alpha$ -2b/RBV without boceprevir.

<b>Post-Baseline Visit Samples Analyzed</b>	<b>Timing of Visits Relative to Treatment Cessation (in Days)</b>	
	<b>Median</b>	<b>Interquartile Range</b>
Subjects with Detectable Substitutions (All Visits)	29	-30 to 253
Visits with Detectable Substitutions	12	-28 to 111
Visits without Detectable Substitutions	324	-36 to 367
Subjects without Detectable Substitutions (All Visits)	69	-40 to 297

The timing of sample visits analyzed for the 78 subjects without any detectable treatment-emergent, resistance-associated substitutions (excludes the 8 subjects with substitutions at baseline) occurred a median 69 days after treatment cessation, with a broad distribution of timing that differed somewhat from the timing for subjects with detectable substitutions (Table 22). Suboptimal post-baseline sample timing is unlikely to account for the lack of detection of resistance-associated substitutions in most cases, as 65% (51/78) of these subjects still had at least one visit sample analyzed that was collected in the -28 to 111 days from treatment cessation window corresponding to the interquartile range for visits with detectable substitutions. However, 35% (27/78) of subjects had no samples collected in this visit window and analyzed for the presence of resistance-associated substitutions. Fifteen (15) subjects had no samples analyzed for post-baseline visits that occurred within 160 days of stopping treatment. It is possible that suboptimal post-baseline sample timing accounts for the lack of detection of treatment-emergent, resistance-associated substitutions in at least some of these subjects.

In summary, these additional analyses indicate that a reduced frequency of virologic breakthrough, suboptimal post-baseline sample timing, the detection of resistance-associated substitutions at baseline, or a combination of these factors may at least partially explain the lack of detection of treatment-emergent, boceprevir resistance-associated substitutions among 37% of treatment failure, non-VF-censored subjects analyzed from clinical trials P05216 and P05101. Also note that substitutions elsewhere in the HCV coding sequence theoretically could be associated with boceprevir resistance, for example NS3/4A protease cleavage sites.

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**4.3.2 Baseline Resistance Analysis**

SVR Rates for Baseline Resistance Analysis Populations

Baseline resistance analyses were conducted focusing on the non-VF-censored population, including only boceprevir-treated subjects in P05216 and P05101 with available baseline NS3/4A sequence data. SVR rates for this baseline analysis population are summarized in Table 23, and further stratified according to Peg-IFN $\alpha$ -2b/RBV lead-in phase virologic response in Table 24.

**Table 23. SVR rates for pooled baseline resistance analysis population.** Analysis includes boceprevir-treated subjects from the non-VF-censored population with available baseline NS3/4A sequence data.

	Genotype 1a-Infected Subjects	Genotype 1b-Infected Subjects	All Subjects
<b>P05216</b>	70.9% (278/392)	82.0% (169/206)	74.7% (447/598)
<b>P05101</b>	64.5% (109/169)	74.8% (86/115)	68.7% (195/284)
<b>Pooled P05216/P05101</b>	69.0% (387/561)	79.4% (255/321)	72.8% (642/882)

**Table 24. SVR rates for pooled baseline resistance analysis population, stratified according to Peg-IFN $\alpha$ -2b/RBV lead-in phase virologic response.** Analysis includes boceprevir-treated subjects from the non-VF-censored population with available baseline NS3/4A sequence data.

Subject Population Analyzed	SVR Rate According to HCV RNA Decline through Treatment Week 4		
	<1 log <sub>10</sub> IU/mL	≥1 to <2 log <sub>10</sub> IU/mL	≥2 log <sub>10</sub> IU/mL
Pooled genotype 1a-infected subjects	44/156 (28%)	88/124 (71%)	255/281 (91%)
Pooled genotype 1b-infected subjects	46/86 (53%)	63/82 (77%)	146/153 (95%)

Independent Baseline Resistance Analysis

An independent analysis was conducted to identify any NS3/4A amino acid substitutions that, when present/enriched at baseline, were associated with poor treatment outcomes in the Phase 3 clinical trials P05216 and P05101. All 4 datasets (two subtype-specific datasets per trial) were analyzed independently, and then compared to identify any detectable amino acid substitutions across the entire NS3/4A coding region that were consistently associated with SVR rates that were reduced compared to those observed for all boceprevir-treated subjects.

In general, there were no baseline amino acid substitutions anywhere in the NS3/4A coding sequence that were clearly associated with a poor treatment outcome when considering all non-VF-censored subjects in clinical trials P05216 and P05101. Table 25 summarizes the SVR rates for subjects with detectable substitutions specifically at NS3/4A positions associated with reduced HCV susceptibility to NS3/4A protease inhibitors. In most cases, the number of subjects with any single baseline NS3/4A substitution relative to a subtype-specific reference was inadequate for meaningful analysis.

The presence of an I170V substitution in HCV genotype 1a-infected subjects at baseline was associated with a reduced SVR rate. However, considering baseline sequence at this position independent of HCV genotype 1 subtype, there is no trend of a V being associated with a reduced response (Table 25). Based on the available data and the highly polymorphic nature of this position it

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is not possible to conclude that an I170V substitution at baseline has a clear negative impact on virologic responsiveness to Boceprevir/Peg-IFN $\alpha$ /RBV.

**Table 25. SVR rates for boceprevir arm subjects with baseline HCV viral populations harboring detectable substitutions at NS3/4A positions associated with reduced HCV susceptibility to NS3/4A protease inhibitors.** Analysis was conducted using as treated, non-VF-censored subject datasets, including only boceprevir-treated subjects with available baseline NS3/4A sequence data. Substitutions shown are based on HCV subtype-specific reference sequences. Specific substitutions that frequently ( $\geq 10\%$ ) emerge in genotype 1a or genotype 1b treatment failure subjects (see Table 14) are indicated in bold type.

Position	Substitution Detected at Baseline	SVR Rate in P05216	SVR Rate in P05101
<b>NS3 V36</b>	V36I	1/1	1/1
	V36L	2/7 (29%)	2/3 (67%)
	<b>V36M</b>	<b>1/1</b>	<b>0/1</b>
<b>NS3 Q41</b>	Q41H	3/4 (75%)	n/a
<b>NS3 F43</b>	none	n/a	n/a
<b>NS3 T54</b>	<b>T54A</b>	<b>1/1</b>	<b>n/a</b>
	<b>T54S</b>	<b>10/13 (77%)</b>	<b>1/3 (33%)</b>
<b>NS3 V55</b>	<b>V55A</b>	<b>14/19 (74%)</b>	<b>1/2 (50%)</b>
	V55I	9/10 (90%)	1/3 (33%)
<b>NS3 Q80</b>	Q80K	120/165 (73%)	41/68 (60%)
	Q80L	10/14 (71%)	3/4 (75%)
	Q80R	4/5 (80%)	4/4 (100%)
<b>NS3 V107</b>	V107I	4/4 (100%)	0/1
<b>NS3 R155</b>	<b>R155K</b>	<b>n/a</b>	<b>0/1</b>
<b>NS3 A156</b>	none	n/a	n/a
<b>NS3 V158</b>	none	n/a	n/a
<b>NS3 D168</b>	D168E	1/1	1/1
<b>NS3 I/V170</b>	I170V (subtype 1a)	12/22 (55%)	0/3 (0%)
	V170I (subtype 1b)	47/55 (85%)	24/31 (77%)
	V@ NS3 170 (any subtype)	133/171 (77.8%)	62/87 (71.3%)
	I@ NS3 170 (any subtype)	313/425 (73.6%)	133/197 (67.5%)
<b>NS3 L/M175</b>	L175M (subtype 1a)	n/a	0/2 (0%)
	M175L (subtype 1b)	1/1	n/a
<b>NS4A V23</b>	NS4A V23A	0/1	n/a
<b>All Genotype 1a-Infected Subjects</b>		70.9% (278/392)	64.5% (109/169)
<b>All Genotype 1b-Infected Subjects</b>		82.0% (169/206)	74.8% (86/115)

Polymorphisms at NS3 position Q80, which are common in HCV genotype 1a-infected patients, have been shown to reduce the anti-HCV activity of certain NS3/4A protease inhibitors, particularly those in the macrocyclic/non-linear subclass. Based on the pooled analysis of P05216 and P05101 (Table 25), Q80 polymorphisms at baseline do not appear have a negative impact on boceprevir efficacy.

Further baseline resistance analyses and role of Peg-IFN $\alpha$ /RBV background therapy

In the pooled clinical trials P05216 and P05101, there were 40 subjects (4.5% of non-VF-censored, boceprevir-treated subjects) who had 1 or more of the following major boceprevir treatment-emergent substitutions detected at baseline: V36M, T54A, T54S, V55A, or R155K. Despite the detection of

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these substitutions at baseline, 28/40 (70%) of the subjects achieved SVR. Virologic responsiveness to the background Peg-IFN $\alpha$ -2b/RBV therapy may contribute to the lack of a clear association between the presence of a detectable boceprevir resistance-associated substitution at baseline and poor treatment outcome. For example, subjects with robust virologic responses to Peg-IFN $\alpha$ /RBV may not need the anti-HCV activity of boceprevir ultimately to achieve SVR, and therefore the presence of any boceprevir resistance-associated substitutions at baseline is of no clinical consequence.

Additional exploratory analyses were conducted to test the hypothesis that virologic responsiveness to background Peg-IFN $\alpha$ /RBV is confounding the relationship between the presence/absence of a detectable baseline boceprevir resistance-associated substitution and treatment outcome. Virologic response through Treatment Week 4, corresponding to the end the Peg-IFN $\alpha$ -2b/RBV lead-in period, was used as a measure of virologic responsiveness to current Peg-IFN $\alpha$ -2b/RBV background therapy. Treatment Week 4 responses were determined for boceprevir-treated subjects with or without detectable boceprevir resistance-associated substitutions at baseline, and the responses were analyzed according to treatment outcome (i.e., SVR). In addition, SVR rates were compared for subjects with or without detectable baseline boceprevir resistance-associated substitutions, with the subjects stratified according to virologic response through Treatment Week 4.

Most of the 28 boceprevir-treated subjects who achieved SVR despite having baseline resistance-associated substitutions did not necessarily require the anti-HCV activity of boceprevir to achieve SVR (note: analysis does not consider possible benefit of shortened treatment duration). In other words, the presence of boceprevir resistance-associated substitutions in these subjects was of little or no clinical consequence, not because the substitutions had no impact on virologic responsiveness to boceprevir, but because virologic responsiveness to the background therapy alone was likely adequate for most subjects to achieve SVR. Boceprevir-treated subjects with baseline V36M, T54A, T54S, V55A or R155K who achieved SVR had a median Treatment Week 4 HCV RNA decline from Baseline of 3.96 log<sub>10</sub> IU/mL, which was approximately 1.4 log<sub>10</sub> IU/mL greater than that of SVR-achieving, boceprevir-treated subjects without any of the baseline substitutions (Table 26). Furthermore, the median Treatment Week 4 HCV RNA decline for boceprevir-treated subjects with baseline resistance-associated substitutions who achieved SVR was ~0.5 log<sub>10</sub> IU/mL greater than that of placebo-treated, control arm subjects who achieved SVR.

**Table 26. Relationship between Treatment Week 4 virologic response and SVR outcome for subjects with or without boceprevir resistance-associated substitutions detected at baseline.** Analysis was conducted using as treated, non-VF-censored subject datasets. Baseline boceprevir resistance-associated substitutions considered in this analysis: V36M, T54A, T54S, V55A and R155K. \*5 of these 28 subjects had undetectable HCV RNA at Treatment Week 4.

Subject Population Analyzed	SVR Subjects		Non-SVR Subjects	
	n	Median Week 4 VL Change from Baseline (log <sub>10</sub> IU/mL)	n	Median Week 4 VL Change from Baseline (log <sub>10</sub> IU/mL)
Boceprevir-Treated Subjects <b>with</b> Baseline Resistance Substitution(s)	28*	-3.96	12	-0.95
Boceprevir-Treated Subjects <b>without</b> Baseline Resistance Substitution(s)	614	-2.55	228	-0.77
All Subjects in Control Arms	137	-3.51	215	-1.21

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Consistent with the results presented in Table 26, subjects with detectable boceprevir resistance-associated substitutions at baseline and a poor virologic response to the Peg-IFN $\alpha$ -2b/RBV background therapy had a low rate of SVR (Table 27). Among subjects with detectable boceprevir resistance-associated substitutions at baseline, 0 of 7 (0%) who achieved a  $<1 \log_{10}$  IU/mL decline through Treatment Week 4, and 3 of 14 (21%) who achieved a  $<2 \log_{10}$  IU/mL decline, eventually achieved SVR on boceprevir/Peg-IFN $\alpha$ -2b/RBV protocol therapy. Considering the SVR rates for control arm subjects, the addition of boceprevir did not appear to provide a major treatment benefit over placebo for subjects with detectable boceprevir resistance-associated substitutions at baseline and a relatively poor virologic response through Treatment Week 4.

**Table 27. SVR outcome for subjects with or without boceprevir resistance-associated substitutions detected at baseline, stratified by virologic response through Treatment Week 4 (end of Peg-IFN $\alpha$ -2b/RBV lead-in period).** Analysis was conducted using as treated, non-VF-censored subject datasets. Baseline boceprevir resistance-associated substitutions considered in this analysis were V36M, T54A, T54S, V55A and R155K.

Subject Population Analyzed	SVR Rate According to HCV RNA Decline through Treatment Week 4		
	$<1 \log_{10}$ IU/mL	$\geq 1$ to $<2 \log_{10}$ IU/mL	$\geq 2 \log_{10}$ IU/mL
Boceprevir-Treated Subjects <b>with</b> Baseline Resistance Substitution(s)	0/7 (0%)	3/7 (43%)	25/26 (96%)
Boceprevir-Treated Subjects <b>without</b> Baseline Resistance Substitution(s)	90/235 (38%)	148/199 (74%)	376/408 (92%)
All Subjects in Control Arms	2/89 (2%)	26/100 (26%)	109/163 (67%)

The numbers of subjects with major detectable boceprevir resistance-associated substitutions (V36M, T54A, T54S, V55A and R155K) at baseline is relatively small,  $<5\%$  of boceprevir-treated subjects, and therefore these exploratory analyses should be interpreted cautiously. Nevertheless, these observations are scientifically rational and consistent with current knowledge regarding antiviral drug resistance; for example, the relationship between genotypic or phenotypic susceptibility scores and efficacy of combination antiretroviral drug regimens to treat HIV-1 infection. As in the case of HIV-1 antiretroviral drug resistance, virologic responsiveness to the anti-HCV background therapy must be considered to fully understand the effect of baseline resistance-associated substitutions on treatment outcome with HCV DAAs. Because IL28B genotype plays a major role in virologic responsiveness to Peg-IFN $\alpha$ /RBV, the negative impact of baseline boceprevir resistance-associated substitutions on boceprevir/Peg-IFN $\alpha$ /RBV treatment outcome is likely to be amplified among subjects with an unfavorable IL28B genotype, for example rs12979860 genotype T/T.

These results may be useful in understanding the potential consequences of boceprevir/Peg-IFN $\alpha$ /RBV treatment failure on future treatment options. Failure to achieve SVR with a boceprevir/Peg-IFN $\alpha$ /RBV treatment regimen is not only associated with treatment-related enrichment of HCV populations with reduced susceptibility to boceprevir and other NS3/4A protease inhibitors, but is also the result of a poor virologic response to the Peg-IFN $\alpha$ /RBV background therapy. Therefore from a virology/resistance perspective, boceprevir/Peg-IFN $\alpha$ /RBV treatment failure subjects may be comparable to the subset of boceprevir treatment-naïve subjects who have (1) baseline HCV populations with reduced susceptibility to boceprevir, and (2) a poor virologic response to Peg-IFN $\alpha$ /RBV.

Similar analyses were conducted to assess the impact of baseline NS3 Q80 or I/V170 genotype on treatment outcome. In contrast to the pooled analysis of V36M, T54A, T54S, V55A, and R155K, there

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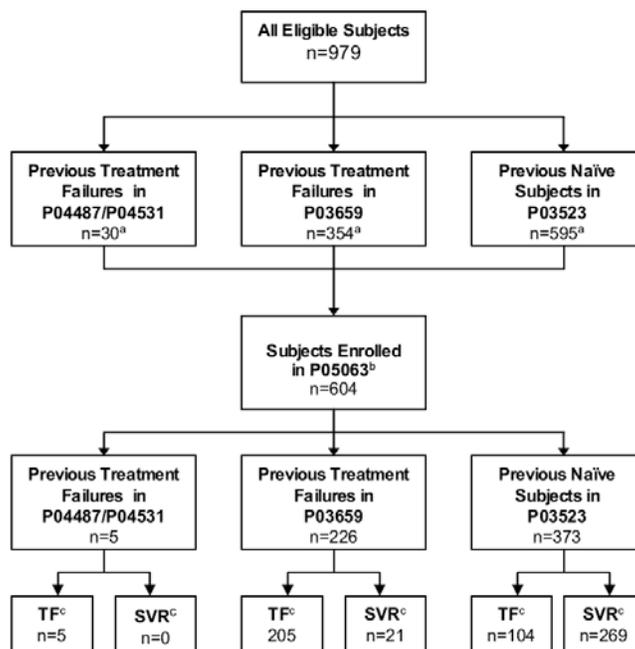
was no consistent evidence indicating that specific amino acids at NS3 positions 80 (Q versus non-Q) or 170 (I versus V) affect treatment outcome among subjects responding poorly to the Peg-IFN $\alpha$ -2b/RBV background therapy (data not shown).

**4.4 Long-term Follow-up Trial P05063**  
**4.4.1 Summary of Trial Design**

Overview

Clinical trial P05063 is an ongoing, long-term follow-up study of subjects previously enrolled in a clinical trial in which boceprevir or narlaprevir (another NS3/4A protease inhibitor) was administered. The primary objectives of the trial can be summarized as follows: (1) to confirm the durability of response in subjects who achieved SVR in the previous study, (2) to characterize long-term safety, and (3) to characterize the persistence of resistance-associated substitutions that emerged as a result of drug exposure in the previous study. Subjects are to be followed for 3.5 years after the end of treatment in the previous study.

In the present NDA submission, the sponsor has provided a study report for subjects who previously participated in a boceprevir clinical trial only, with a data cutoff date of 3/4/2010. As of this cutoff date, 604 subjects (290 who achieved SVR, 314 who did not achieve SVR) had enrolled; 99% (599/604) of the subjects were previously studied in one of the two Phase 2 boceprevir trials P06359 or P03523 (Figure 4; Report pg. 46). The sponsor did not consider this report to represent a formal interim analysis.



TF = treatment failure; SVR = sustained virologic response  
<sup>a</sup> Represents the number of subjects treated  
<sup>b</sup> Not all eligible subjects enrolled in P05063; some subjects elected not to participate in the long-term follow-up.  
<sup>c</sup> Status of subjects at the End of Treatment in the previous treatment protocol

**Figure 4. Disposition of study subjects in P05063 included in this interim report.** The median duration of follow up for all subjects enrolled and included in this report (n=604) is ~2 years.

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Analysis methods to assess durability of SVR

Multiple different HCV RNA assays were used for HCV viral load assessments in the donor protocols. In P05063, (b) (4) conducted the assessments. Initially, the assays performed by (b) (4) were performed using a Roche COBAS<sup>®</sup> TaqMan<sup>®</sup> HCV/High Pure System (HPS) assay with a reported lower limit of quantification of 30 IU/mL and a limit of detection of 15 IU/mL in EDTA plasma. After 7/31/2009, assays were performed using a Roche COBAS<sup>®</sup> TaqMan<sup>®</sup> HCV/HPS v2.0 assay with a reported a lower limit of quantification of 25 IU/mL and a limit of detection of 9.3 IU/mL in EDTA plasma.

A subject was classified as having achieved SVR based on the criteria defined in the donor protocols (undetectable HCV RNA at Follow-up Week 24). All other subjects were considered treatment failures. In P05063, subjects are classified based on the last HCV RNA result available at the time of the data cut-off date as follows:

**SVR:** undetectable serum HCV RNA at a given timepoint with no detectable HCV RNA since the subject was determined to have achieved SVR in the previous study

**Definite Relapser:** SVR in the previous treatment study and became serum HCV RNA detectable with no subsequent undetectable HCV RNA results during long-term follow-up

During the conduct of the study, if an HCV RNA result is inconsistent with previous and/or subsequent results (e.g., transiently high HCV RNA level with multiple undetectable results before and after) and it is suspected to be spurious due to a mislabeled sample, then that sample is sequenced and compared to the baseline (pre-treatment) sequence from that subject to determine if the viral population is genetically the same. According to the sponsor, this comparison is done in a blinded fashion by a scientist not directly involved in the conduct of the trial. In cases where the two samples were deemed not to be from the same subject, the results for the sample in question were suppressed for purposes of analysis providing that the new result was available before the database was locked. Based on the subject's virology results, the subject is classified as follows:

**Subject with HCV Reinfection:** subject was a sustained virologic responder in the previous treatment study and became serum HCV RNA detectable with no subsequent undetectable results during the long-term follow-up and confirmation of mismatch in genotype, subtype, or sequence was reported.

**Subject with Mislabeled Sample:** was a sustained virologic responder in the previous treatment study and became serum HCV RNA detectable with one or more subsequent undetectable results during the long-term follow-up and confirmation of mismatch in genotype, subtype, or sequence was reported.

Sequence analysis methods to assess persistence of resistance-associated substitutions

Plasma samples with an HCV RNA levels of >1,000 IU/mL were analyzed by population nucleotide sequence analysis of the NS3/4A gene. As of the cut-off date for this analysis, sequence data were not available for samples obtained from the 5 subjects who previously participated in P04487/P04531. Because the sponsor changed procedures for HCV sequence analysis during the boceprevir development program, sequence analyses for the P05063 long-term follow-up trial and the two Phase 2 donor trials were performed by two different laboratories, (b) (4) and internally by sponsor (b) (4). For the purposes of this interim analysis the sponsor pooled results from both sources.

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To assess whether the pooling of nucleotide sequence analysis results was appropriate, the sponsor conducted a concordance analysis for data obtained from (b) (4) and (b) (4) for 1,095 samples (out of 4,479 samples total, 24%) that were analyzed by both laboratories, focusing on 12 specific resistance-associated substitutions. Concordance was defined by the sponsor as the proportion of substitutions classified as detected or not detected by both laboratories (Table 28; Report pg. 62). The value of Kappa indicates the strength of the agreement, with a maximum value of 1, corresponding to perfect agreement, and 0, corresponding to agreement equivalent to chance. Kappa was relatively high for the most common resistance-associated substitutions: V36M (0.82), T54S (0.82), and R155K (0.93).

**Table 28. Sponsor’s concordance analysis of (b) (4) and (b) (4)-reported nucleotide sequencing results.** Shown are the detection results for 12 specific boceprevir resistance-associated substitutions for 1,095 samples (out of 4,479 samples total, 24%) that were analyzed by both laboratories.

RAV	(b) (4)				Concordance <sup>a</sup> (%)	Kappa (95% CI)
V36L	1083	3	4	5	99.4	0.59 (0.31, 0.86)
V36M	925	12	33	125	95.9	0.82 (0.77, 0.87)
T54A	1070	5	11	9	98.5	0.52 (0.32, 0.73)
T54S	889	33	21	152	95.1	0.82 (0.77, 0.87)
V55A	1072	17	0	6	98.4	0.41 (0.18, 0.63)
V55I	1087	7	0	1	99.4	0.22 (-0.14, 0.58)
R155K	852	15	12	216	97.5	0.93 (0.90, 0.95)
R155T	1074	1	3	17	99.6	0.89 (0.79, 1.00)
A156S	1046	5	10	34	98.6	0.81 (0.72, 0.91)
A156T	1092	1	2	0	99.7	-0.00 (-0.00, 0.00)
V158I	1082	9	1	3	99.1	0.37 (0.07, 0.67)
I170T	1092	0	1	2	99.9	0.80 (0.41, 1.00)

CI = confidence interval; RAV = resistance-associated variant; - = RAV not detected; + = RAV detected

<sup>a</sup> Proportion of RAV classified as detected or not detected by both (b) (4) laboratories.

Ideally, because RT-PCR and nucleotide sequence analyses conducted by different laboratories can frequently yield different results, the same laboratory would have been used to analyze and report NS3/4A sequence data for all timepoints from a given subject for optimal interpretability of the results. In this reviewer’s opinion, the sponsor’s concordance analysis is flawed because “concordance” in Table 28 is heavily based on lack of detection of a substitution by both laboratories rather than detection of the substitution by both laboratories. It is concerning that for many of the specific substitutions shown, a significant number of samples had the substitution detected with one assay but not the other. This confounds the analysis because the lack of detection of a particular substitution later during follow-up based on a result reported from a different laboratory can be interpreted in two different ways: (1) viral populations harboring the substitution have declined in abundance over time, or (2) the second laboratory’s methodology was less sensitive in detecting the substitution. Fortunately, the results do not indicate that the (b) (4) method, which produced most of the early follow-up data, was consistently more sensitive than the (b) (4) method, which produced the later follow-up data, in detecting a resistance-associated substitution. Based on compiled results presented in Table 28, there were 108 examples of substitutions reported by (b) (4) but not by (b) (4), and 98 examples of substitutions reported by (b) (4) but not by (b) (4). Nevertheless, the potential for discordant laboratory results should be considered when interpreting the nucleotide sequence analysis results reported for P05063. This problem is not anticipated in the long-term follow-up analyses of subjects who failed boceprevir treatment during P05216 or P05101, as (b) (4) conducted

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the sequence analyses for these trials, assuming that (b) (4) will also continue to conduct the analyses as P05063 continues.

Two approaches to analyzing long term follow-up NS3/4A sequence data were conducted by this reviewer to assess the persistence of resistance-associated substitutions:

**Last observation carried forward (LOCF) analysis:** This is a conservative approach to quantify the number/percentage of subjects who had a boceprevir treatment-emergent substitution detected by population-based sequence analysis through specific follow-up timepoints. Data from the last available sample collected up to a specific follow-up timepoint were used to classify whether a subject still had the substitution detected up to that timepoint. For example, if a subject had V36M detected at Follow-up Month 3, and no other follow-up data from this subject are available between Follow-up Month 3 and Follow-up Year 1, the subject was classified as having detectable V36M at the Follow-up Year 1 timepoint. Results reported from this analysis should be interpreted as the maximum number of subjects who still have the substitution detected through a specific follow-up timepoint.

**Snapshot analysis:** This analysis focused on a single timeframe of  $\geq 2.5$  years of follow-up. Only subjects with available data obtained in this time window were included in the analysis. If a subject had a resistance-associated substitution detected in any sample collected at least 2.5 years after stopping treatment, that subject was classified as still having the substitution detected in the time window.

#### **4.4.2 Analysis of SVR Durability**

As of the cutoff date for this interim analysis, none of the 290 sustained virologic responders enrolled in this long-term follow-up study had HCV RNA virology results that met the sponsor's criteria for a "definite relapse." Based on an independent analysis of the virologic response data, this reviewer agrees with the sponsor's conclusion.

One subject (B00397) had evidence of HCV re-infection. For this subject, the last two HCV RNA measurements at Follow-up Days 582 and 680 were  $>10^6$  IU/mL, whereas HCV RNA levels were undetectable for all other prior follow-up timepoints. The sponsor classified this subject as having an HCV re-infection based on results of HCV genotype/subtype testing. In the previous protocol, the subject was classified as being infected with HCV subtype 1a, whereas the viral population that was detected later during follow-up was of HCV subtype 1b. Note that genotype/subtype results in both cases were reported by (b) (4) based on nucleotide sequence analysis of a 329 base pair domain of NS5B.

Three subjects (B01631, B00411 and B00321) who achieved SVR in the previous treatment study had isolated detectable HCV RNA results during the long-term follow-up that did not meet the sponsor's criteria for definite relapse. Each of these subjects had a single occurrence of detectable HCV RNA during long-term follow-up, had not received any antiviral/immunomodulatory therapy, and subsequently had undetectable HCV RNA results on multiple occasions. Of note, for subjects B00411 and B00321, the transient detectable HCV RNA levels were high (4,210,000 and 264,000, respectively), indicating that cross-contamination of the sample or a false-positive measurement are unlikely explanations for these results. The sponsor did not comment on any nucleotide sequence analyses to address whether these measurements are due to a mislabeled sample.

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Four additional subjects (B00404, A00290, A00035 and B00118) who achieved SVR in the previous trial had low level, transiently detectable HCV RNA results at single, early follow-up visits (Days 27-104), prior to the Follow-up Week 24 assessment for determination of SVR.

There was also no evidence of spontaneous clearance of HCV among the 314 subjects who were classified as treatment failures in the previous studies. Of the 314 non-SVR subjects, 2 subjects (A00094 and B05004) each had an undetectable HCV RNA result at a single follow-up timepoint, with multiple prior and subsequent results of detectable, high level HCV RNA, possibly reflecting false-negative test results or problems with the test sample. One other subject (A00047) was classified as not having achieved SVR in the previous trial presumably based on a low level (100 IU/mL) detectable measurement of HCV RNA at Follow-up Week 24. However, the subject had undetectable HCV RNA results at all other prior and subsequent follow-up timepoints, indicating that the subject effectively had achieved SVR.

#### **4.4.3 Analysis of Persistence of Resistance-Associated Substitutions**

An independent analysis of persistence of boceprevir resistance-associated substitutions was conducted focusing on 9 specific NS3 substitutions: V36M, T54A, T54S, V55A, R155K, R155T, A156S, V158I, and I/V170A. These substitutions emerged in at least ~5% of HCV genotype 1a or 1b-infected, boceprevir treatment failure subjects in the two Phase 3 trials. In P05063, follow-up population nucleotide sequence data are available for 230 subjects who received boceprevir in one of the previous Phase 2 trials, failed to achieve SVR, and had 1 or more of these treatment-emergent substitutions. For a small number of subjects, a specific substitution that emerged during boceprevir treatment was not detected at the last on-treatment or first follow-up sample timepoint analyzed, and therefore the persistence of the substitution in the treatment-free follow-up period could not be characterized. Two analysis approaches were conducted (see Section 4.4.1 for details): (1) a conservative, LOCF analysis of several follow-up timeframes, and (2) a snapshot analysis of available data for samples collected >2.5 years of follow-up.

It is critical to be aware of the following key points when interpreting these data:

- The lack 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 may have existed prior to treatment in that patient.
- The long-term clinical impact of the emergence or persistence of boceprevir resistance-associated substitutions is unknown.
- The minimum quantity or abundance of viral subpopulations harboring boceprevir resistance-associated substitutions that results in a reduction in boceprevir efficacy for a given patient is unknown and is likely influenced by many factors, including the activity of other agents in the background regimen.
- No data are available regarding boceprevir efficacy among subjects who were previously exposed to boceprevir, or who previously failed treatment with a boceprevir-containing regimen.

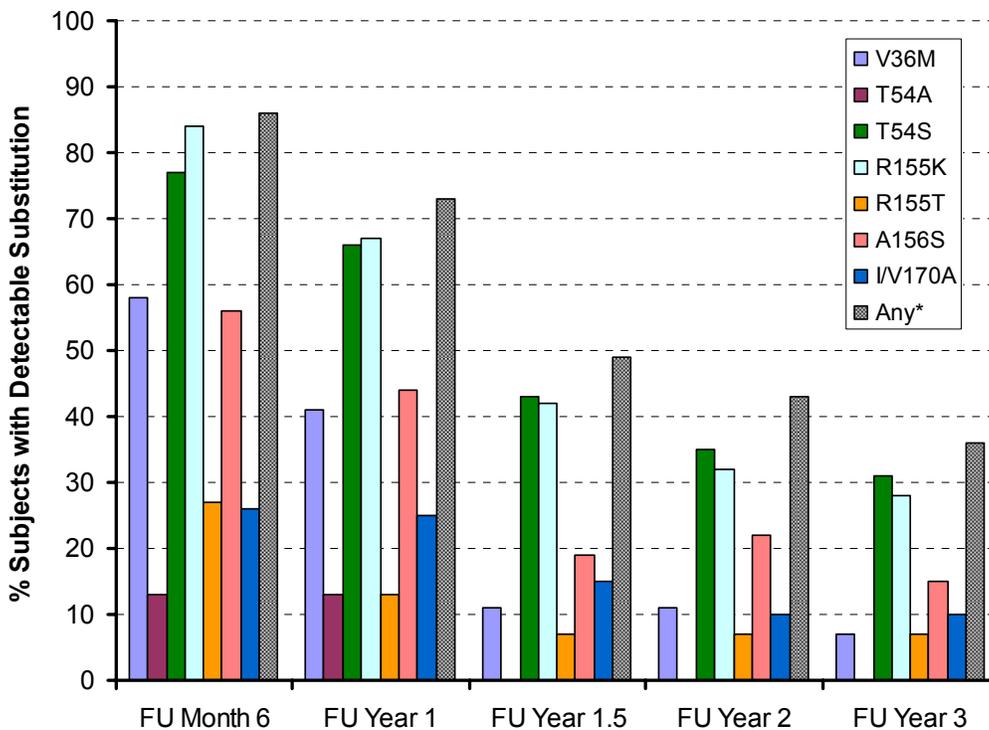
Table 29 summarizes the results of the LOCF analysis, and Figure 5 provides a graphical representation of these data. The overall number of subjects with specific boceprevir treatment-emergent, resistance-associated substitutions detected by population-based sequencing generally declines over time during follow-up, reflecting the outgrowth of viral populations lacking these substitutions. However, different substitutions clearly have different rates at which they become undetectable during follow-up, with T54S and R155K remaining detectable in the most number of subjects up to Follow-up Year 3.

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**Table 29. Frequency of detection (population-based assay) of boceprevir treatment-emergent, resistance-associated substitutions during follow-up.** Conservative, last observation carried forward analysis.

Tx-emergent Substitution	% of Subjects with Substitution Detected at Last Available Timepoint, Up To:				
	Follow-up Month 6	Follow-up Year 1	Follow-up Year 1.5	Follow-up Year 2	Follow-up Year 3
V36M	58% (59/102)	41% (44/108)	11% (12/110)	11% (12/111)	7% (8/111)
T54A	13% (4/30)	13% (4/30)	0% (0/32)	0% (0/32)	0% (0/32)
T54S	77% (104/135)	66% (93/141)	43% (61/143)	35% (50/143)	31% (44/143)
R155K	84% (113/134)	67% (95/141)	42% (60/143)	32% (46/144)	28% (40/144)
R155T	27% (4/15)	13% (2/15)	7% (1/15)	7% (1/15)	7% (1/15)
A156S	56% (15/27)	44% (12/27)	19% (5/27)	22% (6/27)	15% (4/27)
I/V170A	26% (5/19)	25% (5/20)	15% (3/20)	10% (2/20)	10% (2/20)
<b>Any*</b>	<b>86% (183/214)</b>	<b>73% (163/222)</b>	<b>49% (110/226)</b>	<b>43% (97/227)</b>	<b>36% (82/227)</b>

\*Substitutions that emerged in at least ~5% of HCV genotype 1a or 1b-infected, boceprevir treatment failure subjects in Phase 3 trials: V36M, T54A, T54S, V55A, R155K, R155T, A156S, V158I, I/V170A



**Figure 5. Frequency of detection (population-based assay) of boceprevir treatment-emergent, resistance-associated substitutions during follow-up.** Conservative, last observation carried forward analysis. \*Substitutions that emerged in at least ~5% of HCV genotype 1a or 1b-infected, boceprevir treatment failure subjects in Phase 3 trials: V36M, T54A, T54S, V55A, R155K, R155T, A156S, V158I, I/V170A.

Table 30 summarizes the results of the snapshot analysis. Among those subjects with available data, one or more boceprevir treatment-emergent substitutions remained detectable based on population-based nucleotide sequence analysis in 25% of subjects after 2.5 years of follow-up. Consistent with

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the results from the LOCF analysis presented in Table 29 and Figure 5, the most common NS3 substitutions detected after 2.5 years of follow-up were T54S and R155K. These results indicate that viral populations harboring T54S and R155K may decline in abundance at a negligible rate, even in the absence of any drug exposure, in a significant number of patients. One can predict that the presence of a highly abundant viral population harboring T54S or R155K will have a direct impact on the susceptibility of HCV to boceprevir and other NS3/4A protease inhibitors that are affected by these substitutions.

**Table 30. Frequency of detection (population-based assay) of boceprevir treatment-emergent, resistance-associated substitutions at least 2.5 years following end of treatment.** Only subjects with data available in this time window were included in the analysis.

<b>Tx-emergent Substitution</b>	<b>% of Subjects with Detectable Substitution ≥ 2.5 Follow-up Years</b>
V36M	2% (1/49)
T54A	0% (0/18)
T54S	19% (14/73)
R155K	19% (13/67)
R155T	0% (0/5)
A156S	0% (0/8)
I/V170A	0% (0/9)
<b>Any*</b>	<b>25% (26/104)</b>
*V36M, T54A, T54S, V55A, R155K, R155T, A156S, V158I or I/V170A	

The results presented above provide important insight into the relative *in vivo* fitness of viral populations harboring boceprevir resistance-associated substitutions. The observation that T54S and R155K remain detectable years after removal of drug pressure, based on a population-based assay, implies that these substitutions have a minimum impact on HCV replicative fitness within these infected patients. Consistent with the observation that treatment-emergent T54S and R155K may have little impact on HCV replicative fitness in some subjects, both of these substitutions have been detected by population-based sequence analysis surveys of baseline samples from subjects never previously exposed to an NS3/4A protease inhibitor (e.g., [Kuntzen et al., 2008](#)). Among all subjects who enrolled in the two Phase 3 boceprevir trials, and for whom NS3/4A sequence data are available, 22/1436 (1.5%) had detectable T54S at baseline, although only 1/1436 (0.07%) had detectable R155K at baseline.

Of all the treatment-emergent substitutions evaluated, T54A appeared to decline in the treatment-free follow-up period most rapidly, and was no longer detected in any subjects after 1 year of follow-up. Interestingly, in many subjects detection of treatment-emergent T54A preceded the detection of treatment-emergent T54S. The T54A substitution occurs as a result of a single A to G transition mutation (i.e., purine to purine) in the T54 codon (ACx to GCx). The T54S substitution can also occur as a result of a single nucleotide change in the T54 codon (ACx to UCx), but the A to U change is a transversion mutation (i.e., purine to pyrimidine) that is more difficult to generate biochemically and therefore occurs spontaneously at a much lower frequency. An alternative mechanism to generate the T54S substitution (ACx to AG{U/C}) also requires, at minimum, a C to G transversion mutation (i.e., pyrimidine to purine). Taken together, these observations may reflect a replicative fitness advantage of the T54S substitution over the T54A substitution, but the T54S substitution is likely more difficult to generate at the molecular level.

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**4.5 Virology Summaries of Other Supportive Boceprevir Clinical Trials**

This review section includes summaries of two completed Phase 2 trials, P03523 (SPRINT-1) and P03659 (RESPOND-1), which supported the design of the pivotal Phase 3 trials. The final clinical study reports for P03523 and P03659 were submitted to IND 69027 (SDNs 322 and 237, respectively) and reviewed previously. See previously archived Virology reviews of these IND submissions for more detailed reviews of the final clinical study reports. Note that nucleotide sequence analysis data for P03523, which were not part of the previously submitted final clinical study report, were included in the boceprevir NDA. An independent analysis of these data is summarized below.

This section also includes a summary of P05685, a recently completed Phase 3 trial that studied the efficacy of boceprevir dosed in combination with Peg-IFN $\alpha$ -2 $a$ /RBV (previous trials used Peg-IFN $\alpha$ -2 $b$ ). Recently acquired SVR data from this trial were summarized in the NDA 3-month safety update report, received on 2/15/2011.

A brief summary of virologic responses in clinical trial P03648, which was a Phase 1 PK/PD/Safety study of boceprevir monotherapy in treatment-naïve subjects infected with HCV genotype 2 or 3, is also included in this review section.

**4.5.1 P03523 (SPRINT-1)**

Title

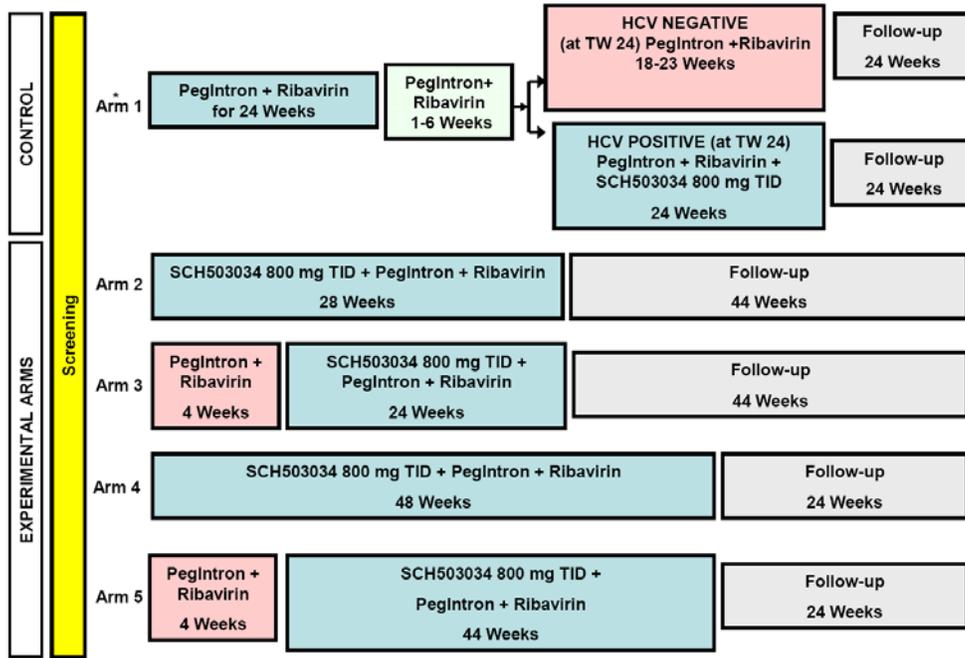
P03523, "A Safety and Efficacy Study of SCH 503034 in Previously Untreated Subjects with Chronic Hepatitis C Infected with Genotype 1."

Summary of Design

Clinical trial P03523 (SPRINT-1) evaluated the efficacy of boceprevir 800 mg TID dosed in combination with Peg-IFN $\alpha$ -2 $b$ /RBV in previously untreated adult chronic HCV genotype 1 infected subjects. A design schematic of P03523 is shown in Figure 6 (Report pg. 2738). This study was an open-label, randomized trial. Part 1 of the trial had 5 treatment arms, with equal randomization across arms. The treatment regimen for Arms 3 and 5 included a 4-week Peg-IFN $\alpha$ -2 $b$ /RBV lead-in period. Part 2 of was conducted at select sites after Part 1 was fully enrolled, and was designed to assess the efficacy of a boceprevir/Peg-IFN $\alpha$ -2 $b$ /RBV regimen using a reduced RBV dose level (400 to 1,000 mg/day). Randomization in Part 2 was 1:4 (standard RBV dose to reduced RBV dose). The primary efficacy endpoint was the achievement of SVR, defined as plasma HCV RNA below the lower limit of quantification at FW 24.

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**Part 1 Study Design Diagram**



\*Arm 1 treatment duration is based on TW24 HCV-RNA results: Subjects who are HCV-RNA negative at TW24 will receive PegIntron+ribavirin for 48 weeks total. Subjects who are HCV-RNA positive at TW24 will be offered PegIntron+ribavirin+SCH503034 800mg TID for an additional 24 weeks (up to 54 weeks total). Reporting of HCV status will vary from 1-6 weeks.

**Part 2 Study Design Diagram**



**Figure 6. Design schematic of Phase 2 clinical trial P03523 (SPRINT-1).**

Summary of Sponsor's Efficacy Analyses

The sponsor's intent-to-treat analyses of SVR, EOT, and Relapse rates for Parts 1 and 2 are shown in Table 31 (Report pg. 85). Boceprevir added to SOC Peg-IFN $\alpha$ -2b/RBV therapy resulted in an increased SVR rate. Forty-eight (48) weeks of the 3-drug combination regimen resulted in a higher SVR rate compared to 28 weeks duration. This difference in SVR could be attributed largely to a reduced relapse rate with the longer treatment duration. The use of low dose RBV in Arm 7 was associated with a poor SVR rate, indicating that adequate RBV exposure is essential for an optimal SVR rate, even when boceprevir is included in the regimen. For subjects in boceprevir arms, failure to achieve undetectable HCV RNA by Treatment Week 12 was associated with a poor SVR rate: in

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Part 1, 1/80 (1.25%) subjects who did not achieve undetectable HCV RNA at Treatment Week 12 achieved SVR. For the Peg-IFN $\alpha$ -2b/RBV lead-in arms, the magnitude of HCV RNA decline during the lead-in period was associated with the SVR rate. There was a high degree of concordance for the rate of undetectable HCV RNA at Follow-up Weeks 12 and 24 (i.e., SVR12 versus SVR24).

**Table 31. Sponsor's efficacy analysis of P03523.**

	Arm 1 <sup>a</sup> P/R 48 wk n=104	Arm 2 P/R/B 28 wk n=107	Arm 3 P/R Lead-in P/R/B 28 wk n=103	Arm 4 P/R/B 48 wk n=103	Arm 5 P/R Lead-in P/R/B 48 wk n=103	Arm 6 P/R/B 48 wk n=16	Arm 7 <sup>b</sup> P/Low- Dose R/B 48 wk n=59
EOT n (%)	53 (51.0)	84 (78.5)	79 (76.7)	76 (73.8)	81 (78.6)	9 (56.3)	28 (47.5)
SVR <sup>c</sup> n (%)	39 (37.5)	58 (54.2)	58 (56.3)	69 (67.0)	77 (74.8)	8 (50.0)	21 (35.6)
Difference vs Arm 1	--	16.7%	18.8%	29.5%	37.3%	--	--
95% CI	--	3.5%, 30.0%	5.5%, 32.2%	16.5%, 42.5%	24.7%, 49.8%	--	--
P value	--	0.0126	0.0048	<.0001	<.0001	NA	NA
Relapse <sup>d,e</sup> n/N (%)	12/51 (23.5)	24/81 (29.6)	18/76 (23.7)	5/73 (6.8)	2/79 (2.5)	1/9 (11.1)	6/27 (22.2)
Difference vs Arm 1	--	6.1%	0.2%	-16.7% <sup>f</sup>	-21.0% <sup>f</sup>	NA	NA

B = boceprevir; CI = confidence interval; EOF = End of Follow-up; EOT = End of Treatment; FW = Follow-up Week; HCV-RNA = hepatitis C virus-ribonucleic acid; NA = not applicable; P = peginterferon alfa-2b 1.5  $\mu$ g/kg QW; QW = once weekly; R = ribavirin 800 to 1400 mg/day; SVR = sustained virologic response.

- a: 36 Arm 1 crossover subjects were considered nonresponders for EOT and SVR and were excluded from Relapse.
- b: Ribavirin 400 to 1000 mg/day weight based.
- c: SVR: The last available value in the period at and after FW 24. If there is no such value, the FW 12 value was carried forward.
- d: Relapse rates were calculated based on subjects with undetectable HCV-RNA at EOT and not missing EOF data.
- e: One subject in Arm 2 had undetectable HCV-RNA at FW 24 that became detectable after FW 24. This subject was not considered a sustained virologic responder.
- f: Relapse rate was significantly less than relapse rate in Arm 1: Arm 4 vs Arm 1 (P=0.0079 [95% CI -29.7%, -3.7%]) and Arm 5 vs Arm 1 (P=0.0002 [95% CI -33.1%, -8.9%]).

For the 48 week treatment duration, the 4-week Peg-IFN $\alpha$ -2b/RBV lead-in arm (Arm 5) had a higher SVR rate compared to the non-lead-in arm (Arm 4): 74.8% vs. 67.0% (Table 32; Report pg. 95). An improvement in SVR rate with the lead-in was less apparent for the 28 week duration (Arm 2 vs. 3). There was a trend of fewer subjects with virologic breakthrough in the Peg-IFN $\alpha$ -2b/RBV lead-in arms, although in this reviewer's opinion the sponsor's definition of virologic breakthrough ("persistent  $\geq 2$  log<sub>10</sub> IU/mL elevation from nadir and viral load  $\geq 50,000$  IU/mL") likely underestimated the total number of subjects who experienced a viral load rebound during treatment. According to the sponsor, the overall difference in SVR rates for pooled Peg-IFN $\alpha$ -2b/RBV lead-in vs. non-lead-in arms was not statistically significant.

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**Table 32. Comparison of SVR, end of treatment response, and virologic breakthrough rates for Peg-IFN $\alpha$ -2b/RBV lead-in versus no-lead-in strategy in clinical trial P03523.**

	Number (%) of Subjects			
	Arm 2 P/R/B 28 wk n=107	Arm 3 P/R Lead-in P/R/B 28 wk n=103	Arm 4 P/R/B 48 wk n=103	Arm 5 P/R Lead-in P/R/B 48 wk n=103
EOT	84 (78.5)	79 (76.7)	76 (73.8)	81 (78.6)
SVR	58 (54.2)	58 (56.3)	69 (67.0)	77 (74.8)
Relapse n/N (%)	24/81 (29.6)	18/76 (23.7)	5/73 (6.8)	2/79 (2.5)
Viral Breakthrough <sup>a</sup>	7 (7)	4 (4)	12 (12)	5 (5)

B = boceprevir; EOT = End of Treatment; IU = international units; P = peginterferon alfa-2b 1.5  $\mu$ g/kg QW; QW = once weekly; R = ribavirin 800 to 1400 mg/day; SVR = sustained virologic response.

a: Persistent  $\geq 2 \log_{10}$  elevation from nadir and viral load  $\geq 50,000$  IU/mL.

There were multiple lines of evidence of bias or randomization imbalance in this open-label trial that make it difficult to draw conclusions regarding the relative efficacy of the Peg-IFN $\alpha$ -2b/RBV lead-in versus non-lead-in treatment regimens. For example, subjects in Arms 3 and 5 had a greater overall virologic response during the 4 week Peg-IFN $\alpha$ -2b/RBV lead-in phase compared to subjects in Arm 1 (Peg-IFN $\alpha$ -2b/RBV standard-of-care control), despite the treatment regimens being identical during this time period: 32% (33/104) of Arm 1 subjects had a  $\geq 2 \log_{10}$  IU/mL decline in HCV RNA compared to 46% (47/103) and 50% (52/103) for subjects in Arms 3 and 5, respectively, at Week 4 of Peg-IFN $\alpha$ -2b/RBV dosing. Also, overall reported treatment compliance for boceprevir-containing arms was associated with treatment outcome, and greater compliance was reported for the Peg-IFN $\alpha$ -2b/RBV lead-in arms compared to the non-lead-in arms. Although part of this difference may be attributed to an elevated number of subjects in the non-lead-in arms who discontinued dosing early due to virologic breakthrough, this does not account for all of the difference in the number of subjects who were considered compliant with dosing for all study treatments for the entire treatment duration. Among subjects who were considered compliant to study treatment for the full duration, an elevated SVR rate was not observed in the lead-in arms relative to non-lead-in arms.

#### Treatment-emergent Resistance Analysis

An independent treatment-emergent resistance analysis was conducted for 192 subjects who were exposed to boceprevir of any duration (including Arm 1 treatment-failure subjects who received boceprevir add-on treatment), failed to achieve SVR, and had appropriate baseline and post-baseline sequence data available for analysis. The results of this analysis, summarized below, are consistent with those from the two Phase 3 trials.

This analysis initially focused on NS3 positions where most boceprevir treatment-emergent substitutions were observed in the two Phase 3 trials P05216 and P05101: V36, T54, V55, R155, A156, V158, and I/V170. All sequence analyses were population-based. Of these 192 subjects, 105 (55%) had one or more of the following treatment-emergent substitutions: V36M, T54A, T54S, V55A, R155K, R155T, A156S, A156T, V158I and I/V170A. The most common treatment-emergent substitutions observed in genotype 1a-infected subjects (>10% of subjects, in descending frequency) were R155K, V36M and T54S. The most common treatment-emergent substitutions observed in genotype 1b-infected subjects (>10% of subjects, in descending frequency) were T54S, I/V170A, A156S, and T54A.

The novel boceprevir resistance-associated substitutions D168N and V107I also emerged in a few boceprevir-treated subjects in this trial. The D168N substitution emerged in 5 HCV genotype 1a-

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infected subjects, who also had treatment-emergent R155T (as in the Phase 3 trials). The V107I substitution emerged in a single HCV genotype 1a-infected subject. The possible resistance-associated substitution P146S emerged in two boceprevir-treated subjects (one 1a, one 1b); for one of the subjects the substitution was not detected later during treatment.

Baseline Resistance Analysis

Baseline population NS3 sequence data were available for 482 boceprevir-treated subjects from this trial. Of these subjects, 23 (4.8%) had one or more of the following major resistance-associated substitutions (based on treatment-emergent analyses) detected as baseline polymorphisms: V36M, T54S, V55A or R155K. Seventeen (74%) of these subjects achieved SVR.

Ideally, the effect of these baseline substitutions on boceprevir efficacy would be analyzed while accounting for treatment response to the Peg-IFN $\alpha$ -2b/RBV background therapy. For the Phase 3 trial baseline resistance analyses, virologic responses through the end of the 4-week Peg-IFN $\alpha$ -2b/RBV lead-in period were used as a measure of virologic responsiveness to current Peg-IFN $\alpha$ -2b/RBV background therapy (see Section 4.3.2). In P03523, only 9 subjects with these baseline resistance-associated substitutions were randomized to one of the two Peg-IFN $\alpha$ -2b/RBV lead-in arms (Arms 3 or 5). Eight (89%) of these 9 subjects achieved SVR. These 8 subjects generally had a robust virologic response to Peg-IFN $\alpha$ -2b/RBV alone, with a -3.7 log<sub>10</sub> IU/mL median HCV RNA change from baseline to Treatment Week 4 (i.e., end of lead-in period); two subjects had undetectable HCV RNA at Treatment Week 4. The single subject who did not achieve SVR had a -2.0 log<sub>10</sub> IU/mL HCV RNA change from baseline to Treatment Week 4. This non-SVR subject also had a Week 4 HCV RNA level of 7,900 IU/mL, which was greater than that of any of the 8 subjects who ultimately achieved SVR (range: undetectable to 4,140 IU/mL).

Taken together, there were an inadequate number of subjects to characterize the effect of baseline boceprevir resistance-associated substitutions on treatment efficacy among subjects with a relatively poor virologic response to Peg-IFN $\alpha$ -2b/RBV background therapy. However, these limited results are consistent with those from the Phase 3 trial analyses, which indicate that virologic responsiveness to Peg-IFN $\alpha$ /RBV background therapy may reduce or negate the impact of having detectable boceprevir resistance-associated substitutions at baseline.

**4.5.2 P03659 (RESPOND-1)**

Title

P03659, "Peg-Intron/Rebetol® vs. Peg-Intron/SCH 503034 with and without Ribavirin in Chronic Hepatitis C HCV-1 Peginterferon alpha/Ribavirin Nonresponders: A SCH 503034 Dose-Finding Phase 2 Study."

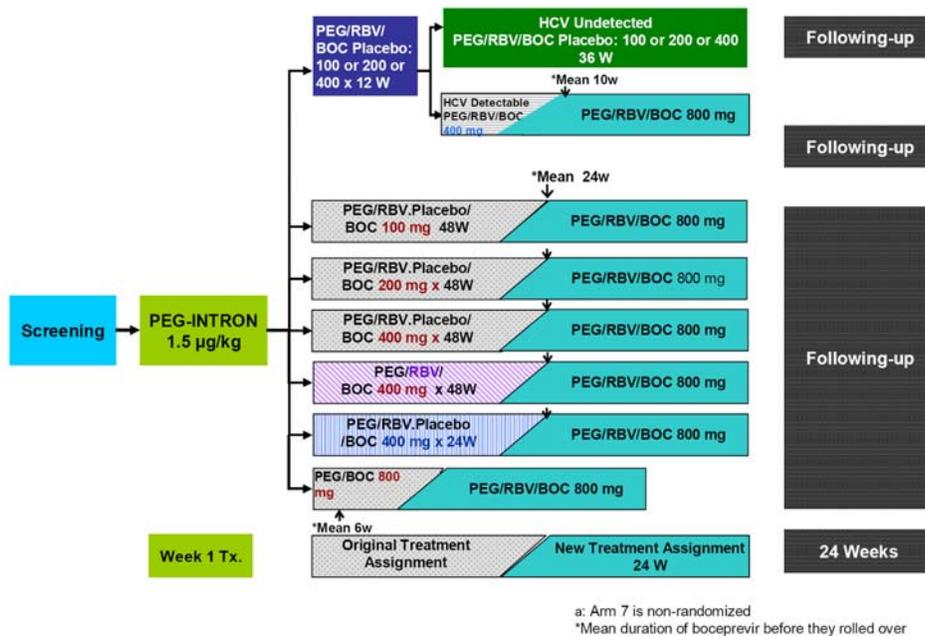
Summary of Design

Clinical trial P03659 studied the safety and efficacy of various levels of boceprevir dosed in combination with Peg-IFN $\alpha$ -2b, with and without RBV, in a treatment-experienced, HCV genotype 1 infected patient population. Enrolled subjects were previous non-responders to Peg-IFN $\alpha$ /RBV treatment, defined as meeting one of the following criteria:

- Previous Peg-IFN $\alpha$ /RBV treatment duration of 12 weeks: never achieved undetectable HCV RNA at any time during treatment, <2 log<sub>10</sub> IU/mL decline in HCV RNA at treatment Week 12 relative to baseline, and had no dose reductions and/or treatment interruptions.
- Previous Peg/RBV treatment duration >12 weeks: never achieved undetectable HCV RNA at any time during treatment, and received  $\geq$ 80% of doses over  $\geq$ 80% of treatment duration

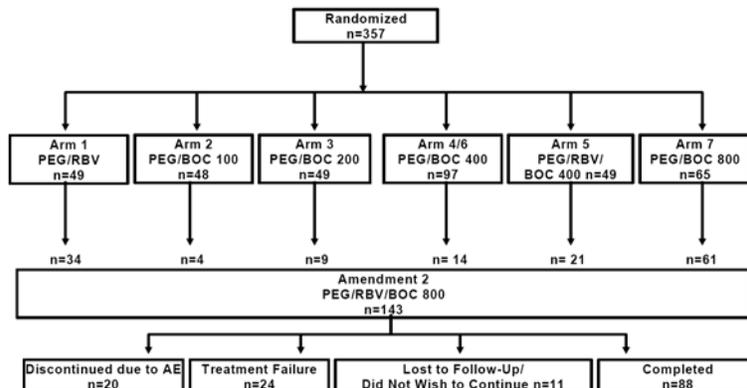
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A total of 357 subjects were enrolled. Initially, 292 subjects were randomized to one of 6 different arms (Figure 7, Report pg. 37). During the trial a Data Review Advisory Board recommended the addition of Arm 7 (Amendment 1), which was a group of 65 subjects to receive Peg-IFN $\alpha$ -2b plus boceprevir 800 mg TID (no RBV). Based on Data Review Advisory Board recommendations after a subsequent review of available data, Amendment 2 was implemented. In Amendment 2, all currently non-responding subjects were to be discontinued, and subjects with HCV RNA  $\leq$ 10,000 IU/mL switched treatment regimens to Peg-IFN $\alpha$ -2b/RBV/boceprevir 800 mg for an additional 24 weeks (Figure 8, Report pg. 56). Most subjects in Arm 7 switched to the new regimen regardless of current HCV RNA status due to the shorter treatment duration at the time of Amendment 2 implementation.



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

**Figure 7. Study design of P03659, incorporating Amendment 1 (addition of Peg-IFN $\alpha$ -2b/boceprevir 800mg arm) and Amendment 2 (cross-over to Peg-IFN $\alpha$ -2b/RBV/boceprevir 800 mg). Boceprevir doses were three times a day (TID). Vertical arrows indicate mean treatment duration for each arm at the time of Amendment 2 implementation.**



**Figure 8. P03659 subject disposition, incorporating Amendment 2.**

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Summary of Sponsor's Efficacy Analyses

Due to protocol modifications, with different cross-over times for different arms and selective cross-over of subjects responding to their initial treatment regimen, it is difficult to interpret and compare efficacy of the different treatment regimens studied in P03659. The primary efficacy endpoint, SVR, was low across all treatment groups (Table 33; Report pg. 66). Overall SVR rates were 8.9% and 6.3%, for subjects infected with HCV genotype 1b versus 1a, respectively. Of the subjects who achieved SVR, 92% (23/25) had undetectable HCV RNA by Week 8 of dosing, and 76% (19/25) had undetectable HCV RNA by Week 4. For subjects with undetectable HCV RNA at the end of treatment, there was a clear association between relapse rate and the duration of HCV RNA undetectable status; those who achieved SVR had undetectable HCV RNA for  $\geq 24$  weeks during treatment.

Subjects randomized to Arm 5, who had the opportunity to receive all three compounds for the entire study duration (mean of ~48 weeks total treatment), had the highest SVR rate of 14.3%. These are the most relevant data from the boceprevir clinical development program that directly address boceprevir efficacy in a prior Peg-IFN $\alpha$ /RBV null responder population, although it should be noted that this trial included both prior null responders and prior partial responders, and presumably the SVR rate in Arm 5 was lower for the prior null responder subpopulation. The primary differences between the treatment regimen in P03659 Arm 5 and the treatment regimens studied in Phase 3 are as follows:

- In P03659 Arm 5, a 400 mg TID boceprevir dose level was administered for the first ~24 weeks, followed by an 800 mg TID dose for the last ~24 weeks; the 800 mg TID dose level was studied in the Phase 3 trials. It is unknown if this 2-fold difference in boceprevir dose level during the first ~24 weeks would have a significant impact on boceprevir efficacy.
- A Peg-IFN $\alpha$ /RBV 4 week lead-in period was not studied in P03659, whereas all boceprevir arms in the Phase 3 trials had this lead-in period.
- Although the mean total duration of treatment in P03659 Arm 5 was 48 weeks, treatment durations for individual subjects could have been longer or shorter.

**Table 33. Sponsor's efficacy analysis for P03659.**

Original Treatment Arm = ITT	Number Switching to AM2	Treatment Follow-Up	
		EOT n (%)	FW 24 n (%)
PEG/RBV/BOC 400/800 (Arm 1) (n=40) <sup>a</sup>	n=34	14 (35.0)	3 (7.5)
PEG/BOC 100 (Arm 2) (n=48)	n=4	3 (6.3)	1 (2.1)
PEG/BOC 200 (Arm 3) (n=49)	n=9	8 (16.3)	6 (12.2)
PEG/BOC 400 (Arms 4/6) (n=97)	n=14	13 (13.4)	5 (5.2)
PEG/RBV/BOC 400 (Arm 5) (n=49)	n=21	10 (20.4)	7 (14.3)
PEG/BOC 800 (Arm 7 <sup>b</sup> ) (n=65)	n=61	14 (21.5)	3 (4.6)
All (n=348) <sup>a</sup>	n=143	62 (17.6)	25 (7.1)
Treatment Week/EOT/Follow-Up			
Arm 1 Subjects Continuing on PEG/RBV (n=5)	W3 n (%) <sup>c</sup>	EOT n (%) <sup>c</sup>	FW 24 n (%) <sup>c</sup>
	2 (4.1)	4 (8.2)	1 (2.0)

AM2 = Amendment No. 2; BOC = boceprevir; D = treatment day; EOT = end of treatment; FW = follow-up week; ITT = intent-to-treat; PEG = PegIntron; RBV = REBETOL; TID = three times a day; W = treatment week.

**Note:** All percentages are based on the total number of subjects originally randomized/enrolled to that particular arm.

a: The denominator for all percentages in Arm 1 is the number of subjects who received at least one dose of boceprevir (n=40).

b: Arm 7 is nonrandomized.

c: Denominator is n=49.

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Summary of Sponsor's Resistance Analysis

Among subjects with available post-baseline sequence analysis results, 82% (265/324) had detectable amino acid substitutions at one of the following NS3 positions believed to be associated with boceprevir resistance: V36, F43, T54, R155, A156 and I170. The most common resistance-associated substitutions that emerged in HCV genotype 1a infected subjects were R155K, V36M and T54S. The most common resistance-associated substitutions that emerged in HCV genotype 1b infected subjects were T54S, T54A, I/V170A and A156S. These resistance patterns were not confirmed independently, but are analogous to those observed in the Phase 3 trials P05216 and P05101, and the Phase 2 trial P03523.

**4.5.3 P05685 (Boceprevir plus Peg-IFN $\alpha$ -2a/RBV)**

The completed Phase 3 and Phase 2 boceprevir trials studied the efficacy of boceprevir dosed in combination with Peg-IFN $\alpha$ -2b/RBV. A second approved Peg-IFN $\alpha$  compound, Peg-IFN $\alpha$ -2a, is frequently used to treat chronic HCV infection. Peg-IFN $\alpha$ -2a and -2b have similar efficacy when dosed in combination with RBV in a standard-of-care treatment regimen ([McHutchison et al., 2009](#)).

Clinical trial P05685 is a clinically complete study that characterized the efficacy of boceprevir dosed in combination with open-label Peg-IFN $\alpha$ -2a/RBV. Eligible subjects previously failed treatment with a Peg-IFN $\alpha$ /RBV regimen with a partial or relapse response; prior Peg-IFN $\alpha$ /RBV null responders were excluded. The boceprevir NDA 3-month safety update report included a brief summary of the sponsor's analysis of efficacy from this trial.

According to the sponsor's efficacy analysis, a significant improvement in SVR rates ( $\Delta$ SVR, 43%;  $p < 0.0001$ ) was observed in the boceprevir arm versus the placebo control arm. Addition of boceprevir to Peg-IFN $\alpha$ -2a/RBV increased the SVR rate compared with Peg-IFN $\alpha$ -2a/RBV therapy alone: 64% versus 21%, respectively. These preliminary results support the use of either Peg-IFN $\alpha$ -2a or Peg-IFN $\alpha$ -2b in combination with boceprevir and RBV, although this trial was not appropriately designed to compare efficacy between Peg-IFN $\alpha$ -2a and Peg-IFN $\alpha$ -2b in the context of a Peg-IFN $\alpha$ /RBV/boceprevir regimen.

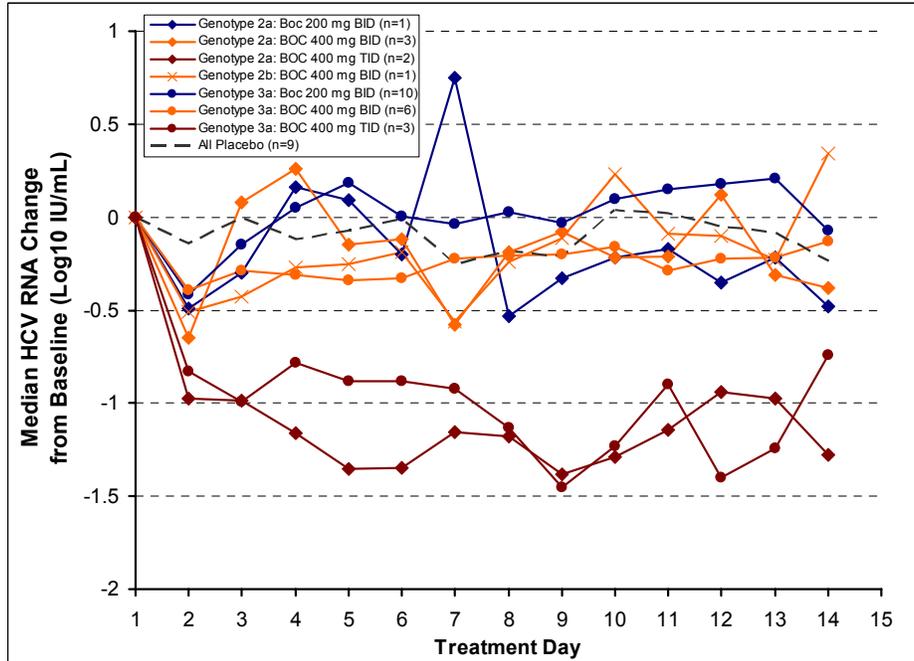
**4.5.4 P03648 (Boceprevir Activity in HCV Genotype 2/3)**

Clinical trial P03648 was a Phase 1 PK/PD/Safety study of boceprevir monotherapy in treatment-naïve subjects infected with HCV genotype 2 or 3. Thirty-nine subjects were dosed with placebo or one of three different dose levels of boceprevir for 14 days. The sponsor did not include summary virologic response data in the original NDA submission, but did include a Virology dataset.

Based on an independent analysis of virologic response data from P03648, boceprevir had dose-related anti-HCV activity in subjects infected with HCV genotype 2a or 3a (Figure 9). Note that 4 of the 39 subjects enrolled in this trial did not have HCV genotype status reported in the Virology dataset, and were therefore not included in this analysis. HCV genotype 2a- and 3a-infected subjects exposed to the highest dose level of boceprevir, 400 mg TID, had the greatest median virologic responses observed in the trial; maximum HCV RNA declines in this treatment group were ~1 to 1.5 log IU/mL from baseline. In general, HCV RNA levels declined to a plateau within 2-4 days of monotherapy dosing, indicating rapid selection of HCV viral populations with reduced susceptibility to boceprevir. Although these data indicate that boceprevir can have anti-HCV activity in subjects infected with HCV genotype 2a or 2b, the number of subjects representing each HCV genotype/subtype for each boceprevir dose level was small, and the virologic responses were variable, making it difficult to fully understand the consistency of boceprevir anti-HCV activity among

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subjects infected with HCV genotype 2 or 3. Furthermore, a longer-term duration trial with an SVR endpoint is needed to demonstrate boceprevir efficacy in these populations.



**Figure 9. Virologic responses to boceprevir monotherapy in subjects infected with HCV genotypes 2 or 3 (Clinical Trial P03648).** Boceprevir dosing was on Days 1-14. Four subjects in the trial without reported HCV genotype data are not included in this analysis.

**4.6 Other Exploratory Virology Analyses**

**4.6.1 Virologic Breakthrough in P05216 and P05101**

During the conduct of clinical trials P05216 and P05101, virologic breakthrough (BT) was defined by the sponsor as having achieved undetectable HCV RNA and subsequently having an HCV RNA level >1,000 IU/mL while on study treatment. Incomplete virologic response (IVR) was defined as having a  $\geq 1 \log_{10}$  IU/mL increase in HCV RNA from nadir with an HCV RNA level >1,000 IU/mL; however, if the time interval from Peg-IFN $\alpha$ -2b injection to HCV RNA sampling was different for two samples, a  $\geq 2 \log_{10}$  IU/mL HCV RNA increase was required to meet the criteria for IVR. These  $\geq 2 \log_{10}$  IU/mL and >1,000 IU/mL requirements were not used in the sponsor’s efficacy analyses related to IVR rates. Rather, an “Expert Review” analysis of the data was conducted, defining IVR simply as a  $\geq 1 \log_{10}$  IU/mL HCR RNA increase from nadir.

An independent analysis was conducted to identify subjects who met the criteria for virologic breakthrough or incomplete virologic response based on commonly used FDA definitions (Table 34). These analyses were conducted by first identifying programmatically any subjects whose virologic responses met the FDA definitions of BT or IVR (identified by Dr. Wen Zeng, biostatistics reviewer). From this listing, individual subject virologic responses were analyzed to confirm that BT or IVR occurred while the subject was on treatment, and also to identify the timing of initial BT or IVR observation. These analyses focused only on boceprevir-containing arms.

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**Table 34. Sponsor and FDA/Virology definitions of virologic breakthrough (BT) and incomplete virologic response (IVR).** Note that FDA typically pools both definitions into one broader category of “virologic breakthrough,” and also typically recommends confirming with a second HCV RNA measurement on a subsequent plasma sample obtained within ~2 weeks of the initial observation.

	<b>Virologic Breakthrough (BT)</b>	<b>Incomplete Virologic Response (IVR)</b>
<b>Sponsor</b>	HCV RNA undetectable on treatment, and subsequent on-treatment HCV RNA >1,000 IU/mL	HCV RNA on-treatment increase $\geq 1 \log_{10}$ IU/mL from on-treatment nadir (“Expert Review”)
<b>FDA/Virology</b>	HCV RNA undetectable on treatment, and subsequent on-treatment HCV RNA value $\geq 25$ IU/mL (or other LLOQ)	HCV RNA on-treatment increase $\geq 1 \log_{10}$ IU/mL from on-treatment nadir (agree w/sponsor’s “Expert Review”)

LLOQ, lower limit of quantification

**P05216**

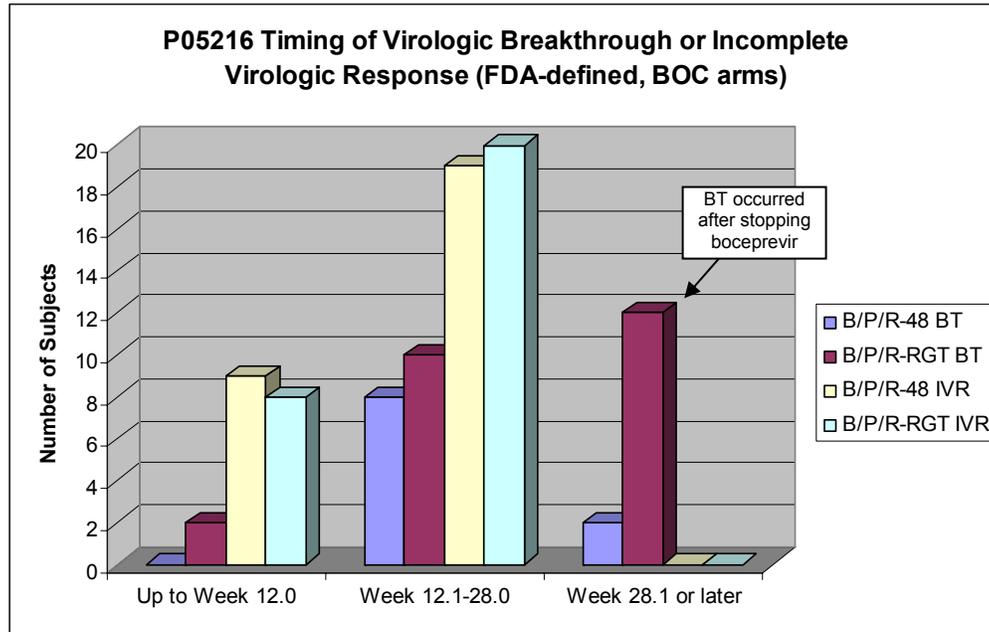
For clinical trial P05216, 90 boceprevir-treated subjects (34.7% of all non-SVR, boceprevir arm subjects) experienced FDA-defined BT or IVR (Table 35). Note that this number excludes 7 subjects whose HCV RNA levels subsequently returned to undetectable and either relapsed following the end of treatment (n=3), or remained undetectable during follow-up (i.e., subject achieved SVR; n=4). For all 7 of these subjects, BT was not confirmed by a second HCV RNA measurement from a subsequent visit. Additional analyses were conducted for the 4 subjects who technically met the definition of on treatment BT but then achieved SVR (see section below, “Virologic Breakthrough and SVR in P05216 or P05101”).

**Table 35. Number of subjects in P05216 (boceprevir arms) who experienced sponsor-defined or FDA-defined virologic breakthrough (BT) and incomplete virologic response (IVR).** B/P/R-RGT, Boceprevir/Peg-IFN $\alpha$ /RBV response-guided therapy (Arm 2); B/P/R-48, Boceprevir/Peg-IFN $\alpha$ /RBV without response guided therapy (Arm 3). See Table 34 for FDA and Sponsor definitions of BT and IVR.

	<b>B/P/R-RGT (non-SVR n=135)</b>		<b>B/P/R-48 (non-SVR n=124)</b>		<b>Both Boceprevir Arms (non-SVR n=259)</b>	
	Sponsor-reported	FDA-defined	Sponsor-reported	FDA-defined	Sponsor-reported	FDA-defined
<b>BT</b>	14	24	7	10	21	34
<b>IVR</b>	24	28	26	28	50	56
<b>Pooled BT+IVR</b>	38	52	33	38	71	90

The number of subjects who experienced IVR, regardless of whether sponsor- or FDA-defined, was similar for both boceprevir arms in P05216. However, BT occurred more frequently in the response guided therapy arm. Interestingly, this difference in BT rates could be largely attributed to a higher rate of BT in the response guided therapy arm after Treatment Week 28, a period when boceprevir was no longer in the treatment regimen for this arm (Figure 10). This observation indicates that boceprevir still had activity in suppressing HCV populations through Treatment Week 28, at least in some subjects, and raises the possibility that continuation of boceprevir treatment beyond Treatment Week 28 could have resulted in a higher SVR rate for the response guided therapy arm.

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**Figure 10. Timing of FDA-defined virologic breakthrough (BT) and incomplete virologic response (IVR) in clinical trial P05216, boceprevir arms.** B/P/R-RGT, Boceprevir/Peg-IFN $\alpha$ /RBV response-guided therapy (Arm 2); B/P/R-48, Boceprevir/Peg-IFN $\alpha$ /RBV without response guided therapy (Arm 3). See Table 34 for FDA definitions of BT and IVR.

**P05101**

For clinical trial P05101, 21 boceprevir arm subjects (17.3% of all non-SVR, boceprevir arm subjects) experienced FDA-defined BT or IVR. The sponsor reported that 16 boceprevir arm subjects experienced BT or IVR. The trend of a lower BT/IVR rate in P05101 versus P05216 may be attributed to the Treatment Week 12 detectable HCV RNA futility rule that was in the P05101 protocol but not in the P05216 protocol. The number of BT/IVR subjects in P05101 was inadequate for a thorough analysis of BT/IVR timing. However, unlike in P05216 there did not appear to be a trend of late BT in the response guided therapy arm for P05101 following cessation of boceprevir at Treatment Week 36: 1 subject in each arm (RGT and non-RGT) experienced virologic BT after Week 36.

**Virologic Breakthrough and SVR in P05216 or P05101**

Despite meeting the FDA/Virology definition of on treatment virologic breakthrough, 5 boceprevir-treated subjects in P05216 (n=4) and P05101 (n=1) ultimately achieved SVR. Note that 2 of these 5 subjects also would have met the sponsor’s definition of virologic breakthrough. In all 5 cases, none of the observations of virologic breakthrough, which occurred more than once in multiple subjects, were confirmed based on an HCV RNA measurement at the next immediate study visit. For all occurrences of breakthrough in these 5 subjects, the very next HCV RNA measurement was either undetectable or detectable <25 IU/mL (i.e., below lower limit of assay quantification). Therefore, SVR was not observed in any boceprevir-treated subjects who experienced a confirmed virologic breakthrough or incomplete virologic response.

**4.6.2 Treatment Week 12 Futility in P05216**

As summarized in Section 4.3.1, a Treatment Week 12 detectable HCV RNA treatment futility rule for a boceprevir/Peg-IFN $\alpha$ /RBV treatment regimen may reduce the overall rate of selection or enrichment of boceprevir resistance-associated substitutions among treatment-failure subjects. However, the

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rationale for its use in practice must consider the response rates for subjects who might meet the futility criterion but continue treatment. Because such a futility rule was not included in the P05216 protocol, SVR rates could be determined for subjects with detectable HCV RNA at the Week 12 visit.

Additional independent analyses of virology data (“Virology” dataset) were conducted. Note that for simplicity SVR rates were defined in the following analyses as subjects who had undetectable HCV RNA at Follow-up Week 12 or Follow-up Week 24. Depending on how the data are analyzed, boceprevir arm subjects in P05216 with detectable HCV RNA at Treatment Week 12 ultimately had SVR rates of ~10-20%:

- If considering all boceprevir arm subjects with available Treatment Week 12 HCV RNA results (not including subjects with missing TW12 data), subjects who had any Treatment Week 12 HCV RNA result of “detectable” ultimately had an SVR rate of 20.6% (32/155).
- Several subjects in the trial had multiple Treatment Week 12 HCV RNA results, and in some cases the results related to HCV RNA status (detectable vs. undetectable) were discordant. If considering all boceprevir arm subjects with available Treatment Week 12 HCV RNA results, subjects who only had Treatment Week 12 HCV RNA results of “detectable” ultimately had an SVR rate of 14.8% (21/142).
- The above analyses do not include subjects with missing Treatment Week 12 data. Subjects with no Treatment Week 12 HCV RNA results of “undetectable” (including those with no reported Treatment Week 12 results) ultimately had an SVR rate of 10.1% (21/207).

In this reviewer’s opinion, when considering how Treatment Week 12 virologic response information may be used in clinical practice, the most relevant analyses described above are those that exclude subjects with missing Treatment Week 12 HCV RNA results. Furthermore, because it is unlikely that treated patients outside of a clinical trial protocol will have multiple blood samples analyzed in a single Treatment Week 12 window, the “any Treatment Week 12 HCV RNA result of ‘detectable’” result (SVR rate=20.6%) seems most appropriate in helping to guide treatment decisions.

Of note, although a Treatment Week 12 *detectable* HCV RNA level may not be an ideal treatment futility/stopping rule (~10-20% SVR rate, noted above), based on a separate analysis it appears that subjects in P05216 with *quantifiable* HCV RNA at Treatment Week 12 had a low probability of achieving SVR. Therefore, HCV RNA that is  $\geq 25$  IU/mL (or “quantifiable”) may represent a more optimal treatment futility/stopping rule (see analysis in Section 4.6.3).

Please see the reviews of Dr. Wen Zeng, Biostatistics Reviewer, and Dr. Jeff Florian, Pharmacometrics Reviewer, for more detailed FDA analyses of on treatment responses and their relationships with treatment outcome.

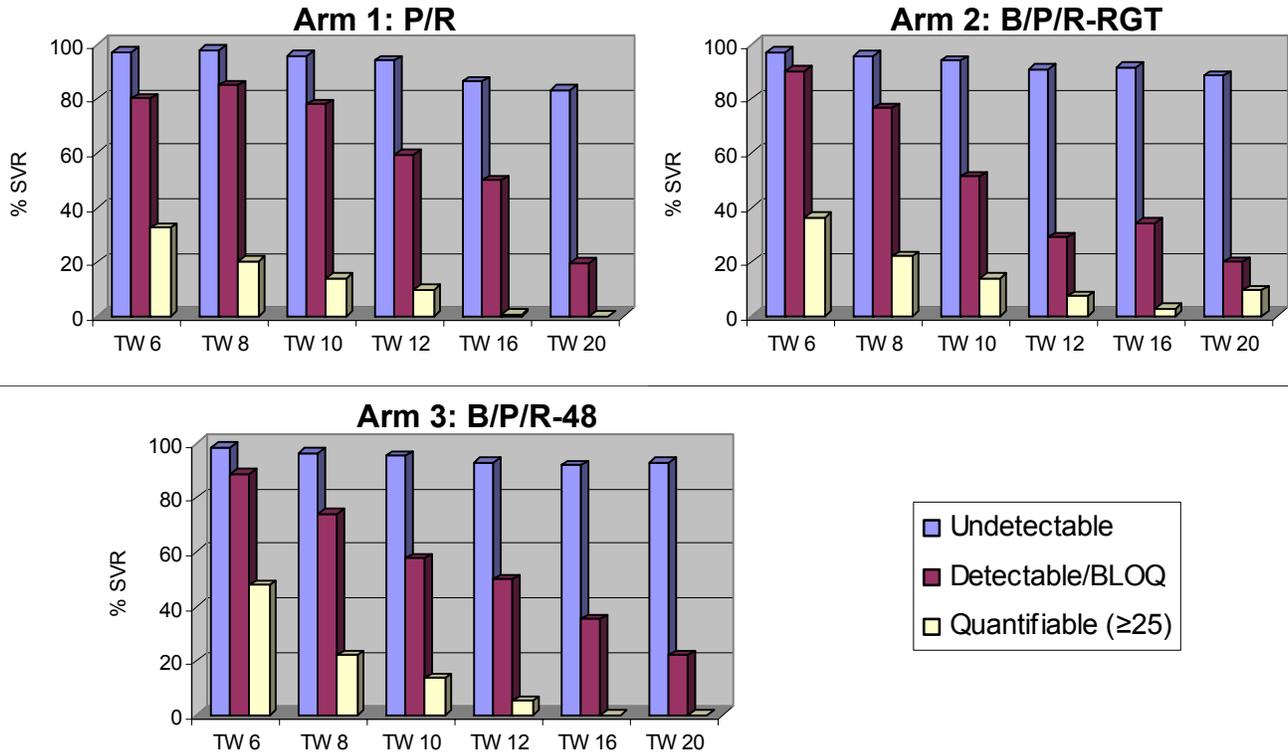
#### **4.6.3 Detectable/Unquantifiable HCV RNA and Treatment Outcome**

HCV viral load assays often can detect viral RNA even when it is present below the validated lower limit of quantification (BLOQ). An analysis was conducted to explore the clinical relevance of HCV RNA levels that were detectable but BLOQ at various on-treatment timepoints. This analysis was conducted for clinical trial P05216 (Phase 3 treatment-naïve trial) using the non-virologic-failure-censored subject listing (described in Section 4.1.3).

As shown in Figure 11, there was a clear and clinically relevant association between on-treatment HCV RNA status (undetectable vs. detectable/BLOQ) and eventual treatment outcome. For all on-treatment timepoints and for all three treatment arms, subjects who had HCV RNA levels that were

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detectable/BLOQ at a particular timepoint consistently had lower SVR rates compared to subjects with undetectable HCV RNA levels at the same timepoint. Furthermore, the negative impact of having detectable/BLOQ HCV RNA levels increased as treatment duration increased.



**Figure 11. SVR rates according to HCV RNA status at selected on-treatment timepoints for clinical trial P05216.** Analysis was conducted using an as-treated, non-VF-censored subject dataset. Note that pooled denominators in this analysis are summarized in Table 37.

Timepoints after Treatment Week 20 in P05216 are confounded by the response guided therapy approach and protocol-defined Treatment Week 24 detectable HCV RNA futility rule, making it problematic to extend this analysis to these later timepoints. Nevertheless, with the limited sample size the trend continues for later on-treatment timepoints (SVR rates: Undetectable > Detectable/BLOQ > Quantifiable). As expected, subjects with 'quantifiable' HCV RNA (i.e.,  $\geq 25$  IU/mL) during treatment had the lowest rates of SVR. Note that a subset of subjects at each timepoint had multiple HCV RNA measurements, either for multiple different timepoints within the same window, or repeat analyses of the same timepoint sample. All available data were used, such that in a few cases a subject had two different results for the same timepoint, and therefore was counted twice in the analysis. Also, for each time point subjects with missing data were not included in the analysis; in many cases the data were missing as a result of treatment discontinuation due to virologic breakthrough.

Subjects in clinical trial P05216 with quantifiable HCV RNA ( $\geq 25$  IU/mL) on or after Treatment Week 12 had a low likelihood of achieving SVR (Figure 11), potentially representing a useful treatment futility rule. Table 36 summarizes the SVR rate specifically according to Treatment Week 12 status.

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**Table 36. SVR rates according to HCV RNA status at Treatment Week 12 for clinical trial P05216.** Analysis was conducted using an as-treated, non-VF-censored subject dataset.

HCV RNA status	SVR rate according to Treatment Week 12 status		
	Arm 2 (BOC-RGT)	Arm 3 (BOC-48)	BOC Arms
Any TW12 Undetectable	219/241 (91%)	224/241 (93%)	443/482 (92%)
Any TW12 Detectable/BLOQ	7/24 (29%)	20/40 (50%)	27/64 (42%)
Any TW12 Quantifiable ( $\geq 25$ IU/mL)	3/40 (7.5%)	2/38 (5.3%)	5/78 (6.4%)

A result of HCV RNA detectable/BLOQ occurs at a significant rate, particularly at early timepoints during therapy. Over the course of study, the percentage of subjects in P05216 with HCV RNA detectable/BLOQ ranged from 2% to 16% (Table 37). Considering all available data from clinical trial P05216 (i.e., uncensored analysis) there were 9,773 reports of HCV RNA  $< 25$  IU/mL, of which 1,048 (11%) were “detectable”.

**Table 37. HCV RNA status at selected on-treatment timepoints for clinical trial P05216.** Analysis was conducted using an as-treated, non-VF-censored subject dataset. These results represent pooled denominators for the analysis shown in Figure 11.

Timepoint	HCV VL Status On-Treatment (All Arms)		
	Undetectable	Detectable/BLOQ	Quantifiable ( $\geq 25$ )
TW 6	301/883 (34%)	123/883 (14%)	466/883 (53%)
TW 8	426/897 (47%)	147/897 (16%)	338/897 (38%)
TW 10	495/884 (56%)	134/884 (15%)	269/884 (30%)
TW 12	581/901 (64%)	106/901 (12%)	232/901 (26%)
TW 16	616/874 (70%)	78/874 (9%)	192/874 (22%)
TW 20	637/855 (75%)	69/855 (8%)	161/855 (19%)
TW 34	433/449 (96%)	11/449 (2%)	9/449 (2%)

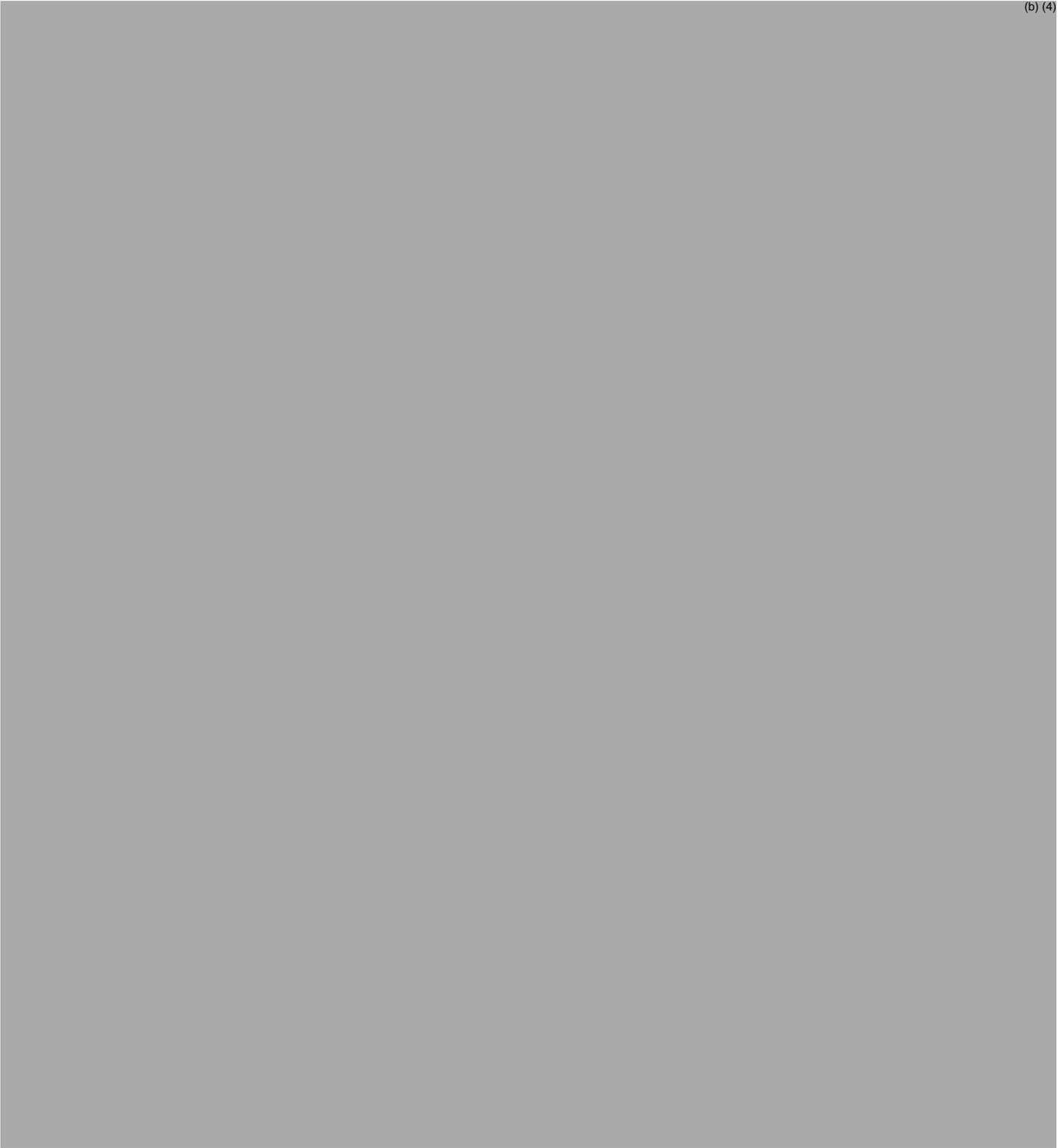
Frequently, HCV RNA results that are detectable/BLOQ are interpreted as being false-positive results. In this reviewer’s opinion a detectable/BLOQ result, particularly during treatment, is not necessarily a false positive result. Rather, in most cases it simply represents an HCV RNA level that is too low to be accurately quantified, but is qualitatively higher than a level reported as undetectable. This interpretation is supported by the clear clinical relevance of a detectable/BLOQ result, as illustrated in Figure 11. Within a given subject, a detectable/BLOQ result likely reflects a ‘transition’ result for a viral load that is either decreasing (i.e., on its way to undetectable) or increasing (i.e., breakthrough). The fact that subjects with detectable/BLOQ HCV RNA are not responding as well as subjects with undetectable HCV RNA at the same timepoint must be considered when using a response-guided therapy approach, and also when designing new protocols to validate a response-guided therapy strategy.

## 5. CONCLUSION

This NDA is approvable from a Virology perspective for the treatment of chronic HCV genotype 1 infected patients who are either naïve to prior anti-HCV therapy, or who failed prior therapy with Peg-IFN $\alpha$ /RBV but achieved at least a partial virologic response to the prior therapy ( $> 2 \log_{10}$  IU/mL decline through 12 weeks, or equivalent).

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**6. PACKAGE INSERT**



(b) (4)

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**6.2 Reviewer's Proposed Package Insert (clean)**

(b) (4)



**12 CLINICAL PHARMACOLOGY**

**12.1 Mechanism of Action**

TRADENAME is an antiviral drug (see 12.4 Microbiology).

**12.4 Microbiology**

***Mechanism of Action***

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

***Antiviral Activity in Cell Culture***

The  $EC_{50}$  and  $EC_{90}$  values for boceprevir against an HCV replicon constructed from a single genotype 1b isolate were approximately 200 nM and 400 nM, respectively, in a 72-hour cell culture assay. Boceprevir cell culture anti-HCV activity was approximately 2-fold lower for an HCV replicon derived from a single genotype 1a isolate, relative to the 1b isolate-derived replicon. In a biochemical assay, boceprevir had approximately 3- and 2-fold reduced activity against NS3/4A proteases derived from single isolates representative of HCV genotypes 2 and 3a, respectively, relative to a genotype 1b-derived NS3/4A protease. The presence of 50% human serum reduced the cell culture anti-HCV activity of boceprevir by approximately 3-fold.

Evaluation of varying combinations of boceprevir and interferon alfa-2b that produced 90% suppression of replicon RNA showed additivity of effect;

(b) (4)



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**Resistance**

*In cell culture*

Resistance to boceprevir was characterized in biochemical and HCV genotype 1b replicon assays. Boceprevir's activity against the HCV NS3/4A protease or genotype 1b replicon was reduced (2- to-10 fold) by the following amino acid substitutions in the NS3 protease domain: V36A/I/M, Q41R, F43C/S, T54A/S, V55A/I, R155K/M/Q, V158I, V170A/T and M175L. A >15-fold reduction in boceprevir anti-HCV activity was conferred by the substitutions T54C, R155G/I, R155T and A156S/T/V. The fold decrease in boceprevir anti-HCV activity conferred by double resistance-associated substitutions was approximately equal to the product of that for the individual substitutions.

*In clinical studies*

An as-treated, pooled genotypic resistance analysis was conducted for subjects who received four weeks of PegIntron/REBETOL followed by TRADENAME 800 mg three times daily in combination with PegIntron/REBETOL in two Phase III studies, P05216 and P05101. Among TRADENAME-treated subjects who did not achieve a sustained virologic response (SVR), and for whom samples were analyzed, (b) (4) had one or more specific post-baseline, treatment-emergent NS3 protease domain amino acid substitutions detected by a population-based sequencing assay (Table xx). Nearly all of these substitutions have been shown to reduce boceprevir anti-HCV activity in cell culture or biochemical assays. Among TRADENAME-treated subjects who did not achieve SVR and for whom post-baseline samples were analyzed, 31% of PegIntron/REBETOL-responsive subjects, as defined by  $\geq 1 \log_{10}$  decline in viral load at Treatment Week 4 (end of 4-week PegIntron/REBETOL lead-in period), had detectable treatment-emergent substitutions, compared to 68% of subjects with  $< 1 \log_{10}$  decline in viral load at Treatment Week 4. Clear patterns of boceprevir treatment-emergent substitutions in the NS3 helicase domain or NS4A coding regions of the HCV genome were not observed.

**Table xx**

**Pooled analysis of treatment-emergent NS3 protease domain amino acid substitutions detected among TRADENAME treated subjects in P05216 and P05101 who did not achieve a sustained virologic response (SVR).**

	<b>Subjects Infected with HCV Genotype 1a</b>	<b>Subjects Infected with HCV Genotype 1b</b>
>10% of TRADENAME treated subjects who did not achieve SVR	V36M, T54S, R155K, (b) (4)	T54A, T54S, V55A, A156S, I/V170A
<1% to 10% of TRADENAME treated subjects who did not achieve SVR	V36A, T54A, V55A, V107I, R155T, A156S, A156T, V158I, D168N, I/V170T	V36A, V36M, V107I, R155K, A156T, A156V, V158I, I/V170T

**Persistence of resistance-associated substitutions**

Data from an ongoing, long-term follow-up study of subjects who did not achieve SVR in Phase 2 TRADENAME trials, with a median duration of follow-up of approximately 2 years, indicate that HCV populations harboring certain post-baseline, TRADENAME treatment-emergent substitutions may decline in relative abundance over time. However, among those subjects with available data, one or more TRADENAME treatment-emergent substitutions remained detectable with a population-based sequencing assay in 25% of subjects after 2.5 years of follow-up. The most common NS3 substitutions detected after 2.5 years of follow-up were T54S and R155K. The lack of detection of a substitution using a population-based assay does not necessarily indicate that viral populations carrying that substitution have declined to a background level that may have existed prior to treatment. The long-term clinical impact of the emergence or persistence of boceprevir resistance-associated substitutions is unknown. No data are available regarding TRADENAME efficacy among subjects who were previously exposed to TRADENAME, or who previously failed treatment with a TRADENAME-containing regimen.

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***Effect of baseline HCV polymorphisms on treatment response***

A pooled analysis was conducted to explore the association between the detection (b) (4) of baseline NS3/4A amino acid polymorphisms and treatment outcome in the two Phase III studies, P05216 and P05101. (b) (4)

***Cross-resistance***

Many of the treatment-emergent NS3 amino acid substitutions detected in TRADENAME-treated subjects who did not achieve SVR in the Phase III clinical trials have been demonstrated to reduce the anti-HCV activity of other HCV NS3/4A protease inhibitors. The impact of prior TRADENAME exposure or treatment failure on the efficacy of other HCV NS3/4A protease inhibitors has not been studied. TRADENAME efficacy has not been established for patients with a history of exposure to other NS3/4A protease inhibitors. Cross-resistance is not expected between TRADENAME and interferons, or TRADENAME and ribavirin.

**6.3 Final Approved Package Insert**

Due to the timing of boceprevir NDA milestones and PDUFA goal deadlines, the final approved package insert was not available at the time of finalization of this review.

**7. RECOMMENDATIONS**

1. 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. A166T, with and without linked V170A, genotype 1b replicon
  - f. V36M, R155K and V36M+R155K, genotype 1a replicon
2. 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 vector for phenotypic characterization related to boceprevir susceptibility.

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3. Report results from P05063 regarding the long term persistence ( $\geq 2$  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.
4. 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-IFN $\alpha$ /RBV treatment regimens among subjects who (1) respond relatively poorly to the Peg-IFN $\alpha$ /RBV 4-week lead-in (e.g.,  $< 1 \log_{10}$  IU/mL decline,  $\geq 1 \log_{10}$  IU/mL to  $< 2 \log_{10}$  IU/mL decline, etc.), or (2) have an unfavorable IL28B genotype.
5. 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.

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**8. APPENDICES**

**APPENDIX A: Subjects Not Included in Sponsor's Phase 3 Resistance Datasets**

**Clinical Trial P05216:**

Subject ID	HCV genotype/subtype (TRUGENE™)	HCV genotype/subtype (NS5B)	Arm	SVR24 (Y or N)	Notes
003744	1a	n/a	PR	Y	BL sequence analysis failed
001908	1b	n/a	BPR-48	Y	BL sequence analysis failed
002244	1	n/a	BPR-RGT	N	BL, TW12, TW48, FUWk36, FUWk72 sequence analyses failed
007747	1b	n/a	PR	Y	BL sequence analysis failed
003727	1a	n/a	BPR-RGT	N	BL sequence analysis failed
000080	1	n/a	BPR-RGT	Y	BL sequence analysis failed
002131	1b	6n	BPR-48	Y	3.06 log <sub>10</sub> IU/mL decline at Week 4
002204	1	6e	BPR-RGT	Y	5.9 log <sub>10</sub> IU/mL decline at Week 4
000101	1	6h	PR	Y	
001957	1b	6n	PR	Y	

Abbreviations: BL, baseline; BPR-48, boceprevir+Peg-IFNα/RBV for 48 weeks; BPR-RGT, boceprevir+Peg-IFNα/RBV response-guided therapy; FUWk, follow-up week; PR, Peg-IFNα/RBV; TW, treatment week

**Clinical Trial P05101:**

Subject ID	HCV genotype/subtype (TRUGENE™)	HCV genotype/subtype (NS5B)	Arm	SVR24 (Y or N)	Notes
011052	1b	6l	BPR-48	Y	4.7 log <sub>10</sub> IU/mL decline at Week 4

Abbreviations: BL, baseline; BPR-48, boceprevir+Peg-IFNα/RBV for 48 weeks; BPR-RGT, boceprevir+Peg-IFNα/RBV response-guided therapy; FUWk, follow-up week; PR, Peg-IFNα/RBV; TW, treatment week

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**APPENDIX B: Subjects Censored from Non-VF-Censored Resistance Datasets**

**P05216: HCV Genotype 1a-Infected Subjects**

<b>Subject Number</b>	<b>Summary of Treatment and Virologic Response</b>
000004	Stopped tx at Week 8, VL declining
000019	VL undetectable Treatment Weeks 6-22, no FU data
000044	VL undetectable Treatment Weeks 8-12, stopped tx at Week ~14, no FU data
000049	VL undetectable treatment Weeks 10-40, completed 48 weeks tx, no EOT or FU data
000055	VL undetectable Treatment Week 10, undetectable Week 12 for 2 of 3 assessments (<LLOQ for 1), undetectable Treatment Weeks 16-24, stopped tx at Week 25, relapsed
000071	VL undetectable Treatment Weeks 16-28, stopped tx at Week 29, relapsed
000075	VL undetectable Treatment Week ~16, stopped tx Week ~16, relapsed
000079	<6 weeks tx duration
000089	Stopped tx at Week 16, no EOT VL measurement, VL undetectable at last on-tx measurement Week 12
000094	<6 weeks tx duration
000095	<6 weeks tx duration
000104	VL undetectable Treatment Week 8 to FU Week 4, no FU Week 12 or FU Week 24 data
000110	<6 weeks tx duration
000115	VL undetectable Treatment Week 10 to FU Week 12, no FU Week 24 data
000119	VL undetectable Treatment Weeks 6-8, stopped tx at Week 8, no FU data
000124	VL undetectable Treatment Weeks 10 to FU Week 12, no FU Week 24 data
000125	VL undetectable Treatment Weeks 2-24, stopped tx Week 24, no FU data
000126	<6 weeks tx duration
000138	<6 weeks tx duration
000140	Stopped tx at Week 19, VL undetectable Treatment Weeks 12-16, no EOT or FU data
000144	VL undetectable Treatment Week 10, stopped tx Week 10, relapsed
000148	<6 weeks tx duration
000154	VL undetectable Treatment Weeks 10-20, stopped tx Week 20, relapsed
000164	Stopped tx at Week 12, VL declined to <LLOQ by Week 10
000167	<6 weeks tx duration
000182	VL undetectable Treatment Weeks 10-16, stopped tx Week 17, relapsed
000189	VL undetectable Treatment Weeks 8-16, stopped tx Week 20, relapsed
000199	<6 weeks tx duration
000211	<6 weeks tx duration
000212	Stopped tx at Week 11, VL declined to <LLOQ by Week 10
000218	VL undetectable Treatment Weeks 6-8, stopped tx at Week 9, relapsed
000221	VL undetectable Treatment Weeks 10-16, stopped tx Week 16, no FU data
000228	<6 weeks tx duration
000237	Stopped tx at Week 12, VL declined to <LLOQ by Week 6
000248	<6 weeks tx duration
000257	Stopped tx at Week 28, VL undetectable at Treatment Week 24, no EOT or FU data
000267	Stopped tx at Week 18, VL declining through Week 16
000269	<6 weeks tx duration
000272	<6 weeks tx duration
000274	VL undetectable Treatment Week 8 to FU Week 4, no FU Week 12 or FU Week 24 data
000276	Stopped tx near Week 48, VL undetectable Treatment Weeks 16-40, no EOT or FU data

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000281	<6 weeks tx duration
000283	<6 weeks tx duration
000290	Stopped tx at Week 8, VL declining
000311	VL undetectable Treatment Weeks 16-24, stopped tx Week 24, relapsed
000313	Stopped tx at Week 12, VL detectable <LLOQ at Week 10
000334	<6 weeks tx duration
000335	VL undetectable Treatment Weeks 8-16, stopped tx Week 17, relapsed
000340	VL undetectable Treatment Weeks 12-28, stopped tx Week 29, no FU data
000353	Stopped tx at Week 30, VL undetectable Treatment Weeks 16-28, no EOT data, 'relapse' for FU timepoints
000357	Stopped tx at Week 16, VL declining
000360	Stopped tx at Week 16, VL undetectable Treatment Weeks 6-12, no EOT data, 'relapse' for FU timepoints
000361	VL undetectable Treatment Weeks 6-8, stopped tx Week 10, relapsed
000364	VL undetectable Treatment Weeks 6-8, stopped tx Week 8, no FU data
000383	VL undetectable Treatment Week 2 to FU Week 12, no FU Week 24 data
000384	VL undetectable Treatment Weeks 6-16, stopped tx Week 19, VL undetectable FU Weeks 4 and 12, no FU Week 24 data
000401	VL undetectable Treatment Weeks 6-16, stopped tx Week 16, no FU data
000402	<6 weeks tx duration
000403	Stopped tx at Week 12, VL declining through Week 10, no EOT or FU data
000415	VL undetectable Treatment Weeks 6-20, stopped tx Week 24, relapsed
000416	Stopped tx at Week 8, VL declining through Week 6
000417	VL undetectable Treatment Week 6, stopped tx Week 7, VL detectable <LLOQ at FU Week 1, no other FU data
000419	VL undetectable Treatment Weeks 6-10, stopped tx Week 10, relapsed
000420	VL undetectable Treatment Weeks 8-20, breakthrough Week 24, stopped tx Week 28, VL undetectable Week 28, VL=2020 at FU Week 12, VL undetectable FU Weeks 24 and 36, called breakthrough by sponsor
000422	VL undetectable Treatment Weeks 10-16, stopped tx Week 16, relapsed
000424	VL undetectable Treatment Weeks 12-16, stopped tx Week 16, no FU data
000438	<6 weeks tx duration
000444	VL undetectable Treatment Weeks 6-12, stopped tx Week 12, VL undetectable FU Week 4, no other FU data
000449	VL undetectable Treatment Weeks 8-20 (1 of 3 Week 20 samples detectable <LLOQ), VL undetectable Week 24, stopped tx Week 24, relapsed
000465	VL undetectable Treatment Weeks 6-12, stopped tx Week 12, relapsed
001864	VL undetectable Treatment Week 6 to EOT, no FU data
001868	Stopped tx at Week 12, VL undetectable Treatment Week 8, VL detectable <LLOQ Treatment Week 10 and FU Week 4
001873	<6 weeks tx duration
001876	Stopped tx at Week 6, no VL data after Week 4, no EOT or FU data
001987	<6 weeks tx duration
001992	<6 weeks tx duration
002006	VL undetectable Treatment Weeks 8-16, stopped tx Week 16, no FU data
002052	VL undetectable Treatment Weeks 8-24, stopped tx Week 26, relapsed
002057	VL undetectable Treatment Weeks 10-28, stopped tx Week 28, relapsed
002075	<6 weeks tx duration
002085	<6 weeks tx duration

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002113	VL undetectable Treatment Week 6 to FU Week 12, no FU Week 24 data
002114	<6 weeks tx duration
002123	<6 weeks tx duration
002130	<6 weeks tx duration
002145	VL undetectable Treatment Weeks 10-24, stopped Tx Week 24, VL detectable <LLOQ at FU Week ~9, no other FU data
002171	<6 weeks tx duration
003722	<6 weeks tx duration
003733	VL undetectable Treatment Weeks 2-28, stopped tx Week ~30, VL undetectable at FU Week 12, no other FU data
003741	VL undetectable Treatment Weeks 2-4, stopped tx Week 5, VL undetectable at FU Week 4, no other FU data
003755	VL undetectable Treatment Weeks 16-24, stopped tx Week 26, no FU data
003763	Stopped tx at Week 9, VL undetectable Treatment Week 8, 'relapse' for FU timepoints
005586	<6 weeks tx duration
005613	VL undetectable Treatment Week 2 to FU Week 12, no FU Week 24 data
007443	Stopped tx at Week 15, VL undetectable or detectable <LLOQ Treatment Weeks 8 to FU Week 4
007446	VL undetectable Treatment Weeks 20-28, stopped tx Week 29, relapsed
007448	VL undetectable Treatment Week 16, detectable <LLOQ for 2 of 3 Week 20 assessments, undetectable Treatment Week 24, stopped tx Week 24, relapsed
007454	Stopped tx at Week 39, VL undetectable Treatment Weeks 24-34, no EOT data, 'relapse' at FU timepoints
007458	<6 weeks tx duration
007460	Stopped tx at Week 11, VL declining
007461	<6 weeks tx duration
007464	VL undetectable Treatment Weeks 8-20, stopped tx Week 21, relapsed
007475	<6 weeks tx duration
007480	VL undetectable Treatment Week 12 to FU Week 4, no FU Week 12 or FU Week 24 data
007487	<6 weeks tx duration
007488	<6 weeks tx duration
007491	VL undetectable Treatment Week 12, stopped tx Week 14, relapsed
007492	VL undetectable Treatment Weeks 6-17, stopped tx Week 17, relapsed
007495	Stopped tx at Week 15, VL undetectable Treatment Week 10, VL detectable <LLOQ at Week 12, no EOT data, 'relapse' for FU timepoints
007510	<6 weeks tx duration
007513	Stopped tx at Week 7, VL declining through Week 6, no EOT or FU data
007514	Stopped tx at Week 35, VL undetectable Treatment Weeks 12-28, no EOT or FU data
007528	Stopped tx at Week 6, VL declining through Week 6
007533	VL undetectable Treatment Weeks 6-28, stopped tx Week 28, relapsed
007536	Stopped tx at Week 7, slow VL decline through Week 6
007545	VL undetectable Treatment Week 6 to FU Week 12, no FU Week 24 data
007744	VL undetectable Treatment Weeks 20-24, stopped tx Week 25, relapsed
007745	<6 weeks tx duration
007769	<6 weeks tx duration
008042	<6 weeks tx duration

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**P05216: HCV Genotype 1b-Infected Subjects**

<b>Subject Number</b>	<b>Summary of Treatment and Virologic Response</b>
001889	VL undetectable Treatment Week 20-23, stopped tx Week 23, relapsed
001893	VL undetectable Treatment Week 10 to FU Week 12, no FU Week 24 data
001914	Stopped tx at Week 7, VL clearly declining
001918	<6 weeks tx duration
001920	<6 weeks tx duration
001929	VL undetectable Treatment Week 6-48, no FU data
001941	VL undetectable Treatment Week 8-10, stopped tx Week 10, relapsed
001949	<6 weeks tx duration
001953	Stopped tx at Week ~9, VL declining to detectable <LLOQ at FU Day 2
001956	VL undetectable Treatment Week 24-48, no FU data
001961	<6 weeks tx duration
001970	VL undetectable Treatment Week 6, 2 of 3 Week 8 samples detectable <LLOQ (1 undetectable), undetectable Treatment Week 10-13, stopped tx Week 13, relapsed
001983	VL undetectable Treatment Week 16 to FU Week 12, no FU Week 24 data
001985	Stopped tx at Week 11, VL declining to near LLOQ by Week 10
002002	Stopped tx at Week 34, VL undetectable Treatment Weeks 8-28, no EOT or FU data
002012	<6 weeks tx duration
002028	Stopped tx at Week 12, VL undetectable Treatment Week 4-6, no EOT data
002048	VL undetectable Treatment Week 24 to FU Week 4, no FU Week 12 or 24 data
002062	<6 weeks tx duration
002065	VL undetectable Treatment Week 8-12, stopped tx Week 13, relapsed
002067	<6 weeks tx duration
002071	VL undetectable Treatment Week 16-48, no FU data
002082	VL undetectable Treatment Week 12-40, stopped tx Week 40, relapsed
002093	VL undetectable Treatment Week 8-34, stopped tx Week 34, no FU data
002097	VL undetectable Treatment Week 4, stopped tx before Week 6, no FU data
002105	VL undetectable Treatment Week 16-48, no FU data
002109	VL undetectable Treatment Week 10 to FU Week 12, no FU Week 24 data
002149	<6 weeks tx duration
002151	<6 weeks tx duration
002157	Stopped tx just after Week 6, VL declining
002160	VL undetectable Treatment Week 16-20, stopped tx Week 20, relapsed
002168	<6 weeks tx duration
002182	<6 weeks tx duration
002189	Stopped tx at Week 31, VL undetectable Treatment Weeks 20-28, no EOT data
002200	<6 weeks tx duration
002208	<6 weeks tx duration
002212	Stopped tx at Week 12, VL declined to near LLOQ at Weeks 10-12
002227	VL undetectable Treatment Week 10-17, stopped tx Week 17, relapsed
002236	Stopped tx at Week 7, VL near LLOQ at Week 4, VL undetectable at Week 6, 'relapsed?'
005597	<6 weeks tx duration
005600	<6 weeks tx duration
005601	Stopped tx at Week 16, VL undetectable Treatment Weeks 6-12, no EOT data, VL=52700 at FU Day 3
005606	<6 weeks tx duration

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005619	Stopped tx at Week 16, VL undetectable Treatment Week 8, VL=230 Week 10, undetectable Week 12, no EOT or FU data
007759	Stopped tx at Week 31, VL undetectable Treatment Weeks 12-24, no EOT or FU data
007761	<6 weeks tx duration
007763	<6 weeks tx duration
007772	VL undetectable Treatment Week 8-20, stopped tx Week 22, no EOT or FU data
007781	<6 weeks tx duration
007783	<6 weeks tx duration
008341	VL undetectable Treatment Week 6-8, 1 of 3 Week 10 samples detectable <LLOQ (other 2 undetectable), undetectable Week 12 to FU Week 12, no FU Week 24 data

**P05101: HCV Genotype 1a-Infected Subjects**

<b>Subject Number</b>	<b>Summary of Treatment and Virologic Response</b>
010007	VL undetectable Treatment Week 8, detectable but <LLOQ at Week 10, undetectable Weeks 12-30, discontinued at Week 30, relapsed
010018	VL undetectable Treatment Week 12, detectable but <LLOQ Weeks 16 and 20, undetectable Week 24, discontinued at Week 25, relapsed
010055	Stopped tx at Week 4
010078	VL undetectable Treatment Weeks 12-48, no FU VL data
010080	VL undetectable Treatment Weeks 6-42, no EOT or FU data
010107	VL undetectable Treatment Week 10, discontinued at Week ~11, relapsed
010117	Stopped tx at Week 4
010123	Stopped tx at Week 3
011074	Stopped tx at Week 6
011105	VL @ FU Week 24 = 2030, but VL undetectable at prior and subsequent FU visits
011120	VL undetectable Treatment Week 8, detectable but <LLOQ at Week 10, detectable but <LLOQ for 2 of 4 Week 12 measurements, undetectable Weeks 16-24, Discontinuation at Week 24, relapsed
012006	VL undetectable Treatment Week 8 to FU Week 4, no FU Week 12 or FU Week 24 data
012008	Stopped tx at Week 4
012013	VL undetectable Treatment Weeks 6-12, discontinued at Week 12, relapsed
012015	VL undetectable Treatment Weeks 6-24, discontinued at Week 24, relapsed
012021	Stopped tx at Week 3
012036	Stopped tx at Week 1
012043	Stopped tx at Week 7, ~2 log decline at Week 4, increase in VL from Week 4 to Week 6
012046	Stopped tx at Week 2
012061	Stopped tx at Week 7, ~3 log decline at Week 6
012064	VL undetectable Treatment Weeks 8-24, discontinued at Week 24, relapsed
012072	Stopped tx at Week 2
012077	VL undetectable Treatment Week 10 to FU Week 12, no FU Week 24 data

**P05101: HCV Genotype 1b-Infected Subjects**

<b>Subject Number</b>	<b>Summary of Treatment and Virologic Response</b>
010031	VL undetectable Treatment Week 6-12, stopped tx Week 13, relapsed
010069	VL undetectable Treatment Week 10-12, stopped tx Week 12, relapsed
011002	VL undetectable Treatment Week 6-48, no FU data
011017	VL undetectable Treatment Week 12-24, stopped tx Week 24, relapsed
011026	VL undetectable Treatment Week 6-10, stopped tx Week 10, relapsed

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011028	VL detectable <LLOQ Treatment Week 6, stopped tx 5 days later, no VL measurements again until FU Week 4, 'relapsed'
011044	Stopped tx Week 8, no on-treatment VL measurements after Week 4
011051	VL undetectable Treatment Week 6 to FU Week 12, FU Week 24 data
011062	<6 weeks tx duration
011067	<6 weeks tx duration
011083	VL undetectable Treatment Week 6-21, stopped tx Week 21, relapsed
011087	<6 weeks tx duration
011102	VL undetectable Treatment Week 10-36, stopped tx Week 36, relapsed
013022	Stopped tx Week ~6, VL declining
013046	VL undetectable Treatment Week 10-17, no FU data
013066	VL undetectable Treatment Week 6-10, stopped tx Week 10, relapsed

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**APPENDIX C: Communications with sponsor during NDA review**

**12/8/2010: Virology requests communicated to sponsor, and sponsor's reply (SDN 10)**

1. Please confirm our understanding of your HCV genotype/subtype analysis methods used for the Phase 3 boceprevir trials P05101 and P05216:
  - c. TRUGENE™ (5'-NCR target) assay was used for screening and stratification.
  - d. Samples identified as subtype 1a by TRUGENE™ assay were subjected to the following secondary analysis:
    - Subtype-designed primers for NS3/4A RT-PCR amplification were used for resistance assessments. If RT-PCR amplification using subtype 1a-designed primers was successful, then the sample was considered subtype 1a. For these instances, NS3/4A RT-PCR amplifications using subtype 1b-designed primers were not conducted.
    - If NS3/4A RT-PCR amplification with subtype 1a-designed primers was unsuccessful, then genotype 1b-designed primers were used; if amplification was successful then sample was considered subtype 1b.
    - NS5B RT-PCR, nucleotide sequencing, and phylogenetic analyses were not conducted for subjects identified as subtype 1a by TRUGENE™ assay.
  - e. Samples identified as subtype 1b (or non-determined subtype) by TRUGENE™ assay were subjected to the following secondary analysis:
    - NS5B RT-PCR, nucleotide sequencing, and phylogenetic analysis.

Sponsor's reply in SDN 10:

We confirm your understanding of the genotyping analysis methods to be correct.

Reviewer's Comment: adequate response.

2. For the resistance datasets for P05101 and P05216, there are 11 subjects not included: 1 subject for P05101 and 10 subjects for P05216. It is our understanding that these subjects were either infected with non-genotype 1 HCV or had an undetermined HCV genotype. Please provide a listing of these subjects, the genotype/subtype analysis methods used, and the genotype/subtype results (indicate if analysis failed or genotype undetermined, etc., as appropriate). Also, if NS3 or NS3/4A sequence analyses were conducted for any of these 11 subjects, please submit the available data; a separate resistance dataset for such subjects is acceptable (i.e., data do not need to be merged with other datasets).

Sponsor's reply in SDN 10:

The data listings for the 11 subjects not included in the Resistance transport file are provided in Tables 1 and 2. Genotyping at (b) (4) was performed using the TRUGENE assay and at (b) (4) NS5B RT-PCR was used. The results obtained from the assays were not fully concordant. Data analysis was based on the (b) (4) results.

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**TABLE 1**

**P05216:**

Site Number	Subject Number	(b) (4) Genotype	(b) (4) Genotype
7	003744	1a	
22	001908	1b	
46	002244	1	
90	007747	1b	
95	003727	1a	
152	000080	1	
44	002131	6n	1b
52	002204	6e	1
113	000101	6h	1
121	001957	6n	1b

**P05101:**

Site Number	Subject Number	(b) (4) Genotype	(b) (4) Genotype
92	011052	6l	1b

Five out of 11 subjects had genotype 6 (Table 1) when NS5B methodology was used for genotyping and for those subjects resistance-associated variant analyses were not performed and therefore these subjects were not included in the resistance dataset.

The remaining 6 subjects from P05216 had only a partial sequence obtained that did not meet quality control standards for the assay as defined by (b) (4) (Table 2). These subjects were also not included in the transport files of resistance data:

**TABLE 2**

SITENBR	SUBJNBR	VIREF	VIDT	VISIT	VICAT	VITEST	VIORRES
7	003744	D681755	01DEC08	D1		SEQUENCE STATUS	N/A
22	001908	D663568	24OCT08	D1		SEQUENCE STATUS	N/A
46	002244	D811718	13APR09	TW48		SEQUENCE STATUS	N/A
46	002244	H806315	13JAN10	F/UW36		SEQUENCE STATUS	N/A
46	002244	R310350	14MAY10	F/UW72		SEQUENCE STATUS	N/A
46	002244	S938637	30DEC08	D1		SEQUENCE STATUS	N/A
46	002244	W915085	25MAR09	TW12		SEQUENCE STATUS	N/A
90	007747	R118647	14NOV08	D1		SEQUENCE STATUS	N/A
95	003727	D210699	28OCT08	D1		SEQUENCE STATUS	N/A
152	000080	D516339	30OCT08	D1	PM	SUBTYPE STATUS	NEG_SUB- <sup>1</sup>

<sup>1</sup> ONLY A PARTIAL SEQUENCE WAS OBTAINED THAT DID NOT MEET QUALITY CONTROL STANDARDS

Subjects 003744, 001908; 007747, 003727 and 000080 had no samples on boceprevir treatment available for testing (all HCV-RNA results after initiation of boceprevir treatment were < 1000 IU/mL). Only one subject (002244) had additional samples available for testing with HCV-RNA results > 1000 IU/mL. Samples collected at TW12, TW48, FU 36 and FU72 were tested, but all of them failed quality control standards, as defined by (b) (4) (Table 2).

Reviewer's comment: adequate response.

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**12/13/2010: Virology request communicated to sponsor, and sponsor's reply (SDN 16)**

We have concerns about your approach to determining HCV genotype/subtype in P05216 and P05101:

- The TRUGENE™ assay, while commercially available, is not acceptable to compare efficacy for patients infected with HCV subtype 1a versus 1b.
- Your secondary genotype/subtype analysis approach, while potentially an improvement over the TRUGENE™ assay, is unconventional, was not universally applied to all subjects, and is highly unlikely to be used to determine HCV genotype/subtype in clinical practice. Furthermore, we do not agree with your rationale of 'inferring' HCV subtype indirectly based on successful RT-PCR amplification of the NS3/4A gene, and no performance data were provided to support this rationale.

**Please conduct at least one of the following analyses for pre-treatment samples from subjects enrolled in P05216 and P05101, and submit the data to the NDA as soon as possible.** The same analysis should be conducted universally for all study subjects (note that the five HCV genotype 6 subjects-by NS5B phylogenetic analysis-can be excluded).

- NS5B phylogenetic analysis, for those subjects not already analyzed by this method
- NS3/4A phylogenetic analysis; this can be conducted using available baseline data collected for resistance analysis purposes
- Line-probe assay targeting 5'-NCR + Core (e.g., VERSANT® HCV Genotype 2.0)

The data should be submitted as individual electronic datasets (1 dataset for each trial). Please include the following line item information in each dataset:

- Subject number
- Treatment arm
- SVR24 result: Y or N
- HCV genotype/subtype method #1: TRUGENE
- HCV genotype/subtype method #1 result: 1a, 1b, 1, not available, etc.
- HCV genotype/subtype method #2: NS3-4A/NS5B (i.e., 'secondary' analysis summarized above)
- HCV genotype/subtype method #2 result: 1a, 1b, 1, not available, etc.
- HCV genotype/subtype method #3: (NS5B phylogenetic analysis, NS3/4A phylogenetic analysis, or LiPA 5'-NCR + Core)
- HCV genotype/subtype method #3 result: 1, 1a, 1b, not available, etc.
- Flag to identify subjects with discordant HCV genotype/subtype data generated from methods #2 and #3

Also, this submission should include a report describing the assay methodology used for genotype/subtype method #3, if different from the NS5B phylogenetic assay used by (b) (4)

Sponsor's reply in SDN 16:

In designing and implementing the boceprevir pivotal Phase 3 trials, the need to use accurate methods for genotype 1 subtype analysis was recognized. The TRUEGENE™ analysis is referred to here as Method 1. However, realizing the possible deficiencies in all of the commercially available tests, a secondary analysis based on NS5B sequence analysis, as outlined in the NDA, was also conducted. This analysis is referred to as Method 2. In order to assess the accuracy of Method 2, phylogenetic studies were performed using all available HCV NS3 or NS3/4a nucleotide sequences (from (b) (4)). The results of this analysis, referred to here as Method 3, are described in detail below.

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In total, 1419/1500 (94.6%) HCV NS3 or NS3/4a baseline sequences were available for phylogenetic analysis from the pivotal Phase studies P05101 and P05216. The remaining 81 sequences (5.4%) were NS3/4a sequencing failures and were excluded from the analysis. Of these, 5/81 were determined to be genotype 6 virus by the (b) (4) NS5B sequencing assay.

The HCV NS3/4a nucleotide sequences were aligned using the ClustalW multiple alignment sequencing package. HCV NS3/4a nucleotide sequences from H77 and Con1 were included in the alignments as prototypical genotype 1a and 1b sequences, respectively; prototypical 2a and 3a sequences were included as a control. Phylogenetic trees were then generated from the alignments using the PHYLIP software package (Version 3.6)<sup>1,2</sup>. From the phylogenetic analysis, viral sequences were scored as genotype 1a if they clustered with the H77 prototypical sequence and 1b if they clustered with the Con1 prototypical sequence. An example of a phylogenetic tree (which has been truncated so that the associated text can be easily viewed) is shown in Figure 1.

Results from the phylogenetic analysis revealed that 1418 out of 1419 HCV sequences clustered correctly with either H77 or Con1 sequences based on the genotype originally assigned by Method 2. The single discrepant sequence was a genotype 1a virus (Patient 12048 in P05101) that clustered with genotype 1b sequences. Therefore, Method 2 correctly identified the viral subtype in 99.9% of cases as determined by the phylogenetic analysis. In all cases, other than the virus from patient 12048, genotype 1a sequences clustered together and with the prototypical genotype 1a H77 sequence but separately from genotype 1b viruses. Furthermore, all genotype 1b sequences clustered together with the prototypical genotype 1b Con1 sequence and separately from genotype 1a sequences (Table 1).

Both genotype 1a and 1b sequences clustered independently from prototypical genotype 2a and 3a sequences (See Figure 1, below). The results from the phylogenetic analysis reported here are highly concordant with the Merck secondary genotype analysis reported in the NDA filing, confirming the genotype assignments as reported in the dossier. SAS transport files accompanying this submission contain the analysis datasets and phylogenetic data for the individual protocols P05101 and P05216.

Study	Genotype	Concordance % (Method 1 vs 2)	Concordance % (Method 1 vs 3)	Concordance % (Method 2 vs 3)
P05101	Genotype 1a	77.5	77.1	99.6
	Genotype 1b	92.6	91.7	100
P05216	Genotype 1a	73.9	74.4	100
	Genotype 1b	86.2	85.7	100
TOTAL	Gen 1a + 1b	82.5	82.2	99.9

Table 1: Concordance analysis of Genotype Method 1 (TRUGENE™, Roche), Method 2 (Either "NS5B" or the "inferred genotype" from (b) (4) NS3/4a assay) and Method 3 (NS3/4a Phylogenetic analysis).

1. Felsenstein, J. 2005. PHYLIP (Phylogeny Inference Package) version 3.6. *Distributed by the author. Department of Genome Sciences, University of Washington, Seattle.*
2. Felsenstein, J. 1989. PHYLIP - Phylogeny Inference Package (Version 3.2). *Cladistics* 5: 164-166.
3. Stephane Chevaliez, Magali Bouvier-Alias, Rozenn Brillat, Jean-Michel Pawlotsky 2009. Hepatitis C Virus (HCV) Genotype 1 Subtype Identification in New HCV Drug Development and Future Clinical Practice, *PLOS-one* Vol 4 (12), pp 1-9.



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confirms that subtype results from Methods 2 and 3 were highly concordant: 1417/1418 (99.9%), excluding missing data.

**01/31/2011: Virology request communicated to sponsor, and sponsor's reply (SDN 23)**

We have the following request for clarification of HCV genotypic resistance dataset formats. Regarding all of the Phase 3 trial resistance datasets (P05101 and P05216) and the long-term follow-up resistance datasets (P05063) included in the boceprevir NDA, please confirm that our following assumptions are correct:

- When amino acid substitutions/variants from reference were detected as mixtures with wild-type/reference amino acid sequences, they were reported in the electronic datasets as the 'variant' sequence. In other words, no mixtures of wild-type/variant sequences are reported as such, rather only the variant sequence is reported.
- Even if the 'variant' amino acid sequence was detected as the minority species in a mixture with the wild-type/reference amino acid sequence, the 'variant' sequence was still the one reported in the electronic datasets.

Sponsor's reply in SDN 23:

The assumptions are correct.

Reviewer's comment: adequate response.

**02/04/2011: Virology/Clinical/Statistics requests communicated to sponsor, and sponsor's reply (SDNs 28, 32, 34)**

1. In order to align primary efficacy analyses (SVR24) for each of the pending marketing applications, we have decided to use HCV RNA <25 IU/mL rather than limit of detection (LOD <10 IU/mL) as the cutoff for SVR24. This will affect only follow-up off treatment timepoints, and is not to be used as a surrogate for 'undetectable HCV RNA' for on-treatment or end-of-treatment timepoints. Please provide a reanalysis of SVR24 in the pivotal studies using the <25 IU/mL cutoff, and compare to the SVR24 analysis using the LOD (<10 IU/mL) cutoff.
2. We concur with your approach to determine SVR24 by imputing HCV RNA data from later follow-up off treatment timepoints, or follow-up week 12 if no other subsequent timepoints, in cases where the 24 week (or within the specified window) data off-treatment are missing.

Sponsor's reply in SDN 28:

Re-analysis of SVR using <25 IU/ml has impacted only 3 subjects (2 in P05101 and 1 in P05216) who are now considered as SVR.

**P5101 (RESPOND 2):**

Only 2 subjects (one in Arm 1, and one in Arm 2), who have 'POS' and <25 IU/mL, were previously considered as non-SVR are now categorized as SVR. The updated SVR rates (using LLQ as cutoff) as well as the original SVR rates in the FAS population are shown below:

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SVR Rate (FAS)	Arm 1 Control	Arm 2 RGT	Arm 3 Boc/PR 48
<b>Re-Analysis –</b> (LLQ: <25 IU/mL)	18/80 (22.5%)	<b>96/162 (59.3%)</b>	107/161 (66.5%) Same as original
<b>Original –</b> (LLD: <9.3 IU/mL)	17/80 (21.3%),	95/162 (58.6%),	107/161 (66.5%),

**P05216 (SPRINT 2):**

Only one subject (non-black, Arm 1), who has 'POS' and <25 IU/mL, was previously considered as non-SVR is now categorized as SVR. The updated SVR rates (using LLQ as cutoff) as well as the original SVR rates in the FAS population (cohort 1 + cohort 2) are shown below:

SVR Rate (FAS)	Arm 1 Control	Arm 2 RGT	Arm 3 Boc/PR 48
<b>Re-Analysis –</b> (LLQ: <25 IU/mL)	<b>138/363 (38.0%)</b>	233/368 (63.3%) Same as original	242/366 (66.1%) Same as original
<b>Original –</b> (LLD: <9.3 IU/mL)	137/363(37.7%)	233/368 (63.3%)	242/366 (66.1%)

(Additional information related to SAS coding provided for the statistics reviewer)

Reviewer's comment: adequate response.

- Because we are changing the viral load cutoff for SVR24, determinations for the primary efficacy analysis, we need to confirm that subjects who had a low detectable, but unquantifiable HCV viral load measurement at follow-up Week 24 based on a sensitive viral load assay continued to remain virologically suppressed over the long term. Using available interim data from long term follow-up trial P05063, please characterize the long term virologic suppression of subjects who did not achieve SVR24 based on an LOD cutoff, but who would have achieved SVR24 if using the lower limit of quantification of the assay used (<25 IU/mL or <30 IU/mL, according to P05063 study report).

Sponsor's reply in SDN 28:

The sponsor provided no response to request #3 (see reply in SDN 32 below).

Sponsor's reply in SDN 32:

Three subjects (two from study P05101 [Subject No. 96/010051 and Subject No. 26/010114] and one from study P05216 [Subject No. 136/000400]) who completed 24 weeks of follow-up in the pivotal trials had HCV-RNA values <LLQ but detectable. Of these three, additional HCV-RNA data were available for Subject No. 96/010051 after enrollment in the long-term follow-up study (P05063). This subject completed the screening, Month 3, and Month 6 visits with HCV-RNA results reported as <LLQ not detected. The remaining two subjects did not have additional HCV-RNA results. The patient profile for this one subject enrolled into P05063 is included in the attachments.

(HCV RNA data pasted below)

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Protocol	Study day/Date@	Genotype	HCV RNA (b) (4) Visit	HCV RNA (IU/ml)	Result Text
P05101	-533/ 09OCT08	1a	Screening	635,000	
P05101	-504/ 07NOV08		Day 1	730,000	
P05101	-490/ 21NOV08		TW 2	225,000	
P05101	-476/ 05DEC08		TW 4	26,000	
P05101	-463/ 18DEC08		TW 6	<25	HCV RNA not detected
P05101	-445/ 05JAN09		TW 8	<25	HCV RNA not detected
P05101	-434/ 16JAN09		TW 10	<25	HCV RNA not detected
P05101	-422/ 28JAN09		TW 12	<25	HCV RNA not detected
P05101	-393/ 26FEB09		TW16	<25	HCV RNA not detected
P05101	-367/ 24MAR09		TW 20	<25	HCV RNA not detected
P05101	-337/ 23APR09		TW 24	<25	HCV RNA not detected
P05101	-294/ 05JUN09		TW 30	<25	HCV RNA not detected
P05101	-252/ 17JUL09		TW 36	<25	HCV RNA not detected
P05101	-224/ 14AUG09		F/U Wk 4	<25	HCV RNA not detected
P05101	-168/ 09OCT09		F/U Wk 12	<25	HCV RNA not detected
P05101	-87/ 29DEC09		F/U Wk 24	<25	HCV RNA not detected
P05101	1/ 26MAR10		F/U Wk 72	<25	HCV RNA detected
P05063	1/ 26MAR10		Screening	<25	HCV RNA not detected
P05063	85/ 18JUN10		Month 3	<25	HCV RNA not detected
P05063	183/ 24SEP10		Month 6	<25	HCV RNA not detected

Reviewer's follow-up comment: the following request was communicated to the sponsor by email on 3/1/2011: "In your response to the Division of Antiviral Products Clinical Question # 3 of February 4, 2011 on the Boceprevir NDA, you reported long-term follow-up data for a single subject who achieved SVR in a Phase 3 boceprevir trial based on an LLOQ cutoff but not based on an LOD cutoff. Please comment if there were any additional subjects from either of the Phase 2 boceprevir trials P03523 or P03659. If so, please summarize any long term follow-up HCV RNA data from these subjects as well."

Sponsor's Reply in SDN 34:

From SPRINT-1 (P03523), there was no such subject that was below the LLQ (<30 IU) and detectable at end of follow-up, so no subject was identified.

From RESPOND-1 (P03629) a single subject assigned to Arm 1 (pegylated interferon plus ribavirin therapy) was later switched to boceprevir plus pegylated interferon and ribavirin therapy, according to protocol amendment 2. This subject had a detectable viral load at end of follow-up (100 IU/mL based on the (b) (4) laboratory assay which was used at that time; LLQ of 125 IU/ml). The subject entered P05063 and viral load was below the LLQ at screening and has remained so through month 24, based on the (b) (4) assay (LLQ of 30 IU/ml). The subject's data listing is provided in the attachment (pasted below).

Subject A00047

Center/ Subject	Sex/ Age/ Race	P05063 Status	Study# Day/ Date	Lab Virology Visit	Lab	Result Text	Result	Viral Load (IU/mL)
23/A00047	M/44/W	Completed	-400/ 25OCT05	SCRN	(b) (4)		POS	2,666,667
			-379/ 15NOV05	TW1D1			POS	2,903,101
			-377/ 17NOV05	TW1D3			POS	368,604
			-372/ 22NOV05	TW2D1			POS	3,441,860
			-370/ 24NOV05	TW2D2			POS	844,961
			-369/ 25NOV05	TW2D3			POS	599,888
			-365/ 29NOV05	TW3D1			POS	2,650,299
			-364/ 30NOV05	TW3D2			POS	2,816,726
			-363/ 01DEC05	TW3D3			POS	1,767,913
			-358/ 06DEC05	TW4			POS	1,017,421
			-351/ 13DEC05	TW5D1			POS	5,186,605
			-350/ 14DEC05	TW5D2			POS	1,390,786
			-344/ 20DEC05	TW6			POS	593,396
			-330/ 03JAN06	TW8			POS	313,005
			-316/ 17JAN06	TW10			POS	342,150
			-295/ 07FEB06	TW13			POS	165,273
			-267/ 07MAR06	TW17			POS	102,205
			-239/ 04APR06	TW21			POS	65
			-211/ 02MAY06	TW25			ND	
			-169/ 13JUN06	ETERM			POS	139,580
			-148/ 04JUL06	TW3A2			ND	
			-134/ 18JUL06	TW6A2			ND	
			-106/ 15AUG06	TW9A2			ND	
			-85/ 05SEP06	TW12A2			ND	
			-43/ 17OCT06	TW18A2			ND	
			-1/ 28NOV06	TW24A2			POS	430
			35/ 02JAN07	FUW4			ND	
			63/ 30JAN07	FUW8			ND	
			91/ 27FEB07	FUW12			ND	
			175/ 22MAY07	FUW24			POS	100
			266/ 21AUG07	SCREENING	(b) (4)	No HCV RNA detected	NEG	<30
			364/ 27NOV07	MONTH 3		No HCV RNA detected	NEG	<30
			455/ 26FEB08	MONTH 6		No HCV RNA detected	NEG	<30
			623/ 12AUG08	MONTH 12		No HCV RNA detected	NEG	<30
			912/ 17FEB09	MONTH 18		No HCV RNA detected	NEG	<30
			987/ 11AUG09	MONTH 24		HCV RNA not detected	NEG	<25
23/A00047	M/44/W	Completed	1197/ 09MAR10	MONTH 30		HCV RNA not detected	NEG	<25

Reviewer's comment: adequate response. The sponsor's replies to these requests confirm there were very few subjects who achieved SVR in a boceprevir phase 2 trial based on an LLOQ cutoff but not based on an LOD

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cutoff for the appropriate follow-up visits. Of those with available longer-term follow-up data (n=2), there is no evidence that SVR was not durable.

**03/14/2011: Virology request communicated to sponsor, and sponsor's reply (SDN 36)**

Two different definitions for "Incomplete Virologic Response" (IVR) were used for the Phase 3 trials P05216 and P05101:

Protocol:  $\geq 1 \log_{10}$  IU/mL increase in HCV RNA from nadir with HCV RNA  $>1,000$  IU/mL if both samples being compared were collected the same number of days after the last PEG2b injection. If timing of PEG2b injection differed, a  $\geq 2 \log_{10}$  IU/mL increase from nadir was required to meet IVR criteria.

Expert Review: Simply defined as a  $\geq 1 \log_{10}$  IU/mL increase from nadir, with no requirement of a  $>1,000$  IU/mL value, and no requirement for a  $\geq 2 \log_{10}$  IU/mL increase depending on PEG2b timing.

It is not entirely clear when each definition is used for specific efficacy analysis purposes. Examples of inconsistencies include:

P05216 Clinical Study Report: first paragraph of Section 11.4.1.7 (pg. 194) states that IVR was based on the Protocol definition, but the last sentence of the same paragraph refers readers to the Expert Review definition. Also, Table 36 (pg. 196) notes the Protocol definition is used to calculate IVR rates, but the source data tables note the Expert Review definition was used.

Summary of Clinical Efficacy: Table 18 (pg. 94) notes that the Protocol definition was used to report IVR rates

Resistance Analysis Update: Table 1 (pg. 13) uses the Expert Review Definition to report IVR rates.

Please clarify exactly when each IVR definition was used for the following purposes related to clinical trials P05216 and P05101:

- Efficacy analysis tables (e.g., reporting IVR rates)
- Resistance reports (e.g., resistance analysis update)
- Resistance datasets

Sponsor's Reply in SDN 36

All Efficacy analysis tables (e.g. reporting Incomplete Virologic Response (IVR) rates), Resistance reports (e.g. resistance analysis update), and resistance datasets, used the Expert Review Definition for IVR. The footnotes in the various tables which indicate the protocol definition were used merely to denote the actual protocol-specified IVR criteria. Although the Expert Review Definition is a more inclusive definition for subjects who meet IVR criteria, the analysis yielded very few additional cases beyond those generated by the Protocol Definition.

Reviewer's comment: adequate response. The sponsor's reply confirms this reviewer's assumption used throughout the NDA review process that reports of Incomplete Virologic Response refer to the "Expert Review" definition.

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)**  
**VIROLOGY REVIEW**  
**NDA: 202258 SDN: 003 DATE REVIEWED: 04/14/2011**  
**Virology Reviewer: Patrick R. Harrington, Ph.D.**

**APPENDIX D: Listing of archived Virology reviews of boceprevir IND 69027**

**Pre-NDA Meeting**

**SDNs 440 and 458**

**Clinical Study Reports**

**SDN 4 (SN 000, Original IND)**

Early non-IND trials (summary form)

**SDN 107 (or SDN 106?, SN 62)**

P03527, "Assessment of the safety, tolerability, pharmacodynamics and pharmacokinetics of SCH 503034 and [REDACTED]<sup>(b) (4)</sup> in HCV positive genotype 1 Peg-Intron treatment nonresponders."

**SDN 236**

P04487 (Core protocol), "A Multi-Dose Study to Evaluate the QID Dosing Regimen of SCH 503034 in Combination with PegIntron on Safety, Pharmacokinetics, and Pharmacodynamics in HCV Genotype 1 Patients,"

P04531 (Maintenance protocol), "A Multiple Dose Maintenance Protocol to Investigate the Safety and Effectiveness of SCH 503034 in Combination with PegIntron after a Long-Term Exposure in HCV Patients Who Complete a Core Treatment Protocol with SCH 503034."

**SDN 237**

P03659, "PEG-Intron/Rebetol® vs. PEG-Intron/SCH 503034 with and without Ribavirin in Chronic Hepatitis C HCV-1 Peginterferon alfa/Ribavirin Nonresponders: A SCH 503034 Dose-Finding Phase 2 Study." Summaries in **SDN 179 (SN 118)**, **SDN 221**

**SDN 322**

P03523, "A Safety and Efficacy Study of SCH 503034 in Previously Untreated Subjects with Chronic Hepatitis C Infected with Genotype 1." Summary in **SDN 179 (SN 118)**

**Protocol Reviews**

**SDN 9 (SN 2)**

P03659, "A Phase 2, Double-Blind, Randomized, Dose-Ranging, Safety and efficacy Study of Three Dose Levels of SCH 503034 in Combination with PEG-Intron 1.5 mcg/kg/week Plus Weight Based Ribavirin (800 to 1400 mg/day) or Placebo in Adult, Non-Responder Genotype 1-High Viral Load Chronic Hepatitis C (CHC) Subjects." Also in **SDN 17 (SN 8)**, draft form in **SDN 004/SN 000**

**SDN 108, 109 or 110? (SN 063) (no review of original protocol documented)**

P05063, "Long-Term Follow-Up of Subjects in a Phase 1, 2, or 3 Clinical Trial in Which Boceprevir or Narlaprevir Was Administered for the Treatment of Chronic Hepatitis C." (updated in **SDN 374**)

**SDNs 187 and 203**

P05216, "A phase 3 safety and efficacy study of boceprevir in previously untreated subjects with chronic HCV genotype 1." Also summarized in **SDN 179 (SN 118)**.

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)**  
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**NDA: 202258 SDN: 003 DATE REVIEWED: 04/14/2011**  
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P05101, "A phase 3 safety and efficacy study of boceprevir in subjects with chronic HCV genotype 1 who failed prior treatment with Peg-IFN $\alpha$ /RBV." Also summarized in **SDN 179 (SN 118)**.

**SDN 238**

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

**SDN 281**

P05411, "A Phase 2b, Safety and Efficacy Study of Boceprevir in Patients Coinfected with HIV and Hepatitis C" Updated in **SDN 320**.

**SDN 335**

P06086, "A Phase 3 Safety and Efficacy Study of Erythropoietin Use during Treatment of Subjects with Chronic Hepatitis C with Boceprevir, Peginterferon Alfa-2b, and Ribavirin." Synopsis in **SDN 301**, amended in **SDN 448**.

**SDN 423**

Pediatric trial, "Assessment of the Efficacy, Safety, and Pharmacokinetics of Boceprevir in Combination with Peginterferon alfa-2b plus Ribavirin in Pediatric Subjects with Chronic Hepatitis C Genotype 1." Comments/responses in **SDN 453**.

**Nonclinical Study Reports**

**SDN 211**

Report, "Crystal Structures of SCH 503034 Complexed with HCV NS3/4A Protease and its A156T Mutant"

**SDN 221**

D-55014, "Mutation Analysis of the HCV Protease (NS3) Region Qualification Report." Also in **SDN 236**.

**SDN 341**

- D46286, "Ancillary Studies of Issues Related to SCH 503034 Activity." Also in **SDN 137 (SN 79)**.
- D55146, "*In Vitro* Counterscreen Results of SCH 503034"
- D55147, "Further Characterization of Resistance Mutations of SCH 503034"
- D55176, "Identification of HCV Protease Inhibitor Resistance Mutations by Selection Pressure-based Method"
- D55850, "Additional Replicon Studies of SCH503034"

**Reviews of Other Communications/Submissions**

**SDN #s: 224, 233, 253, 261, 282, 320, 328, 378, 381, 397, 433, 436, 443, 445**

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)**  
**VIROLOGY REVIEW**  
**NDA: 202258 SDN: 003 DATE REVIEWED: 04/14/2011**  
**Virology Reviewer: Patrick R. Harrington, Ph.D.**

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**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)**  
**VIROLOGY REVIEW**  
**NDA: 202258 SDN: 003 DATE REVIEWED: 04/14/2011**  
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/s/  
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PATRICK R HARRINGTON  
04/15/2011

JULIAN J O'REAR  
04/15/2011

## VIROLOGY FILING CHECKLIST FOR NDA or Supplement

**NDA Number:** 202258

**Applicant:** Merck/Schering

**Stamp Date:** 11/15/2010

**Drug Name:** Boceprevir

**NDA Type:** Original

On **initial** overview of the NDA application for filing:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comments</b>
1	Is the virology information (nonclinical and clinical) provided and described in different sections of the NDA organized in a manner to allow substantive review to begin?	x		
2	Is the virology information (nonclinical and clinical) indexed, paginated and/or linked in a manner to allow substantive review to begin?	x		
3	Is the virology information (nonclinical and clinical) legible so that substantive review can begin?	x		
4	On its face, has the applicant <u>submitted</u> cell culture data in necessary quantity, using necessary clinical and non-clinical strains/isolates, and using necessary numbers of approved current divisional standard of approvability of the submitted draft labeling?	x		
5	Has the applicant <u>submitted</u> any required animal model studies necessary for approvability of the product based on the submitted draft labeling?			n/a
6	Has the applicant <u>submitted</u> all special/critical studies/data requested by the Division during pre-submission discussions?	x		
7	Has the applicant <u>submitted</u> the clinical virology datasets in the appropriate format as described in the relevant guidance documents and are the datasets complete?	x		
8	Has the applicant used standardized or nonstandardized methods for virologic outcome measures? If nonstandardized methods were used, has the applicant included complete details of the method, the name of the laboratory where actual testing was done and performance characteristics of the assay in the laboratory where the actual testing was done?	x		HCV genotype/subtype analysis methods questionable, which may require additional analysis (see request forwarded to sponsor on 12/13/2010)
9	Has the applicant <u>submitted</u> draft labeling consistent with current regulation, divisional and Center policy, and the design of the development package?	x		
10	Has the applicant <u>submitted</u> annotated microbiology draft labeling consistent with current divisional policy, and the design of the development package?	x		
11	Have all the study reports, published articles, and other	x		

## VIROLOGY FILING CHECKLIST FOR NDA or Supplement

	Content Parameter	Yes	No	Comments
	references been included and cross-referenced in the annotated draft labeling or summary section of the submission?			
12	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		x	

**IS THE MICROBIOLOGY SECTION OF THE APPLICATION FILEABLE? \_\_\_ Yes \_\_\_**

If the NDA is not fileable from the microbiology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

A request to conduct additional HCV genotype/subtype analyses was communicated to the sponsor on 12/13/2010. No other potential review issues have been identified at this time.

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Reviewing Microbiologist Date

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Microbiology Team Leader Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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PATRICK R HARRINGTON  
12/13/2010

JULIAN J O'REAR  
12/13/2010