

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202258Orig1s000**

**STATISTICAL REVIEW(S)**

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

**NDA Number: 202,258**

**Applicant: Schering-Plough**

**Stamp Date: Nov. 15, 2010**

**Drug Name: Victrelis™ (Boceprevir) NDA/BLA Type: Priority**

On **initial** overview of the NDA/BLA application for RTF:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comments</b>
1	Index is sufficient to locate necessary reports, tables, data, etc.	<b>x</b>			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	<b>x</b>			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	<b>x</b>			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	<b>x</b>			

**IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? YES** \_\_\_\_\_

If the NDA/BLA is not fileable from the statistical 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.

<b>Content Parameter (possible review concerns for 74-day letter)</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
Designs utilized are appropriate for the indications requested.	<b>x</b>			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	<b>x</b>			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			<b>x</b>	DMC was established for trials. No interim analysis was planned or conducted in phase 3 Studies P05101 and P05216.
Appropriate references for novel statistical methodology (if present) are included.			<b>x</b>	

**STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA**

Safety data organized to permit analyses across clinical trials in the NDA/BLA.	<b>x</b>			Pooled datasets of phase 2 and 3 clinical trials have been created.
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	<b>x</b>			

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Statistical comments to be conveyed to the Sponsor:  
  
 No.

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

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/s/  
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12/10/2010

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12/14/2010



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
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# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

**NDA/BLA Serial Number:** 202-258 / S-0001

**Drug Name:** Victrelis™ (Boceprevir)

**Indication(s):** Chronic Hepatitis C genotype 1 Infection

**Applicant:** Schering-Plough (Part of Meck now)

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**Keywords:** Chronic Hepatitis C Genotype 1 (HCV-1) infection, Superiority, Boceprevir, 800 mg TID, Treatment-naïve, P05216, Previous Treatment-failure, Phase 3, P05101, Standard of Care (SoC), PegIntron and ribavirin (PR), Response Guided Therapy (RGT), 4 Weeks Lead-in Period.

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## 1. EXECUTIVE SUMMARY

### Executive Summary (bottom-line)

The applicant submitted two randomized, controlled, double-blinded, phase 3 clinical trials with boceprevir as part of triple antiviral therapy for HCV-1a or HCV-1b infected adults, one for treatment-naïve (P05216) and one for previous treatment-failure (P05101).

The primary objective of both studies is to demonstrate the superiority of two therapeutic regimens of boceprevir 800 mg three times a day (TID) plus peginterferon and ribavirin (PR) over PR alone in HCV-1a or HCV-1b infected adults either untreated or failed prior treatment with PR.

One of important additional efficacy analyses is to compare the effect of the different boceprevir treatment regimens (Responding Guide Therapy (RGT) of Arm 2 vs. Arm 3 with BOC48 of fixed duration of treatment) on the primary efficacy outcome within overall, early responders, and late responders to determine the appropriate duration of treatment.

In study P05216, the early responder is defined as a subject who achieved suppression (<10 IU/mL) at Treatment Week 8 (TW8) and maintain the suppression through TW24, and received shorter duration of treatment (28 weeks) in RGT arm. The later responder is defined as a subject who did not achieve suppression at TW8, but suppressed at TW24, and received a longer duration of treatment (48 weeks) in RGT arm. In BOC48 arm, the subject must have more than 31 weeks of therapy in order to be considered as either early or late responders in the comparison.

In study P05101, the early responder is defined as a subject who achieved suppression (<10 IU/mL) at TW8 and TW12, and received shorter duration of treatment (36 weeks) in RGT arm. The later responder is defined as a subject who did not achieve suppression at TW8, but suppressed at TW12, and received a longer duration of treatment (48 weeks) in RGT arm. In BOC48 arm, the subject must have more than 39 weeks of therapy in order to be considered as either early or late responders in the comparison.

These two key phase 3 studies have demonstrated that boceprevir plus PR is efficacious for HCV-1a or HCV-1b infected subjects in both treatment-naïve and patients previously failed pegylated interferon alfa plus ribavirin therapy (including relapsers and partial responders only). Both non-black and black population will benefit from the addition of boceprevir to the regimen although the SVR rate of boceprevir contained regimen in black population is relatively lower compared to non-black population.

The duration of boceprevir treatment for early responders after 4 weeks of lead-in PegIntron/ribavirin can be 24 weeks of triple therapy for treatment-naïve and 32 weeks of triple therapy for previous treatment failure subjects as the RGT arm strategy the sponsor used in the trials. For later responders, the duration of boceprevir treatment after 4 weeks of lead-in PegIntron/ribavirin for previous treatment failure subjects can be 32 weeks of triple therapy followed by 12 weeks of PR as the RGT arm strategy the sponsor used in the P05101 trial.

For the early responder in Black subjects in treatment-naïve study, the longer boceprevir treatment duration than what in the RGT arm seems have better SVR. There is a numeric difference in the SVR rate for early responders between RGT arm and BOC48 arm for Black subjects in Cohort 2 of study P05216 although it is not statistically significant. The sample size (<20 subjects per arm) is too small to make any determination.

For the later responders in treatment-naïve population, the duration of boceprevir treatment of 24 weeks plus 20 weeks of PegIntron/ribavirin after 4 weeks of lead-in PegIntron/ribavirin used in the RGT arm of P05216 is not long enough. There is a numeric difference in SVR rate for late responders between RGT arm and BOC48 arm although it is not statistically significant. The study was not designed with adequate power to detect this difference. The recommended duration could either be the 44 weeks of triple therapy as used in the BOC48 arm in P05216 trial or 32 weeks of triple therapy followed by the 12 weeks of PR as the RGT arm for later responder in study P05101 as suggested by the Pharmacometrics reviewer. There was no data available to make a final statistical choice between the two since the later one was not in the trial.

Another remaining issue is whether or not the previous Null responder should be included in the indication. Please refer to clinical review for details.

### Key statistical issues:

1. The cut-off value for SVR rate determination:

In both studies, the primary efficacy endpoint (SVR<sub>24</sub>) was sustained virologic response, SVR (undetectable HCV RNA (< 10 IU/mL)) measured 24 weeks after the end of therapy. The DAVP decided to ask both applicants (for boceprevir and telaprevir) to use an HCV RNA cutoff of < 25 IU/mL (lower limit of assay quantification, LLOQ) for defining SVR for the purposes of the labeling for boceprevir and telaprevir because of issues with false positive HCV RNA using the LOD (< 10 IU/mL) post-treatment. As a result, the primary efficacy endpoint was calculated using both <10 (undetectable) and <25 (unquantifiable).

As you can see in the following table, only one subject in P05216 and 2 subjects in P05101 will be changed from non-responders to responders if using <25 instead of <10 as the cut-off value for SVR summary. Even if <1000 IU/mL was used, only 4 non-responders will be picked up as responders in P05216 study. Ie, this change has no impact on the final conclusion. [In the result section, results using both <10 and <25 cut-off values will be displayed together most of time.](#)

**Table 1:** Number of Subjects with <10 IU/mL or <25 IU/mL at EOF Window (FAS)

Study	PCREof <sup>3</sup> (<10)	PCREof (<25)		PCREof (<50)		PCREof (<1000)		Subtotal
		POS	NEG	POS	NEG	POS	NEG	
P05216 (N=1097)	POS	484	1 <sup>1</sup>	482	3	481	4	485
	NEG	0	612	0	612	0	612	612
P05101 (N=403)	POS	182	2 <sup>2</sup>					184
	NEG		219					219

<sup>1</sup>: One subject in PR48 had HCV RNA viral load <25 with detectable at end of follow-up (EOF) window, and they will become a responder from a non-responder using <25 cut-off value instead of using <10.

<sup>2</sup>: Two subjects in PR48 and RGT arm each had HCV RNA viral load <25 with detectable at end of follow-up (EOF) window, and they will become responders from non-responders using <25 cut-off value instead of using <10.

<sup>3</sup>: **PCREof** stands for the PCR result at EOF window which is the primary efficacy endpoint, SVR<sub>24</sub>, (NEG is a responder and POS is a Non-responder.) In this review, **PCREof** and SVR<sub>24</sub> may used interchangeable.

2. The impact of LOCF of Follow-up Week 12 (FW12) for subjects who missed FW24:

As the SAPs specified for both studies, if a subject is missing FW24 data and has undetectable HCV RNA level at FW12, the subject would be considered as a responder.

The number of subjects having FW12 being carried over to EOF is listed in Table 2 below. As you can see, three arm have similar numbers of subjects who became responders for both <10 or <25 cut-off value even though PR48 arm seems have a low percentage. As a result, FW12 carry forward will be used for the primary efficacy endpoint analyses. Using FW24 results without carrying over FW12 data will give the same conclusion for primary efficacy endpoint analysis.

**Table 2:** Number of Subjects Who having FW12 being Carried Over to EOF (FAS)

Study	<10 as cut-off value (n/N <sup>1</sup> )				<25 as cut-off value (n/N)			
	PR48	RGT	BOC48	total	PR48	RGT	BOC48	total
P05216	4/36	4/15	4/11	12/62	5/36	4/15	4/11	13/62
P05101	0/5	1/4	1/4	2/13	0/5	1/4	1/4	2/13

<sup>1</sup>: N is the number of subjects with FW12 being carried over to EOF; and n is the number of subjects having NEG at FW12 among N subjects.

3. The impact of using the last available viral load within the window for the FW24 instead of worst observation (highest viral load) within the window:

As noted in the section 3.2.1 the analysis windows, the pre-specified visit window for FW24 (X24) is [140, ], ie, the last available viral load observation on and after 140 days post end-of-treatment (EOT) will be used to assess the subject's final responsiveness, either responder or non-responder. What if the worst observation is used for final SVR rate calculation?

If using the worst HCV RNA viral load observation within window [140, ] instead of the last observation, there are 139 subjects (PR48=51, RGT=41, BOC48=47) in study P05216 having numeric value change (none of them change the category, ie, NEG→ POS), and 58 subjects (PR48=16, RGT=23, BOC48=19) in study P05101 having numeric value change (none of them change the category, ie, NEG→ POS) plus one subject (subject ID=011105 in RGT arm in P05101) with category change from NEG to POS. As a result, the impact of selecting late available observation is OK for calculating the primary efficacy endpoint, which will be used in the review.

One note is that the NEG/POS mentioned here is using <10 IU/mL as cut-off value.

4. Population for the indication of this application:

According to the September 2010 draft FDA Guidance for Industry entitled “Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Agents for Treatment,” the definition of response to previous pegylated interferon/ribavirin regimen are the following:

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

The Applicant’s term, “non-responders” refers to subjects who had a  $\geq 2$  log<sub>10</sub> declines in viral RNA after 12 weeks treatment and never achieving undetectable HCV RNA (these subjects will be referred to as previous partial responders according to the Guidance). As a result, HCV guideline defined prior Null responders were not included in its phase 3 study P05101.

The sponsor argued that virologic response at either timepoint (week 4 or 12) could be used to predict which subjects are unlikely to achieve SVR, and that treatment week 4 response to PR therapy could be used to predict SVR, and  $<1$  log<sub>10</sub> decline at TW4 (end of PR lead-in) could be considered as **a surrogate** for null-response to prior PR therapy (defined as  $< 2$  log<sub>10</sub> HCV RNA decline at treatment week 12).

From the study P05101 where only prior partial responders and prior relapsers were enrolled, 25.3% (102/403) of all subjects enrolled achieved a  $<1$  log<sub>10</sub> HCV RNA decline at treatment week 4 (end of PR lead-in). 45% (46/102) of subjects who achieved a  $<1$  log<sub>10</sub> HCV RNA decline at treatment week 4 were prior relapsers. 29% (84/291) of subjects who achieved a  $\geq 1$  log<sub>10</sub> HCV RNA decline at treatment week 4 were prior partial responders (Table 3). The P-value of Fisher exact test is  $<0.0001$ , which seems indicate that  $\geq 1$  log<sub>10</sub> Decline at TW4 (end of PR lead-in) is strongly associated with the prior relapser.

**Table 3:** The Relationship between TW4 Responsiveness and Previous Response in Study P05101

Overall	Previous Response ( <b>PrevCor</b> ), n ( <b>SVR24</b> )		Subtotal
	Prior Partial Responders	Prior Relapsers	
$<1$ log <sub>10</sub> Decline	56 (27%)	46 (33%)	102
$\geq 1$ log <sub>10</sub> Decline	84 (47%)	207 (71%)	291

Overall it may be hard to extend the indication to include Null responders in the label from the statistical point of view. Please refer to clinical review for details.

5. The comparison between RGT vs. BOC48 in early/late responders:

The purpose of comparison of RGT arm vs. BOC48 arm is to demonstrate that regimens in RGT arm design are OK for both early and late responders. The sponsor concluded that the RGT arm represents a clear advantage over standard of care and the 48-week fixed-duration arm by offering a substantially shorter treatment duration for a large patient population and minimizing boceprevir exposure for all patients. **FDA stat reviewer's analysis, however, did not support this conclusion for later responders in study P05216.**

For both studies, the way of selecting early/late responders with RGT arm and BOC48 arm by the sponsor was not consistent and could cause the bias. In RGT arm, the criteria were the definition of early/late responder, ie, group A or B assignment within RGT arm in conducting the trials, the real treatment duration information was not in the consideration and the group assignment may not exactly follow their protocol design. While in BOC48 arm, the duration of treatment information was used to select early/late responders. Please see section 3.2.3 for the detailed definitions.

The stat reviewer used both definitions and the real treatment duration information to select early/late responders in RGT and then conducted the comparison of RGT vs. BOC48 for early/late responders separately. These analyses did not change the conclusions of early responders in study P05216 and the conclusions of early/late responders in study P05101. However, it did change the results for later responders in study P05216 and this leads the different regimen recommendation for later responders in treatment-naïve population. This is the only part where the reviewer's results are not consistent with the sponsor's results in terms of major efficacy analyses reviewed in this review. Please see section 3.2.4 for detailed analyses results.

6. The relapse rate calculation:

The sponsor only included subjects who had undetectable (<10) at the EOT (end-of-treatment) and had observation at the EOF (end-of-follow-up) in the relapse analysis. The potential bias with this is that some subjects who were undetectable at EOT and might have 4-weeks follow-up HCV RNA observation, but did not have any observation at the EOF (including FW12 and FW24) and these subjects were excluded from the current relapse analysis.

In order to assess the impact of this data filtering, sensitivity analyses are conducted, where all subjects who had undetectable at EOT will be included into the analysis. There were 31 subjects in total who were EOT=NEG and EOF=missing excluded from the relapse rate calculation for study P05216 (Table 4). None of those 4 subjects in the RGT arm had any observation beyond EOT, 2 out of those 12 subjects in the BOC48 arm had week 4 follow-up result (both were NEG), and 7 out of those 15 subjects in the PR48 arm had week 4 follow-up result (only 1 out of those 7 was POS). If LOCF (lost observation carry forward), only one subject in PR48 arm will be counted as a relapser, and relapse rates for three arms would be similar to original results.

For study P05101, there were 6 subjects who were EOT=NEG and EOF=missing excluded from the relapse analysis (Table 4). The only subject who had observation after EOT was in the RGT arm with NEG at week 4 follow-up. If LOCF (lost observation carry forward), none of those 6 subjects will be counted as a relapser, and relapse rates for three arms would be almost the same as the original results.

**Table 4:** The Subject's Status in Terms of Relapse Rate Analysis

<b>Study P05216</b>				
		PR48	RGT	BOC48
<b>Original Relapse Rate</b>		39/176 (22.2)	24/257 (9.3)	24/256 (9.1)
EOT=NEG	EOF ^=missing ( <b>Relapse Analysis</b> )	176	257	265
	EOF=missing	<b>15</b>	<b>4</b>	<b>12</b>
Relapse Rate (including EOF=missing), n/N (%)		<b>40/191</b> <b>(20.9)</b>	<b>24/261</b> <b>(9.2)</b>	<b>24/277</b> <b>(8.7)</b>
EOT=POS		162	95	88
EOT=missing		10	12	1
<b>Total</b>		<b>363</b>	<b>368</b>	<b>366</b>
<b>Study P05101</b>				
<b>Original Relapse Rate</b>		8/25 (32)	17/111 (15.3)	14/121 (11.6)
EOT=NEG	EOF ^=missing ( <b>Relapse Analysis</b> )	25	111	121
	EOF=missing		<b>3</b>	<b>3</b>
Relapse Rate (including EOF=missing), n/N (%)		<b>8/25</b> <b>(32)</b>	<b>17/114</b> <b>(14.9)</b>	<b>14/124</b> <b>(11.3)</b>
EOT=POS		55	48	37
EOT=missing				
<b>Total</b>		<b>80</b>	<b>162</b>	<b>161</b>

In summary, as it turned out that the impact of including all subjects with EOT=NEG in the relapse analysis is very small for both studies and the original definition will be used for the label.

## 2. INTRODUCTION

### 2.1 Overview

#### 2.1.1 Class and Indication

Boceprevir (SCH 503034) is a structurally novel, peptidomimetic ketoamide protease inhibitor that binds reversibly to the HCV NS3 active site. It inhibits the HCV NS3 protease, thereby preventing viral replication, a new mechanism of action compared to both interferon alfa and ribavirin.

Combination therapy with peginterferon and ribavirin (PR) is the standard of care (SoC) for the treatment of chronic hepatitis C (HCV). However, with SoC, only 40-50% of treatment-naïve HCV genotype 1 (HCV-1) subjects achieve sustained virologic response (SVR). Among HCV-1 subjects who were previous failures to SoC, re-treatment with peginterferon and ribavirin resulted in an SVR of about 11-23%.

It hopes that the addition of a third active anti-HCV drug may lead to more rapid viral response than therapy with two drugs, and therefore, the addition of boceprevir to peginterferon and ribavirin therapy after a 4-week, lead-in period may allow for both increased rates of SVR and shorter treatment durations (in some populations) than treatment with peginterferon and ribavirin alone.

Boceprevir is indicated for the treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alpha and ribavirin, in adult subjects ( $\geq 18$  years of age) with compensated liver disease who are previously untreated or who have failed previous therapy ([Please see statistical issue section for the comment on this population](#)).

### **2.1.2 History of Drug Development**

At the time of this NDA submission, the sponsor has completed 19 clinical pharmacology studies, 2 phase 2 studies (P03659 and P03523), and 2 phase 3 studies (P05216 and P05101). There are some additional phase 2 and 3 studies ongoing. (Please see module 2.7.6 in the NDA for details.)

The first Phase 2 study (P03659) was a dose-finding study and was conducted in subjects with CHC genotype 1, who failed previous PR treatment. Based on the results from this study, boceprevir 800 mg TID in combination with peginterferon and ribavirin was selected to treat subjects with CHC genotype 1.

The second Phase 2 study (P03523) was conducted in subjects with CHC genotype 1 who were treatment naïve and evaluated several different BOC treatment regimens. Treatment with BOC/PR (triple therapy) yielded a significant increase in SVR and lower relapse rate versus the PR control arm. Based on the results from this study, a 4-week lead in with PR was used in the Phase 3 studies.

There are two phase 3 pivotal studies, P05216 for treatment-naïve subjects and P05101 for previous treatment failure subjects, to support the application along with those two phase 2 studies.

Only two phase 3 studies will be reviewed in this review. Because the study P03659 was a dose-finding study, and study P03523 is an open-label study and many changes in terms of treatment during the trial.

### 2.1.3 Studies Reviewed

The detailed description of two phase 3 studies is listed in Table 5. The common features used in these two studies were 4 week lead-in period with peginterferon and ribavirin and response guide therapy (RGT) in Arm 2.

- **Four Weeks PR Lead-In:** All randomized subjects will initiate with a 4-week lead-in period of PR prior to having boceprevir or placebo added to their regimen in a blinded manner. According the sponsor’s CSR, a 4-week period of PegIntron plus ribavirin, prior to the addition of boceprevir, offers several theoretical advantages over beginning all three drugs simultaneously.
  - 1) By having the lead-in with peginterferon alfa-2b and ribavirin, viral load is reduced prior to the initiation of boceprevir, thereby decreasing the number of replicating virions exposed to boceprevir and potentially decreasing the likelihood for the development of resistance.
  - 2) In addition, ribavirin has reached steady state at Week 4, so that its full effects, possibly including the production of non-replicative virions, will be maximized at this time.
  - 3) Since the immunologic effects of interferon are also activated after the first few weeks of therapy, when boceprevir is added at Week 4 all three drugs should be fully active at the same time. This strategy may minimize any period of time when there is functional ‘monotherapy’ with a direct viral inhibitor.

**Table 5:** List of all studies included in analysis

Study	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
P05216	Phase 3, randomized, double-blind, placebo-controlled, stratified by HCV-1 subtype and by screening visit viral load	Most of subjects will get 48 weeks of treatment. Some early responders may have a shorter duration of treatment (24 weeks)	At least 24 weeks after treatment. The maximum of follow-up is 72 weeks from Day 1.	1099 subjects enrolled with 1:1:1 ratio. 1097 subjects were dosed. In cohort 1 (938): Arm 1=311 Arm 2=316 Arm 3=311 In cohort 2 (159): Arm 1=52 Arm 2=52 Arm 3=55	Treatment-naïve HCV-1 infected subjects
P05101	Phase 3, randomized, parallel-group, multi-center study, double-blinded for BOC or placebo in combination with open-label PR, stratified by HCV-1 subtype and by previous response category	Most of subjects will get 48 weeks of treatment. Some early responders may have a shorter duration of treatment (36 weeks)	At least 24 weeks after treatment. The maximum of follow-up is 72 weeks from Day 1.	404 subjects enrolled with 1:2:2 ratio. 403 subjects were dosed. Arm 1=80 Arm 2=162 Arm 3=161	Previous SoC treatment failed HCV-1 infected subjects (Relapsers and Non-responders). <sup>a</sup>

<sup>a</sup>: Non-responders here were subjects who had at least a 2-log<sub>10</sub> HCV-1 viral load reduction after 12 weeks of SoC treatment. According to the FDA’s HCV guideline, it is called “partial responder” and “Null” responders were not be enrolled in this trial.

- **Response Guide Therapy (RGT):** the duration of boceprevir treatment in Arm 2 will depend on the HCV-RNA status at TW8. If a subject has an undetectable HCV-RNA viral load at TW 8 (early responder), he/she will be assigned to a shorter duration of boceprevir treatment group (24 weeks for treatment-naïve subjects and 36 weeks for treatment failure subjects). If a subject has a detectable HCV-RNA viral load at TW8 (late responder), he/she will be assigned to a longer duration of treatment. The additional treatment for late responders is just additional PegIntron and ribavirin 20 weeks for treatment-naïve and 12 weeks for treatment failure subjects. The total treatment duration for late responders will be 48 weeks as the control Arm. Please see Table 6 below for summary.

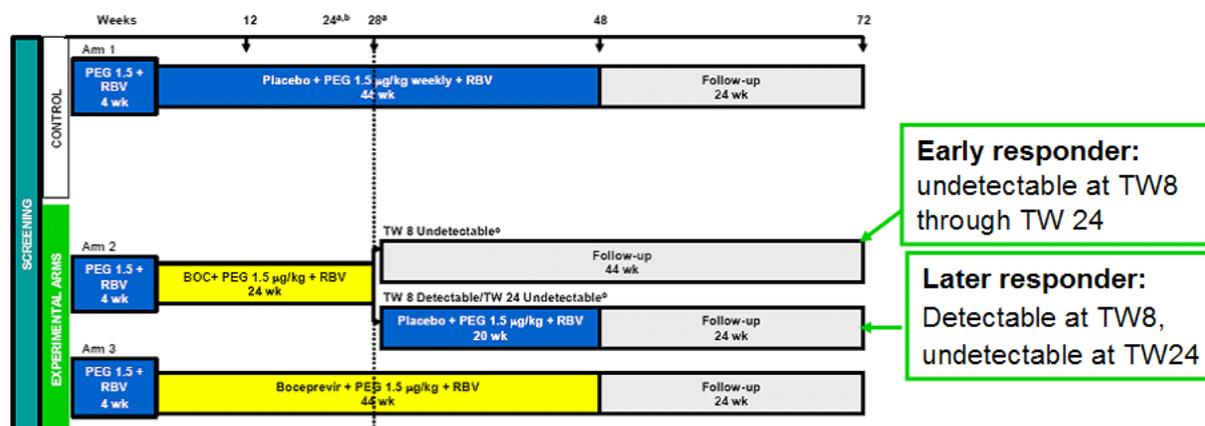
**Table 6:** The Treatment Duration for Early and Late Responders in RGT arm

RGT	Treatment Naïve (P05216)	Treatment Failure (P05101)
Early Responders	4 wks PR + 24 wks BOC/PR	4 wks PR + 32 wks BOC/PR
Late Responders	4 wks PR + 24 wks BOC/PR + 20 wks PR	4 wks PR + 32 wks BOC/PR + 12 wks PR

For treatment-naïve trial, only subjects without any detectable HCV RNA (<10 IU/mL) from TW8 through TW24 will be assigned to shorter duration of treatment (early responder) and subjects with detectable HCV RNA at TW8 and undetectable HCV RNA at TW24 will be assigned to a longer duration of treatment (late responder).

The detailed design characteristics of two phase 3 studies were described below.

❖ **P05216, a phase 3 study for Treatment-naïve HCV-1 subjects:**



**Figure 1:** P05216 Study Design Diagram

This is a randomized, multicenter study, double-blinded for boceprevir or placebo in combination with open-label PegIntron (PEG) and ribavirin (RBV), in previously untreated adult subjects with CHC genotype 1. The design diagram is shown in **Figure 1**. There are three arms:

## Control

- **Arm 1:** PEG 1.5 µg/kg + RBV (WBD) for 4 weeks followed by placebo + PEG 1.5 µg/kg + RBV (WBD) for 44 weeks with 24 weeks post-treatment follow-up.

## Experimental Therapy

- **Arm 2:** PEG 1.5 µg/kg + RBV (WBD) for 4 weeks followed by boceprevir + PEG 1.5 µg/kg + RBV (WBD) for 24 weeks. At the Treatment Week (TW) 28 visit, the interactive voice response system (b) (4) will assign subjects to one of two groups based on their HCV-RNA results on and after TW 8.
  - At the TW 28 visit, subjects whose HCV-RNA was undetectable at TW 8 and at all subsequent assays will be instructed that they have completed their assigned treatment with boceprevir + PEG 1.5 µg/kg + RBV (WBD) and should proceed to 44 week follow-up. **Sites and subjects will remain blinded as to their treatment arm until TW 28.**
  - At the TW 28 visit, subjects with detectable HCV-RNA at TW 8 or at any subsequent assays will be assigned by (b) (4) to continue on therapy with PLACEBO + PEG 1.5 µg/kg + RBV (WBD) for an additional 20 weeks, to complete a total of 48 weeks on treatment with 24 weeks post-treatment follow-up. **The switch from boceprevir to placebo will occur in a blinded fashion.**
- **Arm 3:** PEG 1.5 µg/kg + RBV (WBD) for 4 weeks followed by boceprevir + PEG 1.5 µg/kg + RBV (WBD) for 44 weeks with 24 weeks post-treatment follow-up.

This study is projected to enroll a total of 1080 subjects at approximately 200 sites worldwide. The study will enroll 930 non-black/African American subjects as cohort 1 (310:310:310 in Arms 1, 2, and 3, respectively). Additionally, a minimum of 150 black/African American subjects as cohort 2 will also be enrolled in a 1:1:1 ratio among Arms 1, 2, and 3. There will be no upper limit on the number of black/African American subjects that can be enrolled in the study, but enrollment will be kept open for these subjects until the minimum of 150 black/African American subjects is achieved if that level is not reached at the time when 930 non-black/African Americans have been randomized.

Randomization was stratified by two stratification factors:

- screening HCV RNA viral load ( $\leq 400,000$  IU/mL vs.  $> 400,000$  IU/mL), and
- the HCV-1 subtype (1a vs. 1b)

Subjects with undetermined subtype will be randomly assigned to an arm within their HCV RNA viral load strata. Cohort 1 and 2 were randomized independently.

**There is a 24-week futility rule for all arms.** I.e, subjects who had detectable HCV RNA at treatment week (TW) 24 will be considered to have failed treatment and will be discontinued from treatment and proceed to follow-up.

**Primary Efficacy Endpoint:** The primary efficacy endpoint is the achievement of SVR, defined as undetectable plasma HCV-RNA at Follow-up Week (FW) 24 based on the Full Analysis Set (FAS). [If a subject is missing FW24 data and has undetectable HCVRNA level at FW12, the subject would be considered an SVR.](#)

Subjects will be declared treatment failures in one of the following ways:

- Subjects in any treatment arm with detectable HCV-RNA at TW24 (treatment failure and discontinued from the treatment).
- Subjects in any treatment arm with detectable HCV-RNA at FW24.
- Subjects in any treatment arm who are missing their HCV-RNA at FW24 with detectable HCV-RNA at FW12.

The primary objective is to demonstrate the superiority of two therapeutic regimens of boceprevir 800 mg three times a day (TID) plus PR over PR alone in untreated HCV-1 infected adults.

**Key Secondary Endpoint:** The key secondary efficacy endpoint is the achievement of SVR defined as undetectable HCV-RNA FW24 in randomized subjects who received at least one dose of experimental study drug (placebo for the control arm and boceprevir for the experimental arms), ie, based on the mITT population. [\(This was added in amended protocol #2 on Dec. 02, 2009.\)](#)

**Secondary Endpoints:** The secondary efficacy endpoints in this study are:

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

Analysis Populations

**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 (mITT) Data Set:** all randomized subjects who received at least one dose of boceprevir (for the experimental therapy arms) or placebo (for the control arm), ie, passed 4 weeks lead-in period.

For all efficacy analyses, subjects will be included in the treatment arm to which they are randomized. For all safety analyses, subjects will be included in the treatment arm corresponding to the study treatment they actually received.

All primary and secondary efficacy analyses will be carried out using the two-sided Cochran-Mantel Haenszel (CMH) chi-square test (adjusted for the baseline stratification factors).

In order to control the type 1 error for the two comparisons (Arm 3 vs. Control, and Arm 2 vs. Control) for the primary analysis, step-down approach was used to control multiplicity. First, the Arm 3 will be compared against the control arm (Arm 1) using the 2-sided CMH chi-square test, adjusted for the baseline stratification factors. If this p-value is less than 0.05, efficacy of 48 weeks of treatment with boceprevir over the PegIntron/ribavirin control group will be established and the next comparison will be carried out, ie, the 28/48 week experimental group (Arm 2) will be compared against the control arm using the same CMH test. If this p-value is less than 0.05, then the efficacy of the 28/48 week arm will be established.

To account for multiplicity between the primary and key-secondary analyses, we will step down to the key-secondary analyses only if the significance of the primary comparisons has been established. The same logic also applied to the key-secondary efficacy analyses.

### **Sample size calculation:**

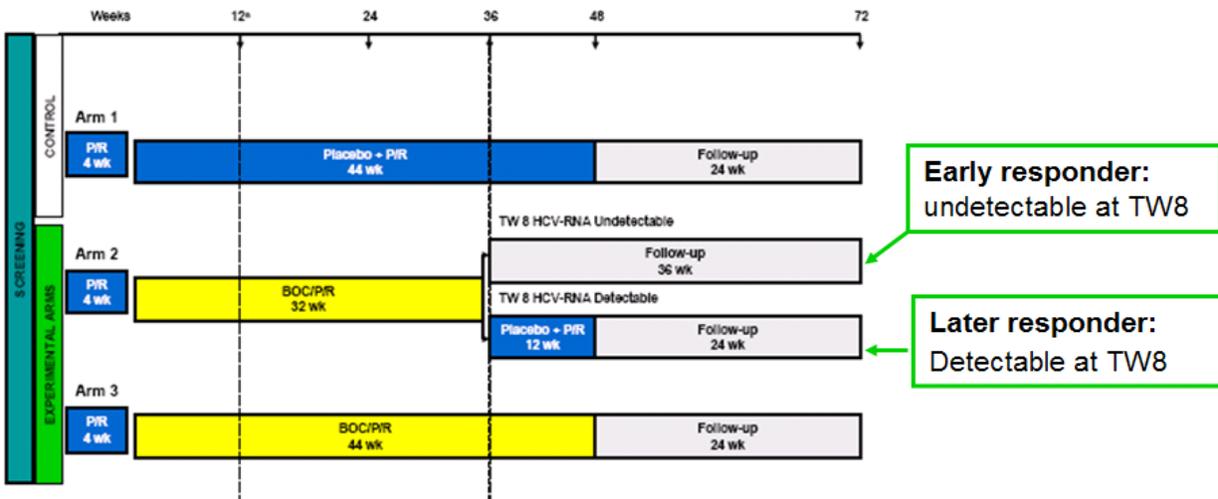
This study is projected to enroll a total of 930 non-black/African American subjects (310:310:310) in Arms 1, 2, and 3, respectively. With 310 subjects per arm, the study will have 90% power to detect a combined 13% improvement in the SVR rate, assuming a control SVR rate of 45% (ie, 58% vs. 45%) using a 2-sided chi-square test at  $\alpha = 0.05$ .

With 50 subjects per arm, the true response rate in the black/African American population can be estimated within  $\pm 14\%$  assuming an estimated response rate of 50% and using a 2-sided 95% confidence interval.

### **❖ P05101, a phase 3 study for Treatment-Failure HCV-1 subjects:**

P05101 is a randomized, multi-center study, double-blinded for boceprevir or placebo in combination with open-label PegIntron and ribavirin (WBD), in adult subjects with CHC HCV-1 who demonstrated interferon responsiveness but failed to achieve SVR on prior treatment with Peginterferon/ribavirin. The primary objective of this study is to compare the efficacy of two therapeutic regimens of boceprevir 800 mg dosed TID orally (PO) in combination with PegIntron™ 1.5 µg/kg QW subcutaneously (SC) plus weight-based dosing (WBD) of ribavirin (600 mg/day to 1400 mg/day) PO to therapy with PEG + RBV (WBD) alone in adult subjects with chronic hepatitis C (CHC) genotype 1 with demonstrated interferon responsiveness who failed prior treatment with peginterferon/ribavirin.

This trial consists of three arms, one control arm (PEG+RBV for 48 weeks) and two experimental arms (see **Figure 2** for study design diagram).



**Figure 2:** P05101 Study Design Diagram

- **Arm 1 (placebo control arm):** PEG + RBV (WBD) for 4 weeks followed by boceprevir placebo + PEG + RBV (WBD) for 44 weeks with 24 weeks post-treatment follow-up.
- **Arm 2:** Subjects will be assigned either a 36-week or 48-week course of therapy based on their HCV-RNA status at TW 8.
  - **36-week regimen:** PEG+RBV (WBD) for 4 weeks followed by boceprevir + PEG+RBV (WBD) for 32 weeks
  - **48-week regimen:** PEG+RBV (WBD) for 4 weeks followed by boceprevir + PEG+RBV (WBD) for 32 weeks and followed by PEG+RBV (WBD) for 12 weeks
- **Arm 3:** PEG + RBV (WBD) for 4 weeks followed by boceprevir + PEG + RBV (WBD) for 44 weeks with 24 weeks post-treatment follow-up.

There is a **12-week futility rule for all arms**, ie, subjects who have detectable HCV-RNA at TW12 are considered treatment failures and are to discontinue treatment no later than TW16.

A total of 404 qualified subjects (375 was planned) will be randomized with 1:2:2 (Arm 1: Arm 2: Arm 3) ratio based on a computer-generated random code schedule provided by the sponsor's Biostatistics Department to the interactive voice response system (b) (4). The randomization was stratified by two factors:

- Previous SoC response ( $\geq 12$  weeks therapy): relapsers vs. non-responders (actually partial responders)
- HCV-1subtype: 1a vs. 1b (based on TRUGENE assay). Undermined will be randomly assigned to an arm within their HCV-RNA strata.

The duration of treatment for Arm 1 and 3 is 48 weeks of treatment with 24 weeks post-treatment follow-up. For Arm 2, the treatment duration is 48 weeks of treatment with 24 weeks

post-treatment follow-up or 36 weeks of treatment with 36 weeks post-treatment follow-up, **based on detectability of HCV-RNA at TW8**. The total duration for all subjects will be 72 weeks from Day 1 (Randomization date).

### **Virologic Failure Rules:**

- **Virologic breakthrough** defined as: Any subject who achieves undetectable HCV-RNA and subsequently has an HCV-RNA >1,000 IU/mL.
- **Incomplete Virologic Response and Rebound** defined as: Any subject who has a 1 log<sub>10</sub> increase in HCV-RNA from their nadir with an HCV-RNA >1,000 IU/mL; if both samples being compared were collected the same number of days after their last PEG injection. In cases where the time from PEG injection to HCV-RNA sample being collected are different for the 2 samples, a 2 log<sub>10</sub> increase is required to meet this criteria.

If a subject has virologic breakthrough or an incomplete virologic response and rebound while on therapy, the subject may be discontinued from boceprevir treatment and continued on PEG + RBV with appropriate clinical follow-up for up to 48 weeks total duration of PEG + RBV.

The primary objective of both studies is to demonstrate the superiority of two therapeutic regimens of boceprevir 800 mg three times a day (TID) plus PR over PR alone in failed prior treatment with PR HCV-1 infected adults.

**Primary Efficacy Endpoint:** The primary efficacy endpoint is the achievement of SVR, defined as undetectable plasma HCV-RNA at Follow-up Week (FW) 24 based on the FAS population. [If a subject is missing FW24 data and has undetectable HCV-RNA level at FW12, the subject would be considered as a responder.](#)

Subjects will be declared treatment failures in one of the following ways:

- Subjects in any treatment arm with detectable HCV-RNA at FW24.
- Subjects in any treatment arm with detectable HCV-RNA at TW12 (treatment failure and discontinued from the treatment).
- Subjects in any treatment arm who are missing their HCV-RNA at FW24 with detectable HCV-RNA at FW12.

**Key Secondary Endpoint:** The key secondary efficacy endpoint is the achievement of SVR defined as undetectable HCV-RNA FW 24 in randomized subjects who received at least one dose of experimental study drug (placebo for the control arm and boceprevir for the experimental arms), ie, based on the mITT population. [\(This was added in amended protocol on Dec. 02, 2009.\)](#)

**Secondary Endpoints:** The secondary efficacy endpoints in this study are:

- The proportion of subjects with an early virologic response (eg, undetectable HCV-RNA at Weeks 2, 4, 8, or 12) in subjects who achieve SVR.

- The proportion of subjects with undetectable HCV-RNA at FW 12.
- The proportion of subjects with undetectable HCV-RNA at 72 weeks after randomization.

Analysis Populations including FAS and mITT dataset and efficacy analyses are the same as study P05216. Please see study P05216 above for details.

### Sample size calculation:

This study is projected to enroll a total of 375 subjects (1:2:2) in Arms 1, 2, and 3, respectively. With 150 subjects in each treatment arm and 75 subjects in the control arm, the study will have 90% power to detect a 21.4% improvement in SVR rate over the control arm (assuming a control response rate of 22% and the treated response rate of 43.4%) using a two-sided chi-square test at  $\alpha = 0.05$ .

Since there are two experimental arms, and the primary hypothesis testing will comprise two statistical comparisons versus the control arm, a step-down approach will be applied to control the overall Type-I error rate at 0.05 level. First, Arm 3 will be compared against the control arm (Arm 1). If this test is statistically significant ( $p < 0.05$ ), then Arm 2 will be compared against the control arm at  $\alpha = 0.05$ . Please see description of controlling multiplicity in Study P05216 above for details.

## 2.2 Data Sources

The submission under NDA 202,258/S-0001 contains the efficacy, safety, and some genotyping results for subjects from 2 Phase III Studies P05216 and P05101, 2 Phase II Studies P03659 and P03523, and some phase I studies. This reviewer conducted efficacy analyses to verify sponsor's results, included the following two parts:

1. Reviewing protocols, statistical analysis plans, efficacy results and conclusions in the following submitted documents entitled "Statistics Section":
  - Module 1- labeling materials
  - Module 2- 2.5 Clinical Overview and 2.7.3 Summary of Clinical Efficacy
  - Module 5- Clinical Study Reports (CSRs) of 2 Phase III Studies P05216 and P05101.
2. Converting SAS transportable files '\*.xpt' in \analysis subfolder as analysis datasets, some of the raw datasets in \tabulations subfolder into SAS data files for verification based on the definitions in 'define.pdf', 'blankcrf.pdf', and Statistical Analysis Plan (SAP) in the CSR. In \analysis subfolder, there are two sets of datasets. One set of datasets directly under \analysis subfolder contains 4 SAS transportable files which are main efficacy analysis datasets. The second set of datasets under the \analysis\ (b) (4) support subfolder, there are approximately 9 SAS transportable files which are the input datasets for creating efficacy analysis datasets. These files are under CDER Electronic Document Room (EDR) directory of <\\Cdsesub1\evsprod\NDA202258\0001\m5\datasets\p05101> and <\\Cdsesub1\evsprod\NDA202258\0001\m5\datasets\p05216>.

### 3. STATISTICAL EVALUATION

Two phase 3 studies, P05216 and P05101, will be reviewed separately under each of following section. All tables and Figures are generated by the stat reviewer, otherwise the citation will be provided.

#### 3.1 Data and Analysis Quality

Overall, the reviewer can reproduce the primary analysis dataset, (b) (4), for both studies using the datasets in subfolder named, \analysis\ (b) (4) support. Those supporting datasets are not the raw datasets and contain many derived variables. The reviewer did check those derived variables used for (b) (4) dataset creation by tracing back to raw datasets when and where possible and this process is time-consuming.

The sponsor did provide two documents, one is “input-data-description.pdf” and another is “stat\_detailed\_comments.pdf”. The later one is very helpful. Still, there are a few variables where the reviewer has to talk to the sponsor for explanation in order to understand them during the review process.

#### 3.2 Evaluation of Efficacy

##### 3.2.1 Study Design and Endpoints

Both studies were randomized, multicenter, and double-blinded for boceprevir or placebo in combination with open-label PR, in adult subjects with HCV-1 infection. There are three arms:

- Arm 1: subjects received 48 weeks of PR, will be notated as **PR48** in this review.
- Arm 2: subjects received a 4-week PR lead-in followed by BOC/PR. The duration of boceprevir will depend on subject’s response. Early responders who had undetectable HCV RNA at TW8 will receive 24 weeks of BOC/PR for treatment-naïve subjects (total of 28 weeks of treatment) or 32 weeks of BOC/PR for treatment-failure subjects (total of 36 weeks of treatment). Late responders who had detectable HCV RNA at TW8 and undetectable at TW24 for treatment-naïve or undetectable at TW12 for treatment-failure subjects will receive 24 weeks of BOC/PR plus 20 weeks of PR for treatment-naïve subjects (total of 48 weeks of treatment) or 32 weeks of BOC/PR plus 12 weeks of PR for treatment-failure subjects (total of 48 weeks of treatment). This arm will be notated as response-guided therapy (**RGT**).
- Arm 3: subjects received a 4-week PR lead-in followed by 44 weeks of BOC/PR, and will be notated as **BOC48** in this review.

**A futility rule** was followed for all three arms, ie, the treatment was discontinued for subjects with detectable HCV RNA at TW24 for treatment-naïve and TW12 for treatment-failure subjects.

For treatment-naïve study P05216, the randomization was stratified by screening HCV viral load ( $\leq 400,000$  IU/mL vs.  $>400,000$  IU/mL) and HCV-1 subtype (1a vs. 1b). The ratio is 1:1:1 among three arms. Cohort 1 (Non-Black) and 2 (Black) were randomized independently.

The stratification factors used in previous treatment-failure study P05101 were previous SoC response (relapser vs. non-responder) and HCV-1 subtype (1a vs. 1b). The ratio is 1:2:2 among Arm1, Arm 2, and Arm 3.

The **primary objective** of both studies is to demonstrate the superiority of two therapeutic regimens of boceprevir 800 mg three times a day (TID) plus PR over PR alone in HCV-1 infected adults either untreated or failed prior treatment with PR.

The **primary efficacy endpoint** is the achievement of SVR<sub>24</sub>, defined as undetectable plasma HCV-RNA ( $<10$ ) at Follow-up Week (FW) 24 based on the Full Analysis Set (FAS). *If a subject is missing FW24 data and has undetectable HCV RNA level at FW12, the subject would be considered an SVR.*

*One note is that the cut-off value of HCV RNA used in the primary and secondary efficacy endpoints was changed from  $<10$  (undetectable) to  $<25$  (detectable, but not quantifiable) in order to be consistent with another NDA (Telaprevir) in terms of the label. This change will only affect the SVR<sub>24</sub> calculation, but not the management of subjects during the trials. In the result section, results using both  $<10$  and  $<25$  will be displayed together wherever possible.*

The **key secondary objective** of both studies is to compare the efficacy of two therapeutic regimens of boceprevir plus PR with PR alone in randomized subjects who received at least one dose of experimental study drug (placebo for the control arm and boceprevir for the experimental arms). I.e, the primary efficacy endpoint will be analyzed in mITT population instead of FAS population for the primary objective.

All primary and secondary efficacy analyses will be carried out using the two-sided Cochran-Mantel Haenszel (CMH) chi-square test (adjusted for the baseline stratification factors).

Analysis Populations are the following:

**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 (mITT) Data Set:** all randomized subjects who received at least one dose of boceprevir (for the experimental therapy arms) or placebo (for the control arm), passed 4 weeks lead-in period.

In order to control the type 1 error for the two comparisons (Arm 3 vs. Control, and Arm 2 vs. Control) for the primary analysis, step-down approach was used to control multiplicity. First, the Arm 3 will be compared against the control arm (Arm 1) using the 2-sided CMH chi-square test, adjusted for the baseline stratification factors. If this p-value is less than 0.05, efficacy of 48 weeks of treatment with boceprevir over the PegIntron/ribavirin control group will be established and the

next comparison will be carried out, ie, RGT arm (Arm 2) will be compared against the control arm using the same CMH test. If this p-value is less than 0.05, then the efficacy of the RGT arm will be established.

To account for multiplicity between the primary and key-secondary analyses, we will step down to the key-secondary analyses only if the significance of the primary comparisons has been established. The same logic also applied to the key-secondary efficacy analyses.

One of important additional Efficacy analyses is to assess the effect of the different boceprevir treatment regimens on the primary efficacy outcome by the following comparisons:

- Comparing boceprevir treatment strategies: Arm 2 vs. Arm 3
- Comparing the early responders in Arm 2 vs. in Arm 3.
  - For study P05216, the question to be answered for this comparison is that if 44 weeks of BOC+PR after 4-weeks lead-in PR is better than 24 weeks of BOC+PR after 4-weeks lead-in PR in early responders.
  - For study P05101, the question to be answered for this comparison is that if 44 weeks of BOC+PR after 4-weeks lead-in PR is better than 32 weeks of BOC+PR after 4-weeks lead-in PR in early responders.
- Comparing the late responders in Arm 2 vs. in Arm 3.
  - For study P05216, the question to be answered for this comparison is that if 20 weeks of PR after 4-weeks lead-in PR plus 24 weeks of BOC+PR is better than 20 weeks of BOC+PR after 4-weeks lead-in PR plus 24 weeks of BOC+PR in late responders.
  - For study P05101, the question to be answered for this comparison is that if 12 weeks of PR after 4-weeks lead-in PR plus 32 weeks of BOC+PR is better than 12 weeks of BOC+PR after 4-weeks lead-in PR plus 32 weeks of BOC+PR in late responders.

Two-sided 95% CI for the difference in SVR (obtained using normal approximation for binary data) will be calculated for the comparisons of Arm 2 vs. Arm 3. **In this analysis, there is no multiplicity adjustment and no stratification factor adjustment.**

### **Analysis Windows**

In order to assess the subject status at each scheduled visit (TW2, TW4, TW6, ..., TW48, EOT, ...), the pre-specified visit windows in terms of range of study days and days after end-of-treatment will be used to extract the HCV RNA viral load for each visit.

For study P05216, the **analysis windows** are listed in Table 7 below:

**Table 7:** The Analysis Windows Used in Study P05216

Period	Derived Visit	Range in Days	Range in Weeks	
Baseline Period	On or before treatment begin date ( <b>TxBegDt == Day 1</b> ) Study Day = Sampling Date - TxBegDt + 1			
Treatment Period (> TxBegDt, <=TxEndDt+7)	Week 2 (W2)	(7, 21]	(1, 3]	
	Week 4 (W4)	(21, BocBegDt]	(3, BocBegDt]	
	Week 6 (W6)	(BocBegDt, 49]	(BocBegDt, 7]	
	Week 8 (W8)	(49, 63]	(7, 9]	
	Week 10 (W10)	(63, 77]	(9, 11]	
	Week 12 (W12)	(77, 98]	(11, 14]	
	Week 16 (W16)	(98, 126]	(11, 14]	
	Week 20 (W20)	(126, 154]	(14, 22]	
	Week 24 (W24)	(154, 182]	(22, 26]	
	Week 28 (W28)	(182, 217]	(26, 31]	
	Week 34 (W34)	(217, 259]	(31, 37]	
	Week 40 (W40)	(259, 308]	(37, 44]	
Week 48 (W48)	(308, 364]	(44, 52]		
End of Treatment (EOT)	As treatment stop date ( <b>TxEndDt</b> ) ±14 days inclusive. The closest one either before <b>TxEndDt</b> or after will be selected. (This is an overlap.)			
Follow-up Period	# of days of Follow-up=sample date - treatment stop date ( <b>TxEndDt</b> )			
	FW4 (X4)	(17, 48]	(2.5, 7)	
	FW12 (X12)	(70, 140)	(10, 20)	
	FW24	X24 <sup>a</sup>	[140, using last available value	[20,
		X24N <sup>b</sup>	[140, 196]	[20, 28]
FW36 (X36)	(224, 280]	(32, 40]		
Last visit	(days from Day 1=visit date - randomization date ( <b>RandDt</b> ) + 1			
	Week 72 (W72)	[462, 546]	[66, 78]	

<sup>a</sup>: The primary efficacy endpoint **SVR<sub>24</sub>: PCREOF**=PCR<sup>X24</sup>. If PCR<sup>X24</sup> missing, then PCR<sup>X12</sup> will be used.

<sup>b</sup>: X24N: if there is no HCV-RNA within window, the closest (in time) value after this window if exist will be considered to be the X24N value.

- **Time Periods**

**Baseline Period:** Period on or before treatment begin date.

**Treatment Begin Date:** Earliest of any study drug begin date (PEG/RBV/Blinded drug)

**Treatment Period:** Period after treatment begin date to treatment stop date+7 days inclusive.

**Follow-up Period:** Period beginning after treatment stop date + 7 days.

Convention of HCV RNA VL calculation:

Baseline (**BS**): **IUBS** is the geometric mean of all available virology values (IU) on or before the treatment begin date.

If there is a '<25' value before the treatment start date and there are other repeat labs within the baseline period, please exclude the '<25' value from the geometric mean calculation as this is likely a sample error.

Treatment and Follow-up periods: The worst virology value (highest HCV-RNA count) found in a window is assigned to that window's time point (Week). If there are 2 values, one of which is '<25 Signal Detected' and '<25 signal not Detected', use '<25 signal detected' as the value.

EOT: the closest value to the TxEndDt will be used. If no value within window, the closest value after the window will be used. If two samples were available within a window, the worst value will be used.

W72: The window is 72 weeks ± 6 weeks, ie [462, 546] in days from first dosing date. If there is no HCV-RNA result and/or no sample collected within the W72 window, the closest (in time) value after this window, if one exists in the database, will be considered to be the W72 value.

For study P05101, the **analysis windows** are listed in Table 8 below:

**Table 8:** The Analysis Windows Used in Study P05101

Period	Derived Visit	Range in Days	Range in Weeks	
<b>Baseline Period</b>	On or before treatment begin date ( <b>TxBegDt == Day 1</b> ) Study Day = Sampling Date - TxBegDt + 1			
<b>Treatment Period</b> (> <b>TxBegDt</b> , <= <b>TxEndDt</b> +7)	Week 2 (W2)	(7, 21]	(1, 3]	
	Week 4 (W4)	(21, <b>BocBegDt</b> ]	(3, <b>BocBegDt</b> ]	
	Week 6 (W6)	( <b>BocBegDt</b> , 49]	( <b>BocBegDt</b> , 7]	
	Week 8 (W8)	(49, 63]	(7, 9]	
	Week 10 (W10)	(63, 77]	(9, 11]	
	Week 12 (W12)	(77, 98]	(11, 14]	
	Week 16 (W16)	(98, 126]	(11, 14]	
	Week 20 (W20)	(126, 154]	(14, 18]	
	Week 24 (W24)	(154, 189]	(18, 22]	
	Week 30 (W30)	(189, 231]	(22, 27]	
	Week 36 (W36)	(231, 273]	(27, 39]	
	Week 42 (W42)	(273, 315]	(39, 45]	
Week 48 (W48)	(315, 357]	(45, 51]		
<b>End of Treatment (EOT)</b>	As treatment stop date ( <b>TxEndDt</b> ) ±14 days inclusive. The closest one either before <b>TxEndDt</b> or after will be selected. (This is an overlap.)			
<b>Follow-up Period</b>	# of days of Follow-up=sample date - treatment stop date ( <b>TxEndDt</b> )			
	FW4 (X4)	(17, 48]	(2.5, 7)	
	FW12 (X12)	(70, 140)	(10, 20)	
	FW24	X24 <sup>a</sup>	[140, using last available value	[20,
		X24N <sup>b</sup>	[140, 196]	[20, 28]
FW36 (X36)	(224, 280]	(32, 40]		
<b>Last visit</b>	(days from Day 1=visit date - randomization date ( <b>RandDt</b> ) +1			
	Week 72 (W72)	[462, 546]	[66, 78]	

<sup>a</sup>: The primary efficacy endpoint **SVR<sub>24</sub>**: **PCREOF**=PCR**X24**. If PCR**X24** missing, then PCR**X12** will be used.

<sup>b</sup>: X24N: if there is no HCV-RNA within window, the closest (in time) value after this window if exist will be considered to be the X24N value.

The only difference is the visit ranges. Others, like time periods and HCV RNA viral load calculation conventions, are the same as study P05216.

Some parameters regarding the virologic failure were also accessed in this review:

**Relapse** is defined as the proportion of subjects who had undetectable HCV RNA at EOT (end of treatment) but detectable at EOF (end of treatment, ie, 24 weeks of follow-up) in subjects who had undetectable HCV RNA at EOT and have HCV RNA observation at EOF.

Because the primary efficacy endpoint was changed from  $<10$  (undetectable) to  $<25$  (detectable but not quantifiable), the relapse rate definition was updated to undetectable at EOT, and  $\geq 25$  at EOF instead of  $\geq 10$  at EOF. Both results will be displayed in the corresponding sections.

**Breakthrough (BT)** is undetectable HCV RNA ( $<10$ ) on treatment and a subsequent on treatment HCV RNA value  $>1,000$  IU/mL, which was used by the sponsor.

**Breakthrough-FDA (BT\_FDA)** is undetectable HCV RNA ( $<10$ ) on-treatment and a subsequent on-treatment HCV RNA value  $\geq 25$  IU/mL, which was preferred by FDA.

**Incomplete Virologic Response (IVR)** is defined as on-treatment increase greater than or equal to  $1\text{-log}_{10}$  IU/mL from on-treatment nadir. Ie, if a subject reached NEG on-treatment, its HCV RNA viral load have to  $\geq 100$  IU/mL after NEG on-treatment in order to meet the IVR definition.

## 3.2.2 Patient Disposition, Demographic and Baseline Characteristics

### 3.2.2.1 Randomization

There were some minor mis-classification occurred during the process of randomization for both studies. Overall, the randomization was OK. The randomizations in two studies are examined separately in the following section.

#### ❖ Study P05216 (treatment-naïve)

In study P05216, Cohort 1 (non-black) and 2 (black) were randomized separately. There are two sets of information for subject's race in the submitted datasets.

- **(b) (4) Coho**: contains the information for race used in the randomization (b) (4) to determine the cohort.
- **RaceCoho**: contains the information collected from case report form (CRF).

There are three subjects whom (b) (4) Coho and RaceCoho were not consistent (See Table below for details.) The final subgroup analysis will be based on the RaceCoho from CRF.

**Table 9:** The Relationship Between two Cohort Variables in Study P05216

(b) (4) Coho	RaceCoho		Total
	1	2	
<b>1 (Non-Black)</b>	939	<b>2</b>	<b>941</b>
<b>2 (Black)</b>	<b>1</b>	157	<b>158</b>
	<b>940</b>	<b>159</b>	<b>1099</b>
Three subjects (ID=002054, 007755, and 001870) are all in Arm 3.			

Within each cohort, the randomization was stratified by two factors:

- Viral load at screening visit:  $\leq 400,000$  IU/mL vs.  $> 400,000$  IU/mL at screening visit
- HCV-1 virus subtype from (b) (4) 1a vs. 1b.

Subjects with undetermined subtype, ie, HCV-1, will be randomly assigned to an arm within their HCV RNA viral load strata.

In the submitted datasets, there were three variables for HCV-1 subtype:

- **GENO** (b) (4): Genotype used in (b) (4), but actually from (b) (4)
- **GENO** (b) (4): Genotype assigned by (b) (4)
- **GENO** (b) (4): Genotype assigned by (b) (4)

Between Genc (b) (4) and Genc (b) (4) there were 31 subjects with different subtype even though they are from the same test. According the sponsor's explanation, these 31 subjects got incorrect subtype value during the (b) (4) process, ie, at least 15 (who switched between 1a and 1b) out of 31 were randomized to wrong strata during the randomization process (Table 10).

**Table 10:** The Relationship among Three Subtype Variables in Study P05216

Geno (b) (4)	Geno (b) (4)			total	(b) (4) (b) (4) lab)					total
	1	1a	1b		1a	1b	6e	6h	6n	
1	151	6	0		108	45	1	1	0	
1a	5	534	10		515	7	0	0	0	
1b	5	5	383		76	310	0	0	2	
Total				1099						1065

The subtype information from (b) (4) lab is more accurate according to the Microbiological reviewer comparing to (b) (4) results. As you can see, there were 34 subjects who missed subtype results from (b) (4) lab. Four subjects had subtype 6 which were not HCV-1 and should not be included in this study.

In the primary efficacy endpoint analysis, STRATA which were based on Geno (b) (4) and (b) (4) Coho will still be used for the CMH stratification analysis.

The numbers of subjects by arm in each Stratum was listed in Table 11 and 12 for Cohort 1 and 2 respectively. As you can see, the maximum difference among arms in terms of number of subject in each stratum is 2, which is OK for this 1:1:1 randomization ratio with block size of 6. Out of all 1099 subjects, there were 8 subjects in total who were randomized into wrong stratum. Overall, the randomization seems OK even through there were some mis-assignment.

**Table 11:** Number of Subjects by Arm in each Stratum for Cohort 1 in Study P05216

Strata	VL at BSL	Geno (b) (4)	Subtotal	PR48	RGT	BOC48	Max-diff [Range]
1	>400,000	1	63	23	24	16	2 [156, 158]
		1a	407	133	133	141	
		1a/≤400,000*	1		1		
3	>400,000	1	66	23	23	20	0 [128,,128]
		1b	316	104	104	108	
		1b/≤400,000*	2	1	1		
2	≤400,000	1	6	1	4	1	1 [15, 16]
		1a	39	13	12	14	
		1/>400,000*	1	1			
4	≤400,000	1	6	4	1	1	1 [13, 14]
		1b	31	9	12	10	
		1b/>400,000*	3		1	2	
<b>Subtotal</b>			<b>941</b>				

\*: Subjects got wrong stratum assignment.

**Table 12:** Number of Subjects by Arm in each Stratum for Cohort 2 in Study P05216

Strata	VL at BSL	Geno (b) (4)	Subtotal	PR48	RGT	BOC48	Max-diff [Range]
<b>1</b>	>400,000	<b>1</b>	9	4	2	3	<b>0</b>
		<b>1a</b>	99	32	34	33	[36, 36]
<b>1</b>		6	4	1	1	<b>2</b>	
<b>1b</b>		40	12	13	15	[14, 16]	
<b>2</b>	≤400,000	<b>1</b>					<b>2</b>
		<b>1a</b>	2		2		[0, 2]
<b>1a/&gt;400,000*</b>		1				1	
<b>1</b>							<b>1</b>
<b>4</b>		<b>1b</b>	1			1	[0, 1]
		<b>1</b>					
<b>Subtotal</b>			<b>158</b>				

\*: Subjects got wrong stratum assignment.

❖ **Study P05101 (previous treatment-failure)**

In study P05101, the randomization was stratified by two factors:

- HCV-1 virus subtype from (b) (4): 1a vs. 1b.
- Previous SoC response (≥12 weeks therapy): relapsers vs. non-responders (actually partial responders)

Subjects with undetermined subtype, ie, HCV-1, will be randomly assigned to an arm within their HCV RNA viral load strata.

Like the study P05216, there were three variables (**GENO (b) (4)**, **GENO (b) (4)**, and **GENO (b) (4)**) for HCV-1 subtype in the submitted datasets. The relationship among them is listed in Table 13.

Between Geno (b) (4) and Geno (b) (4), there were 10 subjects with different subtype even though they are from the same test. According the sponsor’s explanation, these 10 subjects got incorrect subtype value during the (b) (4) process, ie, at least 5 (who switched between 1a and 1b) out of 10 were randomized to wrong strata during the randomization process. As you can see, there were 3 subjects who missed subtype results from (b) (4) lab (Table 13). One subject had subtype 6 which were not HCV-1 and should not be included in this study.

**Table 13:** The Relationship among Three Subtype Variables in Study P05101

Geno (b) (4)	Geno (b) (4)			total	Geno (b) (4) ( (b) (4) lab)			total
	1	1a	1b		1a	1b	61	
1	32	0	<b>1</b>		<b>24</b>	<b>9</b>		
1a	<b>3</b>	186	<b>1</b>		185	<b>3</b>		
1b	<b>1</b>	<b>4</b>	176		<b>30</b>	149	<b>1</b>	
Subtotal				404				401

In the primary efficacy endpoint analysis, STRATA which were based on Geno (b) (4) will still be used for the CMH stratification analysis.

There are three variables in the submitted datasets for previous SoC response:

- **PREVRESP:** Previous Virologic Response used in (b) (4)
- **PREVSVR:** Previous Virologic Response collected from CRF in inform
- **PrevCor:** Adjusted Previous Virologic Response, which is created from **PrevResp** and **PrevSVR** during the dataset creation process.

The relationship between **PrevResp** and **PrevSVR** is listed in Table 14 below. As you can see, there were total of 48 subjects who seems had inconsistent information. Those 4 subjects who had **PrevSVR**=Relapser and **PrevResp**=Never Negative were mis-stratified and should be relapser according to the sponsor's response to our query. Other 44 subjects could be explained by the difference in terms of definitions used.

**Table 14:** The Relationship between PrevResp and PrevSVR in Study P05101

PrevResp (b) (4)	PrevSVR		Subtotal
	Non-Responder	Relapser	
Never Negative	144	4	148
Some Negative	44	211	255
			403 <sup>1</sup>

<sup>1</sup>: One subject (010075 in arm 2) missed PrevSVR value but, PrevResp=Some Negative.

For **PrevResp** collected in (b) (4) process, the definition used is the following:

- **Never Negative:** a subject who never achieved negative PCR throughout the previous study.
- **Some Negative:** a subject who had at least one negative PCR value in the previous study

While **PrevSVR** collected on the CRF, the definition used is:

- **Relapser:** a subject was negative at EOT but became positive in follow-up
- **Non-responder:** any previously failed subject who was not a previous relapser.

As a result, a subject can be classified as **PrevResp**=Some Negative since he/she was suppressed at the some point during the previous HCV treatment. However, if the suppression occurred at EOT, the subject will have **PrevSVR**=Relapser, and if the suppression did not occur at EOT, the subject will have **PrevSVR**=Non-Responder.

In order to solve this, the sponsor created another variable named **PrevCor** during the process of dataset creation. **PrevCor**=Never Negative occurred only if **PrevResp**=Never Negative and **PrevSVR**=Non-Responder, and **PrevCor**=Some Negative when **PrevResp** was not missing. By doing this, all 48 subjects were classified as relapsers in the new variable **PrevCor**.

In the primary efficacy endpoint analysis, STRATA which were based on **PrevResp** will still be used for the CMH stratification analysis.

The numbers of subjects by arm in each stratum was listed in Table 15. As you can see, the maximum difference among arms in terms of number of subject in each stratum is 3, which is OK for this 1:2:2 randomization ratio with block size of 10. Overall, the randomization is OK.

**Table 15:** Number of Subjects by Arm in each Stratum in Study P05101

Strata	PrevRESP	<sup>(b) (4)</sup>	Subtotal	PR48	RGT	BOC48	Max-diff
<b>1</b>	<b>Some Negative</b>	<b>1</b>	13	2	6	5	2
		<b>1a</b>	113	22	45	46	2
<b>2</b>		<b>1</b>	12	2	5	5	1
		<b>1b</b>	118	24	47	47	1
<b>3</b>	<b>Never Negative</b>	<b>1</b>	4		3	1	3
		<b>1a</b>	77	16	29	32	3
<b>4</b>		<b>1</b>	4	1	0	3	3
		<b>1b</b>	63	13	27	23	3
	<b>Subtotal</b>		<b>404</b>	<b>80</b>	<b>162</b>	<b>162</b>	<b>2</b>

### 3.2.2.2 Disposition

For both studies, there are four variables (**TxStat**, **FuStat24**, **FuStat72**, and **FuStat**) for subject's disposition in the disposition dataset named **DisPos**. These represented the subject's status at different time points during the trial.

Two of them were collected from CRF:

- **TxStat** is the subject's status at the end of the treatment phase.
- **FuStat** is the subject's status at the end of the follow-up phase.

Two of them were derived during the dataset creation from **FuStat**:

- **FuStat24** is the subject's status at the follow-up week 24 (SVR<sub>24</sub> time point)
- **FuStat72** is the subject's status at the study week 72

The algorithm used was the following:

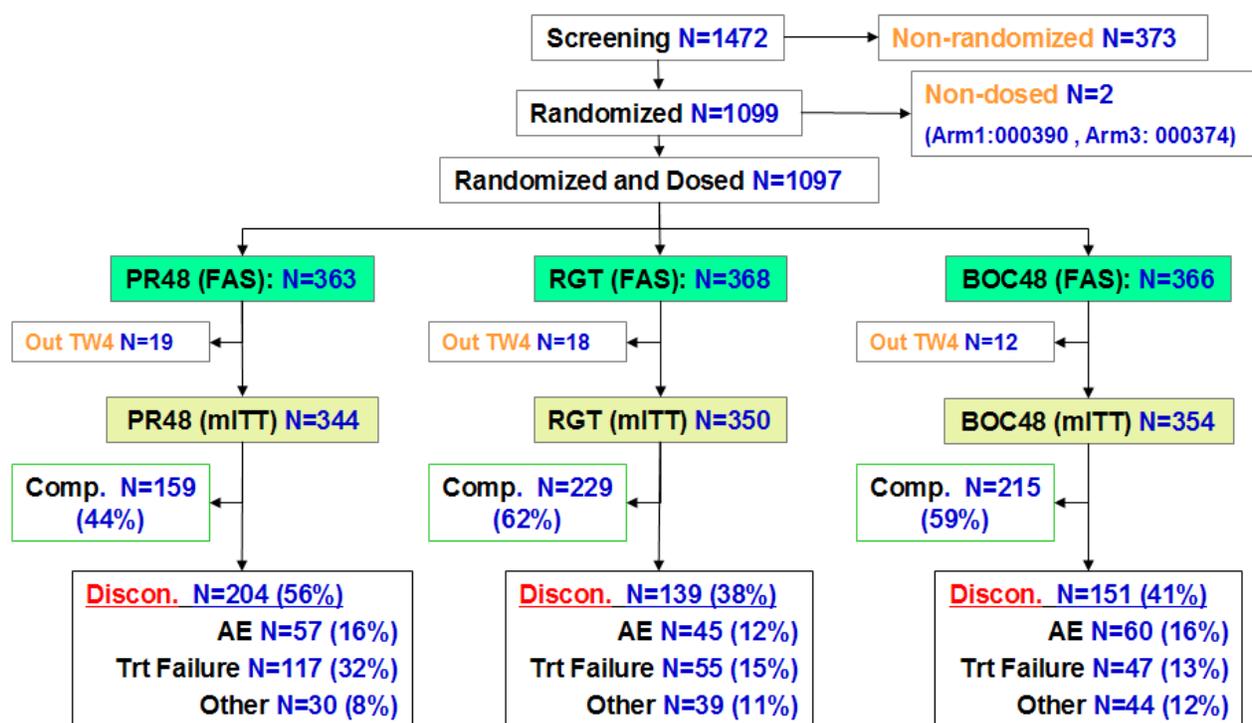
- If the subject duration of follow-up was > 18 weeks (126 days),
  - **FuStat24** was assigned the value 'COMPLETED', and
  - **FuStat72** was assigned the value of **FuStat** (AE, Treatment failure, etc).
- If the subject duration of follow-up was ≤ 18 weeks (126 days), then
  - **FuStat24** was assigned the value of **FuStat**, and
  - **FuStat72** was assigned missing since subject did not participate beyond follow-up week 24.

In this review, only **TxStat** and **FuStat** (collected from CRF) will be summarized by study below.

### ❖ Study P05216 (treatment-naïve)

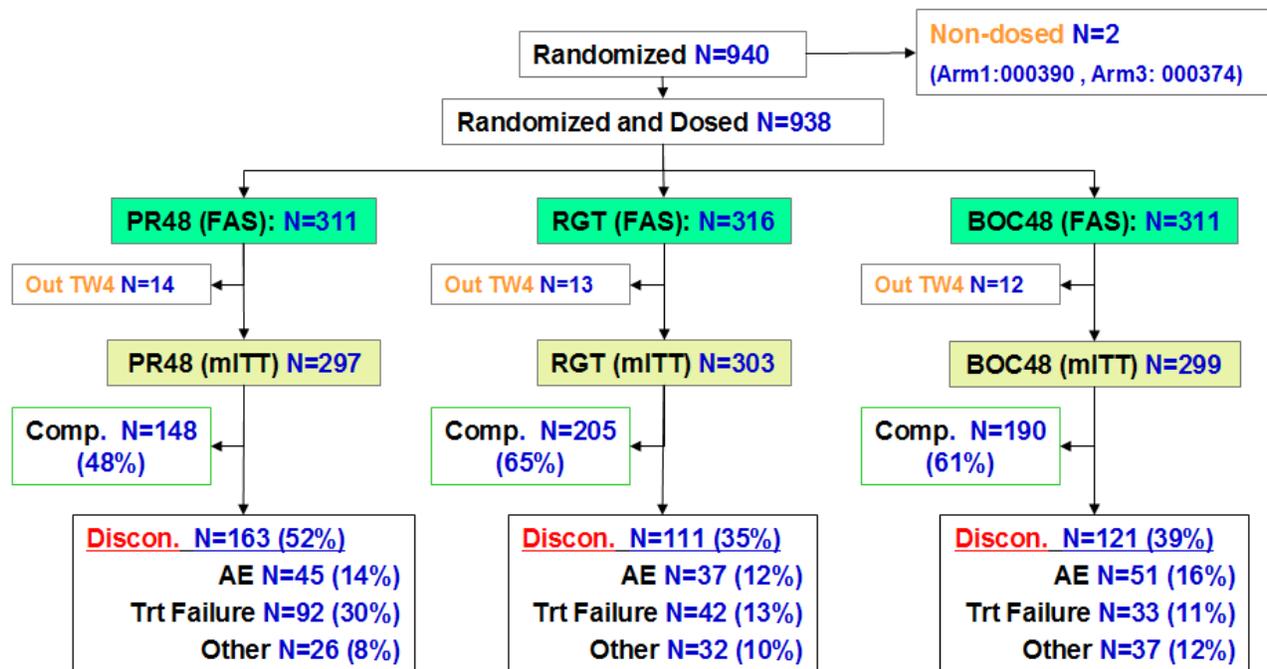
Out of 1472 screened subjects, a total of 1099 subjects were randomized, 1097 subjects received at least one dose of PR, and 1048 subjects received at least one dose of boceprevir or placebo (Figure 3). Forty-nine (4%) subjects discontinued treatment during the PR lead-in and never received boceprevir/placebo and will be excluded from the mITT analysis. A total of 603 (55%) subjects completed planned treatment. The treatment completion rates (59-62%) in two boceprevir arms are higher than that in control arm (44%). The main reasons for treatment discontinuation after the lead-in were treatment failure and discontinuation due to Adverse Events (AEs). More subjects in control arm (32%) were discontinued due to treatment failure than that in two boceprevir arms (13-15%).

Other category includes Lost to Follow-up, Subject withdrew consent, not wish continue unrelated to treatment assignment, not wish continue related to treatment assignment, non-compliant with protocol.

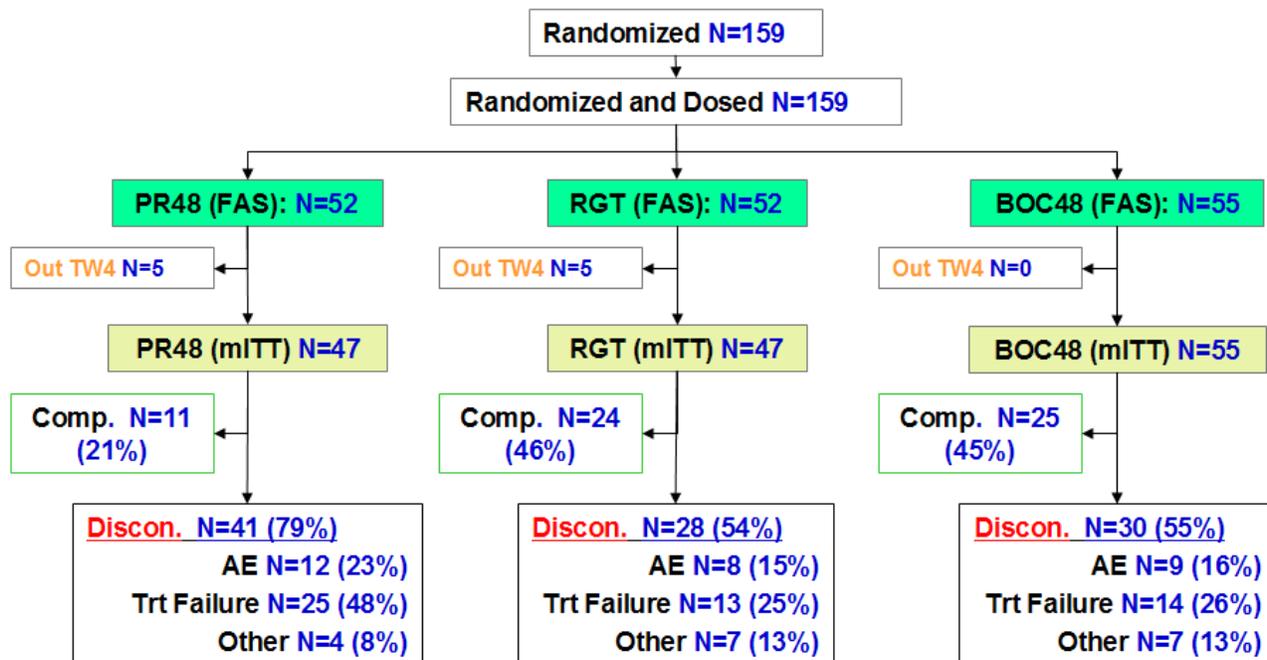


**Figure 3:** Patient Disposition at the End of Treatment for Study P05216

The disposition at the end of treatment phase for cohort 1 and 2 were listed in Figure 4 and 5 respectively. The completion rates and discontinuation due to AE and Treatment failure are slightly lower than overall across three arms in cohort 1 (Non-Black), while it is higher than overall across three arms in cohort 2 (Black).



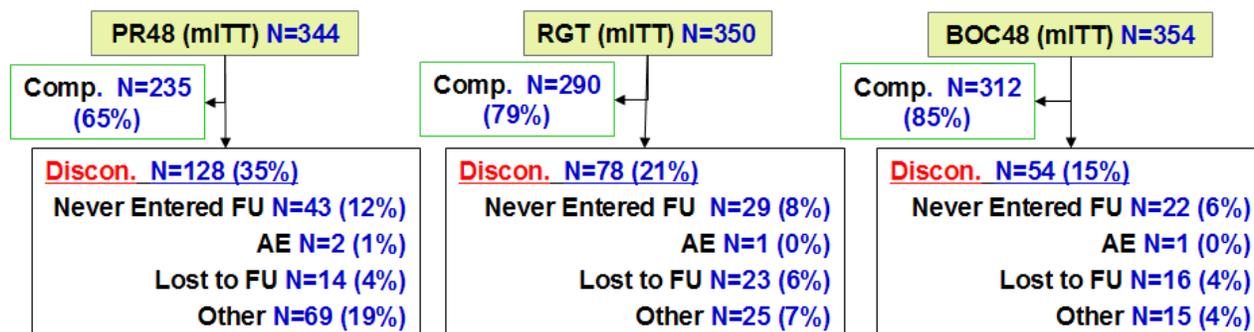
**Figure 4:** Patient Disposition at the End of Treatment for Cohort 1 (Non-Black) Study P05216



**Figure 5:** Patient Disposition at the End of Treatment for Cohort 2 (Black) Study P05216

For the disposition of subjects at the end of study in study P05216, the rates of study completion (79-85% in two boceprevir arms and 65% in control arm) are higher than that at the end of treatment for all three arms due to the fact that a subject could complete the study even though he/she did not complete the planned treatment (Figure 6). The category of Never Entered Follow-

Up became a majority part of reason of discontinuation at the end of study. The rates of discontinuation due to AE are very low and this may mis-lead.



**Figure 6:** Patient Disposition at the End of Follow-up for Study P05216

The numbers of subjects in FAS, mITT, and PP are listed in Table 16 below. Two subjects who did not receive any drug are excluded from FAS which is used for the primary efficacy analyses. Additional 49 subjects who did not receive study drug (either boceprevir or its placebo) are excluded from the mITT population which is used for the key secondary efficacy analysis.

**Table 16:** Number of Subjects in FAS, mITT, and PP (Per Protocol) Populations in study P05216

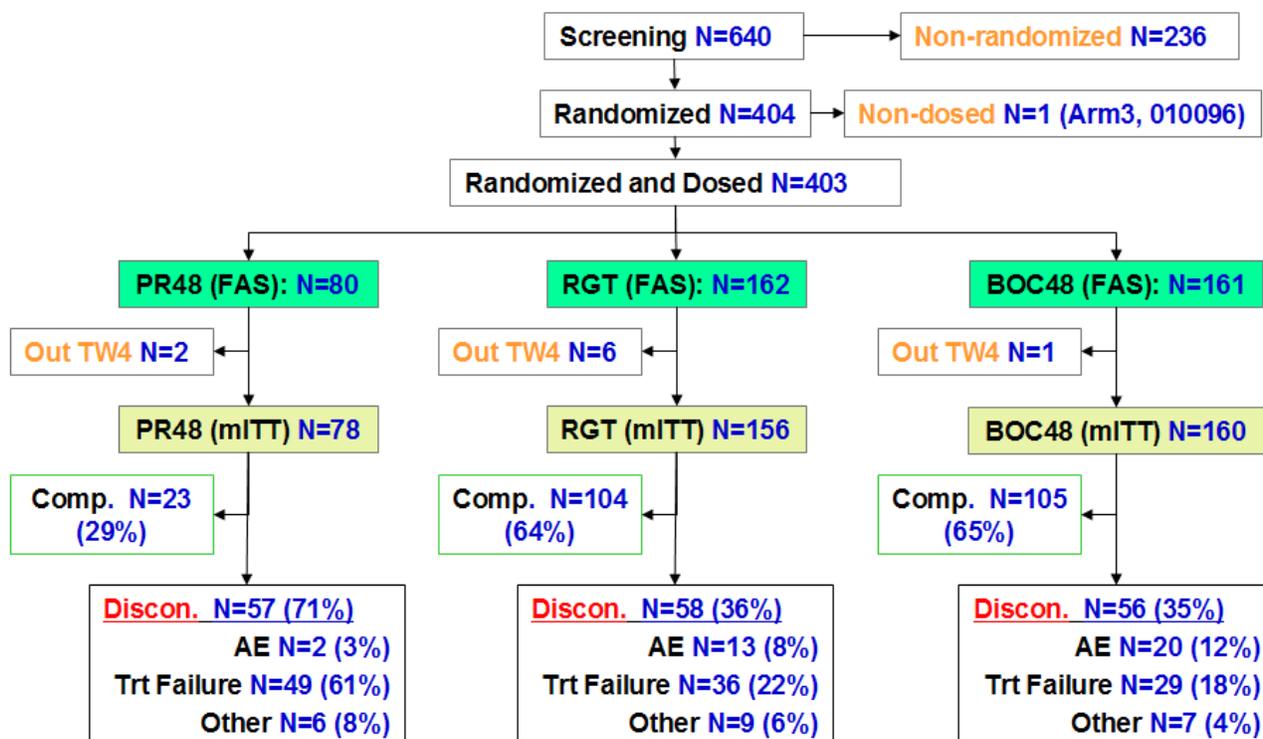
FAS	mITT	PP	Reason	PR48	RGT	BOC48	total
		N	Unacceptable CM	1	1		2
		N	Insufficient Washout Ribavirin	1			1
	N	N	Never Received Study Treatment	19	18	12	49
N <sup>1</sup>	N	N	Never dosed	1		1	2
1097	1048	1045		22	19	13	54

<sup>1</sup>: N means excluded from the analysis population.

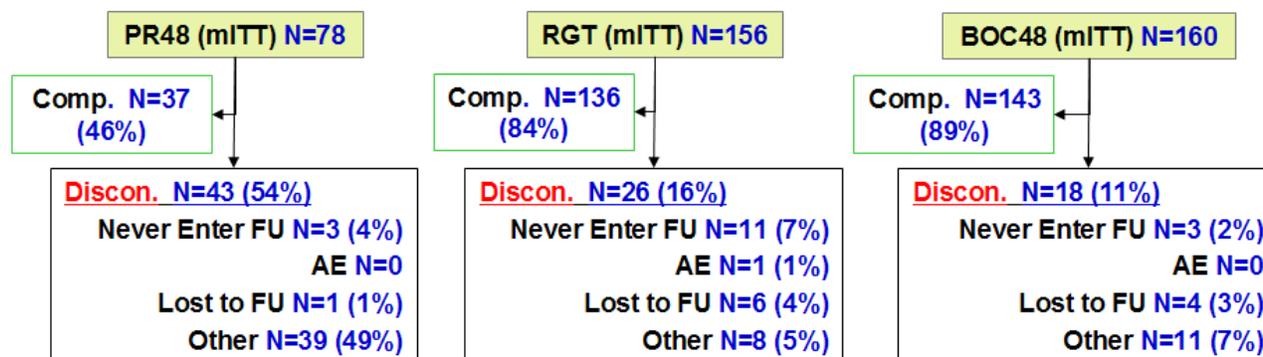
#### ❖ Study P05101 (previous treatment-failure)

Out of 640 screened subjects, a total of 404 subjects were randomized, 403 subjects received at least one dose of PR or BOC, and 394 subjects received at least one dose of boceprevir or placebo (Figure 7). Nine (2%) subjects discontinued treatment during the PR lead-in and never received boceprevir/placebo and will be excluded from the mITT analysis. A total of 232 (57%) subjects completed planned treatment. The treatment completion rates (64-65%) in two boceprevir arms are higher than that in control arm (29%). The main reasons for treatment discontinuation after the lead-in were treatment failure and discontinuation due to AEs. More subjects in control arm (61%) were discontinued due to treatment failure than that in two boceprevir arms (18-22%).

Other category includes Lost to Follow-up, Subject withdrew consent, not wish continue unrelated to treatment assignment, not wish continue related to treatment assignment, non-compliant with protocol.



**Figure 7:** Patient Disposition at the End of Treatment for Study P05101



**Figure 8:** Patient Disposition at the End of Follow-up for Study P05101

For the disposition of subjects at the end of study in study P05101, the rates of study completion (84-89% in two boceprevir arms and 46% in control arm) are higher than at the end of treatment for all three arms (Figure 8). The category of Never Entered Follow-Up became a majority part of reason of discontinuation at the end of study. The rate of discontinuation due to other in the control arm is about 49%, thirty-one subjects (39%) were due to withdrew consent (Table 17).

**Table 17:** Subject Disposition at the End of Follow-Up for Study P05101 (FAS)

Category	PR48	RGT	BOC48	Total
n	80	162	161	403
COMPLETED	37 ( 46.3%)	136 ( 84.0%)	143 ( 88.8%)	316 ( 78.4%)
Not Complete	43 ( 53.8%)	26 ( 16.0%)	18 ( 11.2%)	87 ( 21.6%)
NEVER ENTERED FOLLOW UP	3 ( 3.8%)	11 ( 6.8%)	3 ( 1.9%)	17 ( 4.2%)
ADVERSE EVENT	. ( . %)	1 ( 0.6%)	. ( . %)	1 ( 0.2%)
LOST TO FOLLOW-UP	1 ( 1.3%)	6 ( 3.7%)	4 ( 2.5%)	11 ( 2.7%)
SUBJECT WITHDREW CONSENT	31 ( 38.8%)	4 ( 2.5%)	5 ( 3.1%)	40 ( 9.9%)
NOT WISH CON. UNRELATED	3 ( 3.8%)	4 ( 2.5%)	5 ( 3.1%)	12 ( 3.0%)
NON-COMPLIANCE WITH PROTOCOL	5 ( 6.3%)	. ( . %)	1 ( 0.6%)	6 ( 1.5%)

The numbers of subjects in FAS, mITT, and PP are listed in Table 18 below. One subject who did not receive any drug is excluded from FAS which is used for the primary efficacy analyses. Additional 9 subjects who did not receive study drug (either boceprevir or its placebo) are excluded from the mITT population which is used for the key secondary efficacy analysis.

**Table 18:** Number of Subjects in FAS, mITT, and PP (Per Protocol) Populations in study P05101

FAS	mITT	PP	Reason	PR48	RGT	BOC48	total
		N	Unacceptable CM	1			1
		N	Insufficient Washout Ribavirin		1	1	2
	N	N	Never Received Study Treatment	2	6	1	9
N	N	N	Never dosed			1	1
403	394	391		3	7	3	13

### 3.2.2.3 Demographic and Baseline Characteristics

Overall, the demographic and baseline characteristics are balanced among three arms within both studies.

#### ❖ Study P05216 (treatment-naïve)

There are 15% Black and 85% non-Black enrolled (Table 19). Over 70% of subjects were from North America, and 65% were from US. There is a higher proportion of male than female and a higher proportion of 1a subtype than 1b subtype. Over 90% of subjects had  $\geq 150,000$  for baseline platelets count, over 75% of subjects had ALT elevation at baseline, majority of subjects ( $>80\%$ ) had baseline viral load  $>800,000$  IU/mL, and about 5% of subjects had cirrhosis at baseline. Only 19 of the 1097 treated subjects were on Statin therapy at baseline.

The demographic and baseline disease characteristics of the FAS were similar for both cohorts (Table 20 and 21). In terms of median weight and BMI, cohort 2 is higher than that in cohort 1. The proportion of subjects with 1a subtype is higher in cohort 2 than that in cohort 1. Only 7/159 subject in cohort 2 were not from US.

**Table 19: Demographic and Baseline Characteristics for Study P05216 (FAS)**

Subgroup	PR48	RGT	BOC48
As Randomized and Dosed (FAS)			
N	363	368	366
Race Group			
BLACK	52 ( 14.3%)	52 ( 14.1%)	55 ( 15.0%)
NON-BLACK	311 ( 85.7%)	316 ( 85.9%)	311 ( 85.0%)
WHITE	296 ( 81.5%)	304 ( 82.6%)	295 ( 80.6%)
AMERICAN INDIAN Or ALASKAN NATIVE	1 ( 0.3%)	1 ( 0.3%)	4 ( 1.1%)
ASIAN	9 ( 2.5%)	4 ( 1.1%)	8 ( 2.2%)
MULTIRACIAL	5 ( 1.4%)	5 ( 1.4%)	4 ( 1.1%)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	.( . %)	2 ( 0.5%)	.( . %)
Gender			
F	157 ( 43.3%)	139 ( 37.8%)	145 ( 39.6%)
M	206 ( 56.7%)	229 ( 62.2%)	221 ( 60.4%)
Age (Year)			
Mean (SE)	48.58 ( 0.529)	49.80 ( 0.484)	48.85 ( 0.460)
median	50	51	50
range	( 18.0, 75.0)	( 21.0, 76.0)	( 21.0, 67.0)
std <sup>a</sup>	10.0	9.2	8.7
Age Group			
<40 yr	57 ( 15.7%)	48 ( 13.0%)	53 ( 14.5%)
>=45-<65	291 ( 80.2%)	308 ( 83.7%)	306 ( 83.6%)
>=65 yr	15 ( 4.1%)	12 ( 3.3%)	7 ( 1.9%)
Weight (Kg)			
MEAN (SE)	79.75 ( 0.836)	82.10 ( 0.886)	81.79 ( 0.902)
median	80	81	81
range	( 46.0, 124.3)	( 44.0, 124.6)	( 45.4, 124.9)
std	15.9	17.0	17.2
Weight Group			
<75 Kg	146 ( 40.2%)	131 ( 35.6%)	131 ( 35.8%)
>=75 Kg	217 ( 59.8%)	237 ( 64.4%)	235 ( 64.2%)
Height (CM)			
MEAN (SE)	171.00 ( 0.526)	171.50 ( 0.559)	171.26 ( 0.501)
median	172	171	171
range	(144.8, 195.6)	(144.8, 198.1)	(144.8, 199.6)
std	10.0	10.7	9.5
BMI			
MEAN (SE)	27.19 ( 0.241)	27.84 ( 0.257)	27.85 ( 0.288)
median	26	27	27
range	( 18.8, 44.3)	( 17.2, 50.4)	( 17.7, 51.7)
std	4.5	4.9	5.5

Baseline Platelets Count			
<150,000/ul	27 ( 7.4%)	33 ( 9.0%)	38 ( 10.4%)
>=150,000/ul	336 ( 92.6%)	335 ( 91.0%)	328 ( 89.6%)
Baseline ALT Status			
Elevated at BSL	269 ( 74.1%)	293 ( 79.6%)	281 ( 76.8%)
Normal at BSL	94 ( 25.9%)	75 ( 20.4%)	85 ( 23.2%)
Baseline Hemoglobin Level			
Mean (SE)	14.74 ( 0.070)	14.84 ( 0.068)	14.77 ( 0.067)
median	14	14	14
range	( 9.7, 18.9)	( 10.4, 18.7)	( 11.4, 19.2)
std	1.3	1.3	1.2
Baseline Log10 of HCV Viral Geometric Mean (IU/mL)			
Mean (SE)	6.54 ( 0.032)	6.52 ( 0.032)	6.53 ( 0.033)
median	6	6	6
range	( 3.6, 7.7)	( 3.1, 7.5)	( 3.5, 7.5)
std	0.6	0.6	0.6
Baseline HCV Viral Category (IU/mL)			
<=200,000	13 ( 3.6%)	18 ( 4.9%)	14 ( 3.8%)
>200,000-400,000	13 ( 3.6%)	14 ( 3.8%)	11 ( 3.0%)
>400,000-800,000	29 ( 8.0%)	22 ( 6.0%)	28 ( 7.7%)
>800,000	308 ( 84.8%)	314 ( 85.3%)	313 ( 85.5%)
Baseline Statin Use			
N	360 ( 99.2%)	359 ( 97.6%)	359 ( 98.1%)
Y	3 ( 0.8%)	9 ( 2.4%)	7 ( 1.9%)
Baseline Steatosis Score			
0	128 ( 35.3%)	107 ( 29.1%)	108 ( 29.5%)
1	170 ( 46.8%)	187 ( 50.8%)	190 ( 51.9%)
2	50 ( 13.8%)	53 ( 14.4%)	54 ( 14.8%)
3	4 ( 1.1%)	6 ( 1.6%)	3 ( 0.8%)
Missing	11 ( 3.0%)	15 ( 4.1%)	11 ( 3.0%)
Metavir Fibrosis Score			
0	17 ( 4.7%)	20 ( 5.4%)	10 ( 2.7%)
1	246 ( 67.8%)	238 ( 64.7%)	246 ( 67.2%)
2	65 ( 17.9%)	61 ( 16.6%)	57 ( 15.6%)
3	11 ( 3.0%)	18 ( 4.9%)	18 ( 4.9%)
4	13 ( 3.6%)	16 ( 4.3%)	24 ( 6.6%)
Missing	11 ( 3.0%)	15 ( 4.1%)	11 ( 3.0%)
Liver Cirrhosis at Baseline			
N	339 ( 96.3%)	337 ( 95.5%)	331 ( 93.2%)
Y	13 ( 3.7%)	16 ( 4.5%)	24 ( 6.8%)
Opioid Replacement Therapy			
N	362 ( 99.7%)	365 ( 99.2%)	358 ( 97.8%)
Y	1 ( 0.3%)	3 ( 0.8%)	8 ( 2.2%)
HCV-1 Subtype (b) (4)			
1	60 ( 16.5%)	55 ( 14.9%)	42 ( 11.5%)

1a	177 ( 48.8%)	182 ( 49.5%)	188 ( 51.4%)
1b	126 ( 34.7%)	131 ( 35.6%)	136 ( 37.2%)
HCV-1 Subtype	(b) (4)		
1	60 ( 16.5%)	55 ( 14.9%)	46 ( 12.6%)
1a	177 ( 48.8%)	179 ( 48.6%)	187 ( 51.1%)
1b	126 ( 34.7%)	134 ( 36.4%)	133 ( 36.3%)
HCV-1 Subtype	(b) (4)		
1a	228 ( 65.0%)	234 ( 65.2%)	237 ( 66.8%)
1b	121 ( 34.5%)	124 ( 34.5%)	117 ( 33.0%)
6e	. ( . %)	1 ( 0.3%)	. ( . %)
6h	1 ( 0.3%)	. ( . %)	. ( . %)
6n	1 ( 0.3%)	. ( . %)	1 ( 0.3%)
Region			
EU	99 ( 27.3%)	79 ( 21.5%)	86 ( 23.5%)
LA	10 ( 2.8%)	12 ( 3.3%)	10 ( 2.7%)
NA	254 ( 70.0%)	277 ( 75.3%)	270 ( 73.8%)
Location (US vs. International)			
US	225 ( 62.0%)	245 ( 66.6%)	239 ( 65.3%)
International	138 ( 38.0%)	123 ( 33.4%)	127 ( 34.7%)

<sup>a</sup>: std stands for standard deviation.

**Table 20: Demographic and Baseline Characteristics in Cohort 1 only for Study P05216**

Subgroup	PR48	RGT	BOC48
As Randomized and Dosed (FAS)			
N	311	316	311
Race Group			
NON-BLACK	311 (100.0%)	316 (100.0%)	311 (100.0%)
Race			
WHITE	296 ( 95.2%)	304 ( 96.2%)	295 ( 94.9%)
AMERICAN INDIAN OR ALASKAN NATIVE	1 ( 0.3%)	1 ( 0.3%)	4 ( 1.3%)
ASIAN	9 ( 2.9%)	4 ( 1.3%)	8 ( 2.6%)
MULTIRACIAL	5 ( 1.6%)	5 ( 1.6%)	4 ( 1.3%)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	. ( . %)	2 ( 0.6%)	. ( . %)
Gender			
F	140 ( 45.0%)	116 ( 36.7%)	123 ( 39.5%)
M	171 ( 55.0%)	200 ( 63.3%)	188 ( 60.5%)
Age (Year)			
Mean (SE)	48.25 ( 0.584)	49.38 ( 0.531)	48.49 ( 0.513)
median	49	50	50
range	( 18.0, 75.0)	( 21.0, 76.0)	( 21.0, 67.0)
std	10.2	9.4	9.0

Age Group			
<40 yr	51 ( 16.4%)	45 ( 14.2%)	49 ( 15.8%)
>=45-<65	246 ( 79.1%)	261 ( 82.6%)	255 ( 82.0%)
>=65 yr	14 ( 4.5%)	10 ( 3.2%)	7 ( 2.3%)
Weight (Kg)			
Mean (SE)	78.56 ( 0.901)	81.46 ( 0.968)	80.09 ( 0.937)
median	78	80	79
range	( 46.0, 124.3)	( 44.0, 124.6)	( 45.4, 124.0)
std	15.8	17.2	16.5
Weight Group			
<75 Kg	137 ( 44.1%)	120 ( 38.0%)	121 ( 38.9%)
>=75 Kg	174 ( 55.9%)	196 ( 62.0%)	190 ( 61.1%)
Height (CM)			
Mean (SE)	170.82 ( 0.576)	171.49 ( 0.605)	171.17 ( 0.553)
median	172	172	171
range	(144.8, 195.6)	(144.8, 198.0)	(144.8, 199.6)
std	10.1	10.7	9.7
BMI			
Mean (SE)	26.84 ( 0.257)	27.59 ( 0.273)	27.30 ( 0.296)
median	26	27	26
range	( 18.8, 44.3)	( 17.2, 50.4)	( 17.7, 47.6)
std	4.5	4.8	5.2
Baseline Platelets Count			
<150,000/ul	25 ( 8.0%)	30 ( 9.5%)	34 ( 10.9%)
>=150,000/ul	286 ( 92.0%)	286 ( 90.5%)	277 ( 89.1%)
Baseline ALT Status			
Elevated at BSL	233 ( 74.9%)	252 ( 79.7%)	247 ( 79.4%)
Normal at BSL	78 ( 25.1%)	64 ( 20.3%)	64 ( 20.6%)
Baseline Hemoglobin Level			
Mean (SE)	14.75 ( 0.075)	14.89 ( 0.073)	14.86 ( 0.072)
median	14	14	14
range	( 9.7, 18.9)	( 11.7, 18.7)	( 11.4, 19.2)
std	1.3	1.2	1.2
Baseline Log10 of HCV Viral Geometric Mean (IU/mL)			
Mean (SE)	6.52 ( 0.036)	6.52 ( 0.036)	6.50 ( 0.037)
median	6	6	6
range	( 3.6, 7.7)	( 3.1, 7.5)	( 3.5, 7.5)
std	0.6	0.6	0.6
Baseline HCV Viral Category (IU/mL)			
<=200,000	13 ( 4.2%)	15 ( 4.7%)	14 ( 4.5%)
>200,000-400,000	13 ( 4.2%)	14 ( 4.4%)	9 ( 2.9%)
>400,000-800,000	27 ( 8.7%)	19 ( 6.0%)	26 ( 8.4%)
>800,000	258 ( 83.0%)	268 ( 84.8%)	262 ( 84.2%)
Baseline Statin Use			
N	309 ( 99.4%)	308 ( 97.5%)	308 ( 99.0%)
Y	2 ( 0.6%)	8 ( 2.5%)	3 ( 1.0%)

Baseline Steatosis Score			
Missing	11 ( 3.5%)	11 ( 3.5%)	10 ( 3.2%)
0	108 ( 34.7%)	92 ( 29.1%)	93 ( 29.9%)
1	144 ( 46.3%)	161 ( 50.9%)	158 ( 50.8%)
2	45 ( 14.5%)	47 ( 14.9%)	47 ( 15.1%)
3	3 ( 1.0%)	5 ( 1.6%)	3 ( 1.0%)
Metavir Fibrosis Score			
Missing	11 ( 3.5%)	11 ( 3.5%)	10 ( 3.2%)
0	16 ( 5.1%)	17 ( 5.4%)	9 ( 2.9%)
1	206 ( 66.2%)	212 ( 67.1%)	208 ( 66.9%)
2	55 ( 17.7%)	50 ( 15.8%)	48 ( 15.4%)
3	10 ( 3.2%)	13 ( 4.1%)	14 ( 4.5%)
4	13 ( 4.2%)	13 ( 4.1%)	22 ( 7.1%)
Liver Cirrhosis at Baseline			
N	287 ( 95.7%)	292 ( 95.7%)	279 ( 92.7%)
Y	13 ( 4.3%)	13 ( 4.3%)	22 ( 7.3%)
Opioid Replacement Therapy			
N	310 ( 99.7%)	313 ( 99.1%)	305 ( 98.1%)
Y	1 ( 0.3%)	3 ( 0.9%)	6 ( 1.9%)
HCV-1 Subtype (b) (4)			
1	52 ( 16.7%)	52 ( 16.5%)	37 ( 11.9%)
1a	145 ( 46.6%)	146 ( 46.2%)	154 ( 49.5%)
1b	114 ( 36.7%)	118 ( 37.3%)	120 ( 38.6%)
HCV-1 Subtype (b) (4)			
1	53 ( 17.0%)	52 ( 16.5%)	41 ( 13.2%)
1a	144 ( 46.3%)	144 ( 45.6%)	153 ( 49.2%)
1b	114 ( 36.7%)	120 ( 38.0%)	117 ( 37.6%)
HCV-1 Subtype (b) (4)			
1a	187 ( 62.1%)	195 ( 63.5%)	197 ( 65.2%)
1b	112 ( 37.2%)	111 ( 36.2%)	104 ( 34.4%)
6e	. ( . %)	1 ( 0.3%)	. ( . %)
6h	1 ( 0.3%)	. ( . %)	. ( . %)
6n	1 ( 0.3%)	. ( . %)	1 ( 0.3%)
Region			
EU	98 ( 31.5%)	78 ( 24.7%)	83 ( 26.7%)
LA	10 ( 3.2%)	12 ( 3.8%)	10 ( 3.2%)
NA	203 ( 65.3%)	226 ( 71.5%)	218 ( 70.1%)
Location (US vs. International)			
US	174 ( 55.9%)	195 ( 61.7%)	188 ( 60.5%)
International	137 ( 44.1%)	121 ( 38.3%)	123 ( 39.5%)

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**Table 21: Demographic and Baseline Characteristics in Cohort 2 only for Study P05216**

Subgroup	PR48	RGT	BOC48
As Randomized and Dosed (FAS)			
N	52	52	55
Race Group			
BLACK	52 (100.0%)	52 (100.0%)	55 (100.0%)
Gender			
F	17 ( 32.7%)	23 ( 44.2%)	22 ( 40.0%)
M	35 ( 67.3%)	29 ( 55.8%)	33 ( 60.0%)
Age (Year)			
Mean (SE)	50.54 ( 1.179)	52.37 ( 1.102)	50.91 ( 0.942)
median	52	53	52
range	( 24.0, 65.0)	( 22.0, 73.0)	( 22.0, 63.0)
std	8.5	7.9	6.9
Age Group			
<40 yr	6 ( 11.5%)	3 ( 5.8%)	4 ( 7.3%)
>=45-<65	45 ( 86.5%)	47 ( 90.4%)	51 ( 92.7%)
>=65 yr	1 ( 1.9%)	2 ( 3.8%)	. ( . %)
Weight (Kg)			
Mean (SE)	86.82 ( 1.998)	86.03 ( 2.107)	91.37 ( 2.472)
median	87	85	89
range	( 57.1, 118.0)	( 57.8, 124.3)	( 55.0, 124.9)
std	14.4	15.1	18.3
Weight Group			
<75 Kg	9 ( 17.3%)	11 ( 21.2%)	10 ( 18.2%)
>=75 Kg	43 ( 82.7%)	41 ( 78.8%)	45 ( 81.8%)
Height (CM)			
Mean (SE)	172.11 ( 1.269)	171.54 ( 1.459)	171.79 ( 1.181)
median	172	170	172
range	(149.9, 188.0)	(151.9, 198.1)	(154.9, 190.5)
std	9.1	10.5	8.7
BMI			
Mean (SE)	29.31 ( 0.611)	29.34 ( 0.720)	30.95 ( 0.817)
median	28	29	30
range	( 22.2, 39.7)	( 19.6, 42.9)	( 19.6, 51.7)
std	4.4	5.1	6.0
Baseline Platelets Count			
<150,000/ul	2 ( 3.8%)	3 ( 5.8%)	4 ( 7.3%)
>=150,000/ul	50 ( 96.2%)	49 ( 94.2%)	51 ( 92.7%)
Baseline ALT Status			
Elevated at BSL	36 ( 69.2%)	41 ( 78.8%)	34 ( 61.8%)
Normal at BSL	16 ( 30.8%)	11 ( 21.2%)	21 ( 38.2%)

Baseline Hemoglobin Level			
Mean (SE)	14.69 ( 0.209)	14.51 ( 0.187)	14.29 ( 0.163)
median	14	14	14
range	( 11.7, 18.1)	( 10.4, 18.3)	( 12.0, 17.1)
std	1.5	1.3	1.2
Baseline Log10 of HCV Viral Geometric Mean (IU/mL)			
Mean (SE)	6.69 ( 0.057)	6.52 ( 0.074)	6.69 ( 0.068)
median	6	6	6
range	( 5.8, 7.7)	( 5.0, 7.3)	( 5.4, 7.5)
std	0.4	0.5	0.5
Baseline HCV Viral Category (IU/mL)			
<=200,000	.( . %)	3( 5.8%)	.( . %)
>200,000-400,000	.( . %)	.( . %)	2( 3.6%)
>400,000-800,000	2( 3.8%)	3( 5.8%)	2( 3.6%)
>800,000	50( 96.2%)	46( 88.5%)	51( 92.7%)
Baseline Statin Use			
N	51( 98.1%)	51( 98.1%)	51( 92.7%)
Y	1( 1.9%)	1( 1.9%)	4( 7.3%)
Baseline Steatosis Score			
Missing	.( . %)	4( 7.7%)	1( 1.8%)
0	20( 38.5%)	15( 28.8%)	15( 27.3%)
1	26( 50.0%)	26( 50.0%)	32( 58.2%)
2	5( 9.6%)	6( 11.5%)	7( 12.7%)
3	1( 1.9%)	1( 1.9%)	.( . %)
Metavir Fibrosis Score			
Missing	.( . %)	4( 7.7%)	1( 1.8%)
0	1( 1.9%)	3( 5.8%)	1( 1.8%)
1	40( 76.9%)	26( 50.0%)	38( 69.1%)
2	10( 19.2%)	11( 21.2%)	9( 16.4%)
3	1( 1.9%)	5( 9.6%)	4( 7.3%)
4	.( . %)	3( 5.8%)	2( 3.6%)
Liver Cirrhosis at Baseline			
N	52(100.0%)	45( 93.8%)	52( 96.3%)
Y	.( . %)	3( 6.3%)	2( 3.7%)
Opioid Replacement Therapy			
N	52(100.0%)	52(100.0%)	53( 96.4%)
Y	.( . %)	.( . %)	2( 3.6%)
HCV-1 Subtype (b) (4)			
1	8( 15.4%)	3( 5.8%)	5( 9.1%)
1a	32( 61.5%)	36( 69.2%)	34( 61.8%)
1b	12( 23.1%)	13( 25.0%)	16( 29.1%)
HCV-1 Subtype (b) (4)			
1	7( 13.5%)	3( 5.8%)	5( 9.1%)
1a	33( 63.5%)	35( 67.3%)	34( 61.8%)
1b	12( 23.1%)	14( 26.9%)	16( 29.1%)

HCV-1 Subtype ( (b) (4)			
1a	41 ( 82.0%)	39 ( 75.0%)	40 ( 75.5%)
1b	9 ( 18.0%)	13 ( 25.0%)	13 ( 24.5%)
Region			
EU	1 ( 1.9%)	1 ( 1.9%)	3 ( 5.5%)
NA	51 ( 98.1%)	51 ( 98.1%)	52 ( 94.5%)
Location (US vs. International)			
US	51 ( 98.1%)	50 ( 96.2%)	51 ( 92.7%)
International	1 ( 1.9%)	2 ( 3.8%)	4 ( 7.3%)

### ❖ Study P05101 (previous treatment-failure)

Most subjects were Non-black and black subjects only are 12% and the mean age was 53 (Table 22). Overall, most of subjects were male (66%), and male proportion in the RGT arm (60%) is less than that in two other arms (70-72%). At the baseline, there were about 13% of subjects with liver cirrhosis, 88% of subjects with HCV RNA viral load >800,000 IU/mL, 31% of subject with normal ALT value, and 88% of subjects with Platelets count ≥150,000/ul. The proportion of subjects with 1a subtype was 47% using (b) (4) results and was 60% using (b) (4) lab results. The proportion of relapsers was 53% and 47% of subjects having Peg2a as previous Peginterferon type. 71% of subjects enrolled were from North American and 58% of subjects were US.

**Table 22:** Demographic and Baseline Characteristics for Study P05101 (FAS)

Subgroup	PR48	RGT	BOC48	Total
As Randomized and Dosed (FAS)				
N	80	162	161	403
Race Group				
BLACK	12 ( 15.0%)	18 ( 11.1%)	19 ( 11.8%)	49 ( 12.2%)
NON-BLACK	68 ( 85.0%)	144 ( 88.9%)	142 ( 88.2%)	354 ( 87.8%)
Race				
ASIAN	. ( . %)	1 ( 0.6%)	5 ( 3.1%)	6 ( 1.5%)
BLACK OR AFRICAN	12 ( 15.0%)	18 ( 11.1%)	19 ( 11.8%)	49 ( 12.2%)
MULTIRACIAL	. ( . %)	1 ( 0.6%)	1 ( 0.6%)	2 ( 0.5%)
NATIVE HAWAIIAN O	1 ( 1.3%)	. ( . %)	1 ( 0.6%)	2 ( 0.5%)
WHITE	67 ( 83.8%)	142 ( 87.7%)	135 ( 83.9%)	344 ( 85.4%)
Gender				
F	22 ( 27.5%)	64 ( 39.5%)	49 ( 30.4%)	135 ( 33.5%)
M	58 ( 72.5%)	98 ( 60.5%)	112 ( 69.6%)	268 ( 66.5%)
Age (Year)				
Mean (SE)	52.90 (0.904)	52.89 (0.584)	52.30 (0.608)	52.66 (0.382)
median	53	53	53	53
Range	(29.00, 70.0)	(29.00, 74.0)	(26.00, 74.0)	(26.00, 74.0)

std	8.0	7.4	7.7	7.6
Age Group				
<40 yr	4 ( 5.0%)	5 ( 3.1%)	7 ( 4.3%)	16 ( 4.0%)
>=45-<65	70 ( 87.5%)	146 ( 90.1%)	146 ( 90.7%)	362 ( 89.8%)
>=65 yr	6 ( 7.5%)	11 ( 6.8%)	8 ( 5.0%)	25 ( 6.2%)
Weight (Kg)				
Mean (SE)	85.55 (1.808)	85.15 (1.212)	84.18 (1.201)	84.84 (0.771)
median	83.5	83.7	83.9	83.8
Range	(48.0, 124.4)	(50.5, 124.7)	(51.0, 123.0)	(48.0, 124.7)
std	16.2	15.4	15.2	15.5
Weight Group				
<75 Kg	17 ( 21.3%)	42 ( 25.9%)	44 ( 27.3%)	103 ( 25.6%)
>=75 K	63 ( 78.8%)	120 ( 74.1%)	117 ( 72.7%)	300 ( 74.4%)
Height (CM)				
Mean (SE)	174.0 (1.175)	172.0 (0.799)	172.6 (0.727)	172.7 (0.492)
median	175.0	173.0	175.3	174.0
Range	(143.0, 198.1)	(148.0, 195.1)	(147.3, 198.1)	(143.0, 198.1)
std	10	10.2	9.2	9.9
BMI				
Mean (SE)	28.16 (0.485)	28.76 (0.361)	28.23 (0.361)	28.43 (0.226)
median	27.6	28.2	27.8	27.8
Range	(21.8, 42.9)	(19.1, 43.5)	(17.4, 42.1)	(17.4, 43.5)
std	4.3	4.6	4.6	4.5
Baseline Platelets Count				
<150,000/ul	10 ( 12.5%)	21 ( 13.0%)	19 ( 11.8%)	50 ( 12.4%)
>=150,000/ul	70 ( 87.5%)	141 ( 87.0%)	142 ( 88.2%)	353 ( 87.6%)
Baseline ALT Status				
Elevated at BSL	55 ( 68.8%)	109 ( 67.3%)	115 ( 71.4%)	279 ( 69.2%)
Normal at BSL	25 ( 31.3%)	53 ( 32.7%)	46 ( 28.6%)	124 ( 30.8%)
Baseline Hemoglobin Level				
Mean (SE)	14.95 (0.135)	15.10 (0.102)	15.15 (0.097)	15.09 (0.063)
median	15.2	15.1	15.3	15.2
Range	(12.1, 17.7)	(11.7, 18.3)	(12.1, 19.4)	(11.7, 19.4)
std	1.2	1.3	1.2	1.3
Baseline Log10 of HCV Viral Geometric Mean (IU/mL)				
Mean (SE)	6.52 (0.074)	6.63 (0.042)	6.69 (0.045)	6.63 (0.029)
median	6.55	6.75	6.80	6.74
Range	(4.62, 7.52)	(5.02, 7.68)	(4.58, 7.69)	(4.58, 7.69)
std	0.659	0.530	0.574	0.577
Baseline HCV Viral Category (IU/mL)				
<=200,000	2 ( 2.5%)	2 ( 1.2%)	3 ( 1.9%)	7 ( 1.7%)
>200,000-400,000	4 ( 5.0%)	5 ( 3.1%)	4 ( 2.5%)	13 ( 3.2%)
>400,000-800,000	9 ( 11.3%)	8 ( 4.9%)	13 ( 8.1%)	30 ( 7.4%)
>800,000	65 ( 81.3%)	147 ( 90.7%)	141 ( 87.6%)	353 ( 87.6%)

Baseline Statin Use

N	76 ( 95.0%)	154 ( 95.1%)	159 ( 98.8%)	389 ( 96.5%)
Y	4 ( 5.0%)	8 ( 4.9%)	2 ( 1.2%)	14 ( 3.5%)
Liver Cirrhosis at Baseline				
N	66 ( 86.8%)	132 ( 88.6%)	128 ( 85.3%)	326 ( 86.9%)
Y	10 ( 13.2%)	17 ( 11.4%)	22 ( 14.7%)	49 ( 13.1%)
Opioid Replacement Therapy				
N	80 (100.0%)	161 ( 99.4%)	157 ( 97.5%)	398 ( 98.8%)
Y	. ( . %)	1 ( 0.6%)	4 ( 2.5%)	5 ( 1.2%)
Previous Peginterferon Type Used				
PEG2A	42 ( 52.5%)	79 ( 48.8%)	68 ( 42.2%)	189 ( 46.9%)
PEG2B	38 ( 47.5%)	83 ( 51.2%)	93 ( 57.8%)	214 ( 53.1%)
Previous Response (b) (4)				
Never Negative	30 ( 37.5%)	59 ( 36.4%)	59 ( 36.6%)	148 ( 36.7%)
Some Negative	50 ( 62.5%)	103 ( 63.6%)	102 ( 63.4%)	255 ( 63.3%)
Previous Response (Inform)				
NON-RESPONDER	41 ( 51.3%)	75 ( 46.6%)	72 ( 44.7%)	188 ( 46.8%)
RELAPSER	39 ( 48.8%)	86 ( 53.4%)	89 ( 55.3%)	214 ( 53.2%)
HCV-1 Subtype (b) (4)				
1	5 ( 6.3%)	14 ( 8.6%)	14 ( 8.7%)	33 ( 8.2%)
1a	38 ( 47.5%)	74 ( 45.7%)	77 ( 47.8%)	189 ( 46.9%)
1b	37 ( 46.3%)	74 ( 45.7%)	70 ( 43.5%)	181 ( 44.9%)
HCV-1 Subtype (b) (4)				
1	6 ( 7.5%)	13 ( 8.0%)	17 ( 10.6%)	36 ( 8.9%)
1a	38 ( 47.5%)	74 ( 45.7%)	77 ( 47.8%)	189 ( 46.9%)
1b	36 ( 45.0%)	75 ( 46.3%)	67 ( 41.6%)	178 ( 44.2%)
HCV-1 Subtype (b) (4)				
1a	46 ( 57.5%)	96 ( 59.3%)	97 ( 61.0%)	239 ( 59.6%)
1b	34 ( 42.5%)	66 ( 40.7%)	61 ( 38.4%)	161 ( 40.1%)
6l	. ( . %)	. ( . %)	1 ( 0.6%)	1 ( 0.2%)
Region				
EU	29 ( 36.3%)	46 ( 28.4%)	42 ( 26.1%)	117 ( 29.0%)
LA	. ( . %)	1 ( 0.6%)	. ( . %)	1 ( 0.2%)
NA	51 ( 63.8%)	115 ( 71.0%)	119 ( 73.9%)	285 ( 70.7%)
Location (US vs. International)				
US	43 ( 53.8%)	92 ( 56.8%)	97 ( 60.2%)	232 ( 57.6%)
International	37 ( 46.3%)	70 ( 43.2%)	64 ( 39.8%)	171 ( 42.4%)

### 3.2.3 Statistical Methodologies

CMH method with adjustment of stratification factors was used to analyze the primary and key secondary efficacy endpoints. In this review, the number of subjects within each stratum was used as a weight to adjust the randomization strata in CMH method. PROC Freq in SAS V9.2 was used to calculate the CMH test P-value for SVR rate difference.

For the comparison of Arm 2 vs. Arm 3, the exact confidence interval will be calculated using StatXact PORCs instead of normal approximation approach. Two 95% CIs using two one-sided score tests and one two-sided score test from PROC Binomial in PROC StatXact will be presented for between-treatment group difference in the observed proportions. Since both methods gave almost the same result in the analyses, the results from the two one-sided method will be used in text presentation although both results will be listed in tables.

In order to compare Arm 2 (**RGT**) to Arm 3 (**BOC48**) fairly, subjects within these arms will be classified into three groups. The group of subjects in Arm 2 was assigned during the trial.

- For treatment-naïve study, P05216, actual HCV RNA status (detectable or undetectable) from TW8 through TW24 were considered in order to assign the duration of treatment. If there was NO detectable HCV RNA between TW8 through TW24, the subject will be assigned to 28 weeks of treatment (4 weeks lead-in+24 weeks of BOC/PR) called **Group A** in Arm 2. If there was any detectable HCV RNA from TW8 through TW24 and undetectable at TW24, the subject will be assigned to 48 weeks of treatment (4 weeks lead-in+24 weeks of BOC/PR+20 weeks of PR) called **Group B** in Arm 2. If the subject discontinued early and did not get a chance to be assigned to either Group A or B, he/she will be in other/assigned called **Group C** in Arm 2.
- For treatment-failure study, P05101, if undetectable HCV RNA at TW8, the subject will be assigned to 36 weeks of treatment (4 weeks lead-in+32 weeks of BOC/PR) called **Group A** in Arm 2. If detectable HCV RNA at TW8 and undetectable at TW12, the subject will be assigned to 48 weeks of treatment (4 weeks lead-in+32 weeks of BOC/PR+12 weeks of PR) called **Group B** in Arm 2. If the subject discontinued early and did not get a chance to be assigned to either Group A or B, he/she will be in other/assigned called **Group C** in Arm 2.

The group of subjects in Arm 3 was assigned during the analysis phase after the trial, and it is post-trial information in order to facilitate the fair comparison between Arm 2 and Arm 3.

- For treatment-naïve study, P05216, subjects in Arm 3 will be classified into three groups as following:
  - “**A**”: HCV RNA undetectable (NEG) at TW8 through TW24, and treatment duration > 217 days (31 weeks). These are the early responders.
  - “**B**”: HCV RNA detectable (POS) at TW8 or at any subsequent visits up to TW24, undetectable at TW24, and treatment duration > 217 days (31 weeks). These are the late responders.
  - “**C**”: If not above, subjects in Arm 3 will be assigned to other/assigned.

One note is that 31 week is the upper bound of TW28 visit window (See Table 6). If using >196 days (28 weeks) to classify subjects, a few more subjects will be included in the group A and B in arm 3. (See Table 30 in the review for details).

- For treatment-failure study, P05101, subjects in Arm 3 will be classified into three groups as following:
  - “A”: HCV RNA undetectable (NEG) at TW8 and treatment duration > 273 days (39 weeks). These are the early responders.
  - “B”: HCV RNA detectable (POS) at TW8 and treatment duration > 273 days (39 weeks). These are the late responders.
  - “C”: If not above, subjects in Arm 3 will be assigned to other/assigned.

One note is that 39 week is the upper bound of TW36 visit window (See Table 7).

Another note is that the futility rule for P05216 (detectable at TW24) and P05101 (detectable at TW12) will also play role in the classification.

### **Missing data handling**

For the primary and key secondary efficacy endpoints, LOCF method was used, ie, if a subject is missing FW24 data and has undetectable HCV RNA level at FW12, the subject would be considered an SVR. This LOCF approach had a minimum impact on the final results after examination, and the results will be displayed in the corresponding section below.

The relapse rate was defined as the proportion of subjects who had undetectable HCV RNA at EOT (end of treatment) but detectable at EOF (end of treatment, ie, 24 weeks of follow-up) in subjects who had undetectable HCV RNA at EOT and have HCV RNA observation at EOF. According to this definition, some subjects who had undetectable at EOT but missing observation at EOF will be excluded from this relapse analysis. A sensitive analysis will be conducted in the corresponding section.

## **3.2.4 Results and Conclusions**

### **3.2.4.1 Summary of Applicant’s Results**

The results of the sponsor’s analyses on the primary efficacy for study P05216 are listed in Table 23. The applicant concluded that:

- SVR rates in both boceprevir arms were similar and significantly higher than in the PR48 control (P<.0001). Addition of boceprevir to PR demonstrated a significant improvement in CHC (HCV genotype-1) treatment. SVR rates in subjects who received boceprevir treatment were 63% and 66% in RGT and BOC/PR48 arms, respectively, vs. 38% in the control arm. SVR rates reached as high as 67% to 68% in white subjects vs. 40% in controls. Although SVR rates were numerically lower in blacks who received boceprevir (42% to 53%), these rates were approximately double the SVR rate for the PR48 control (23%).

- When comparing the two boceprevir regimens, whether based on per-protocol (TW 8 through TW 24) assignment or TW 8 response, the data suggest that early responders can be successfully treated with the 28-week regimen, whereas late responders require 48 weeks of PR therapy in their regimen. Ie, the RGT arm represents a clear advantage over standard of care and the 48-week fixed-duration arm by offering substantially shorter treatment duration for a large patient population and minimizing boceprevir exposure for all patients. Approximately 60% of HCV genotype-1 infected subjects would be eligible to complete treatment at TW 28 (had undetectable HCV-RNA at TW 8). Approximately 20% of subjects would benefit from a longer treatment duration with PR alone for the last 20 weeks of therapy (up to 48 weeks of total duration).

**Table 23: The Primary Efficacy Results for Studies P05216 from the Sponsor**

P05216 (FAS)			
	Control	Experimental	
	Arm1 (PR48)	Arm 2 (RGT)	Arm 3 (BOC/PR48)
<b>Cohort 1 + Cohort 2</b>	<b>N=363</b>	<b>N=368</b>	<b>N=366</b>
EOT (<10), n (%)	191 (52.6)	261 (70.9)	277 (75.7)
SVR (<10), n (%)	137 (37.7)	233 (63.3)	242 (66.1)
Δ SVR (exp - Arm1)		25.6	28.4
95% CI for Δ		18.6, 32.6	21.4, 35.3
P value		<0.0001	<0.0001
Relapse, n/N (%)	39/176 (22.20)	24/257 (9.3)	24/265 (9.1)
<b>SVR by HCV-RNA Detectability From TW8 Through TW24, n/N (%)</b>			
Undetectable		156/162 (96.3)	155/161 (96.3)
Detectable		59/82 (72.0)	55/73 (75.3)
<b>Cohort 1</b>	<b>N=311</b>	<b>N=316</b>	<b>N=311</b>
EOT (<10), n (%)	176 (56.6)	235 (74.4)	241 (77.5)
SVR (<10), n(%)	125 (40.2)	211 (66.8)	213 (68.5)
Δ SVR (exp - Arm1)		26.6	28.3
95% CI for Δ		19.1, 34.1	20.8, 35.8
P value		<0.0001	<0.0001
Relapse, n/N (%)	37/162 (22.8)	21/232 (9.1)	18/230 (7.8)
<b>SVR by HCV-RNA Detectability From TW8 Through TW24, n/N (%)</b>			
Undetectable		143/147 (97.3)	137/142 (96.5)
Detectable		52/70 (74.3)	48/65 (73.8)
<b>Cohort 2</b>	<b>N=52</b>	<b>N=52</b>	<b>N=55</b>
EOT (<10), n (%)	15 (28.8)	26 (50.0)	36 (65.5)
SVR (<10), n (%)	12 (23.1)	22 (42.3)	29 (52.7)
Δ SVR (exp - Arm1)		19.2	29.7
95% CI for Δ		1.6, 36.9	12.2, 47.1
P value		0.0440	0.0035
Relapse, n/N (%)	2/14 (14.3)	3/25 (12.0)	6/35 (17.1)
<b>SVR by HCV-RNA Detectability From TW8 Through TW24, n/N (%)</b>			
Undetectable		13/15 (86.7)	18/19 (94.7)
Detectable		7/12 (58.3)	7/8 (87.50)

The results of the sponsor's analysis on the primary efficacy for study P05101 are listed in Table 24. The applicant concluded that:

- SVR rates in the boceprevir arms were significantly higher than in the control arm ( $p < 0.0001$ ). SVR rates in subjects who received boceprevir were 59% and 66% in the RGT and BOC/PR48 arms, respectively, vs. 21% in the control arm. Even in subjects with  $< 1.0$  log<sub>10</sub> decrease in HCV-RNA at TW 4 (poorly IFN responsive), who comprised roughly one-third of the study population, SVR rates of 33-34% were observed in the boceprevir arms, compared with 0% in the control arm. Interferon responsive subjects achieved SVR rates of 73-79% with the 3-drug regimen, compared with 25% in the control arm.
- Relapse rates were lower in two boceprevir arms (15% and 12% in the RGT and BOC/PR48 arms respectively) than that in the control arm (32%).
- When comparing the two boceprevir regimens, whether based on per-protocol assignment or TW 8 response, data suggest that early responders can be successfully treated with the 36-week regimen, whereas late responders require 48 weeks of PR therapy in their regimen. For late responders, boceprevir is not required for the final 12 weeks of the 48-week course of therapy. Approximately 50% of subjects would be eligible to complete treatment at TW 36, while approximately 20% of subjects would benefit from a longer treatment duration with PR alone for the last 12 weeks of therapy (up to 48 weeks of total duration).

**Table 24:** The Primary Efficacy Results for Studies P05101 from the Sponsor

P05101 (FAS)			
	Control	Experimental	
	Arm 1 (PR48) N=80	Arm 2 (RGT) N=162	Arm 3 (BOC/PR48) N=161
EOT (<10), n (%)	25 (31.3)	114 (70.4)	124 (77.0)
SVR (<10), n (%)	17 (21.3)	95 (58.6)	107 (66.5)
Δ SVR (exp - Arm 1)		37.4	45.2
95% CI for Δ		(25.7, 49.1)	(33.7, 56.8)
P value		<0.0001	<0.0001
Relapse, n/N (%)	8/25 (32.0)	17/111 (15.3)	14/121 (11.6)
<b>SVR by Previous Response, n/N (%)</b>			
Previous Non-responder	2/29 (6.9)	23/57 (40.4)	30/58 (51.7)
Previous Relapser	15/51 (29.4)	72/105 (68.6)	77/103 (74.8)
<b>SVR by TW4 Response, n/N (%)</b>			
< 1-log <sub>10</sub> Decline	0/12 (0.0)	15/46 (32.6)	15/44 (34.1)
≥ 1-log <sub>10</sub> Decline	17/67 (25.4)	80/110 (72.7)	90/114 (78.9)
Missing	0/1 (0.0)	0/6 (0.0)	2/3 (66.7)
<b>SVR by TW8 Response, n/N (%)</b>			
Undetectable	7/7 (100)	64/74 (86.5)	74/84 (88.1)
Detectable	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)

### 3.2.4.2 Treatment-naïve Study (P05216)

Overall, the stat reviewer replicated the sponsor’s results for the primary efficacy endpoint. There are some disagreements in terms of comparison between two boceprevir arms.

Since only about 49 (4%) of subjects dropped out FAS population and this will not change the conclusion of FAS results. mITT analysis results will not be displayed here.

#### ➤ Primary Efficacy Analysis Results

The primary efficacy endpoint is the percentage of subjects with undetectable plasma HCV-RNA (<10) at Follow-up Week (FW) 24 based on the Full Analysis Set (FAS). If a subject is missing FW 24 data and has undetectable HCV RNA level at FW 12, the subject would be considered an SVR. [Results using <25 cut-off will also be presented here for label purpose.](#)

SVR rates in subjects who received boceprevir treatment were 63% and 66% in RGT and BOC48 arms, respectively, vs. 38% in the control arm [P-value<0.0001 for each boceprevir arm vs. control] (Table 25). The high SVR rates were primarily driven by higher response rate at EOT (71% to 76% in RGT and BOC48 arms vs. 53% PR48 control), plus relapse rates were lower in the RGT and BOC48 arms (9%) than in the PR48 control arm (22%) as shown in Table 28. The response rate at each visit was listed in Figure 9.

Results in cohort 1 (non-black) were very similar to overall results (Table 26 and 28). SVR rates were 67% to 68% for RGT and BOC48 arms vs. 40% in controls. The relapse rates were 8% to 9% in two boceprevir arms vs. 23% in control arm.

For cohort 2 (black), SVR rates were numerically lower for two boceprevir arms (42% to 53%) comparing to overall results, however, the benefits of boceprevir were still there as the SVR rate in control arm in cohort 2 was 23% (Table 27 and 28). Relapse rates among three arms were similar in cohort 2 (PR48=14%, RGT=12%, BOC48=17%), which is not the case for cohort 1 and overall.

**Table 25:** The Primary Efficacy Endpoint (SVR24) Results for Study P05216 (FAS)

Efficacy Parameter	PR48	RGT	BOC48
SVR at EOF (<10)			
SVR Rate	137/363 ( 37.7)	233/368 ( 63.3)	242/366 ( 66.1)
Diff in SVR	-	25.4	28.2
95% CI for Diff	-	[ 18.4, 32.3]	[ 21.4, 35.1]
CMH P_value	-	<0.0001	<0.0001
SVR EOF (<25) [140, ]			
SVR Rate	138/363 ( 38.0)	233/368 ( 63.3)	242/366 ( 66.1)
Diff in SVR	-	25.1	28.0
95% CI for Diff	-	[ 18.2, 32.0]	[ 21.1, 34.8]
CMH P_value	-	<0.0001	<0.0001

SVR_EOT (<10) [EOT ± 14]			
SVR Rate	191/363 ( 52.6)	261/368 ( 70.9)	277/366 ( 75.7)
Diff in SVR	-	18.1	23.0
95% CI for Diff	-	[ 11.3, 25.0]	[ 16.2, 29.7]
CMH P_value	-	<0.0001	<0.0001
SVR_X4 (<10) [17, 48]			
SVR Rate	146/363 ( 40.2)	228/368 ( 62.0)	234/366 ( 63.9)
Diff in SVR	-	21.6	23.6
95% CI for Diff	-	[ 14.6, 28.6]	[ 16.6, 30.6]
CMH P_value	-	<0.0001	<0.0001
SVR_X12 (<10) [70, 140]			
SVR Rate	138/363 ( 38.0)	230/368 ( 62.5)	238/366 ( 65.0)
Diff in SVR	-	24.3	26.9
95% CI for Diff	-	[ 17.4, 31.2]	[ 20.0, 33.8]
CMH P_value	-	<0.0001	<0.0001
SVR24 (<10) [140, ]			
SVR Rate	133/363 ( 36.6)	229/368 ( 62.2)	238/366 ( 65.0)
Diff in SVR	-	25.4	28.3
95% CI for Diff	-	[ 18.5, 32.3]	[ 21.4, 35.1]
CMH P_value	-	<0.0001	<0.0001
SVR24N (<10) [140, 196]			
SVR Rate	133/363 ( 36.6)	229/368 ( 62.2)	239/366 ( 65.3)
Diff in SVR	-	25.4	28.5
95% CI for Diff	-	[ 18.5, 32.3]	[ 21.7, 35.4]
CMH P_value	-	<0.0001	<0.0001
SVR_X36 (<10) [224, 280]			
SVR Rate	10/363 ( 2.8)	153/368 ( 41.6)	33/366 ( 9.0)
Diff in SVR	-	38.8	6.2
95% CI for Diff	-	[ 33.5, 44.1]	[ 2.8, 9.7]
CMH P_value	-	<0.0001	<0.0001
SVR_W72 (<10) [462, 546]			
SVR Rate	131/363 ( 36.1)	214/368 ( 58.2)	232/366 ( 63.4)
Diff in SVR	-	21.9	27.2
95% CI for Diff	-	[ 14.9, 28.8]	[ 20.3, 34.1]
CMH P_value	-	<0.0001	<0.0001

**Table 26: The Primary Efficacy Endpoint (SVR24) Results for Cohort 1 in Study P05216 (FAS)**

Efficacy Parameter	PR48	RGT	BOC48
SVR at EOF (<10)			
SVR Rate	125/311 ( 40.2)	211/316 ( 66.8)	213/311 ( 68.5)
Diff in SVR	-	26.5	28.3
95% CI for Diff	-	[ 19.1, 33.9]	[ 20.9, 35.7]
CMH P_value	-	<0.0001	<0.0001
SVR EOF (<25) [140, ]			
SVR Rate	126/311 ( 40.5)	211/316 ( 66.8)	213/311 ( 68.5)

Diff in SVR	-	26.2	28.0
95% CI for Diff	-	[ 18.7, 33.6]	[ 20.6, 35.4]
CMH P_value	-	<0.0001	<0.0001
-----			
SVR_EOT (<10) [EOT ± 14]			
SVR Rate	176/311 ( 56.6)	235/316 ( 74.4)	241/311 ( 77.5)
Diff in SVR	-	17.7	20.9
95% CI for Diff	-	[ 10.4, 25.0]	[ 13.7, 28.1]
CMH P_value	-	<0.0001	<0.0001
SVR_X4 (<10) [17, 48]			
SVR Rate	136/311 ( 43.7)	206/316 ( 65.2)	205/311 ( 65.9)
Diff in SVR	-	21.4	22.2
95% CI for Diff	-	[ 13.8, 29.0]	[ 14.6, 29.8]
CMH P_value	-	<0.0001	<0.0001
SVR_X12 (<10) [70, 140]			
SVR Rate	127/311 ( 40.8)	209/316 ( 66.1)	209/311 ( 67.2)
Diff in SVR	-	25.2	26.4
95% CI for Diff	-	[ 17.7, 32.7]	[ 18.9, 33.8]
CMH P_value	-	<0.0001	<0.0001
SVR24 (<10) [140, ]			
SVR Rate	122/311 ( 39.2)	207/316 ( 65.5)	210/311 ( 67.5)
Diff in SVR	-	26.2	28.3
95% CI for Diff	-	[ 18.7, 33.6]	[ 20.9, 35.7]
CMH P_value	-	<0.0001	<0.0001
SVR24N (<10) [140, 196]			
SVR Rate	122/311 ( 39.2)	207/316 ( 65.5)	211/311 ( 67.8)
Diff in SVR	-	26.2	28.6
95% CI for Diff	-	[ 18.7, 33.6]	[ 21.2, 36.0]
CMH P_value	-	<0.0001	<0.0001
SVR_X36 (<10) [224, 280]			
SVR Rate	9/311 ( 2.9)	143/316 ( 45.3)	33/311 ( 10.6)
Diff in SVR	-	42.3	7.7
95% CI for Diff	-	[ 36.5, 48.1]	[ 3.7, 11.7]
CMH P_value	-	<0.0001	<0.0001
SVR_W72 (<10) [462, 546]			
SVR Rate	120/311 ( 38.6)	194/316 ( 61.4)	205/311 ( 65.9)
Diff in SVR	-	22.7	27.3
95% CI for Diff	-	[ 15.2, 30.2]	[ 19.9, 34.8]
CMH P_value	-	<0.0001	<0.0001
-----			

**Table 27:** The Primary Efficacy Endpoint (SVR24) Results for Cohort 2 in Study P05216 (FAS)

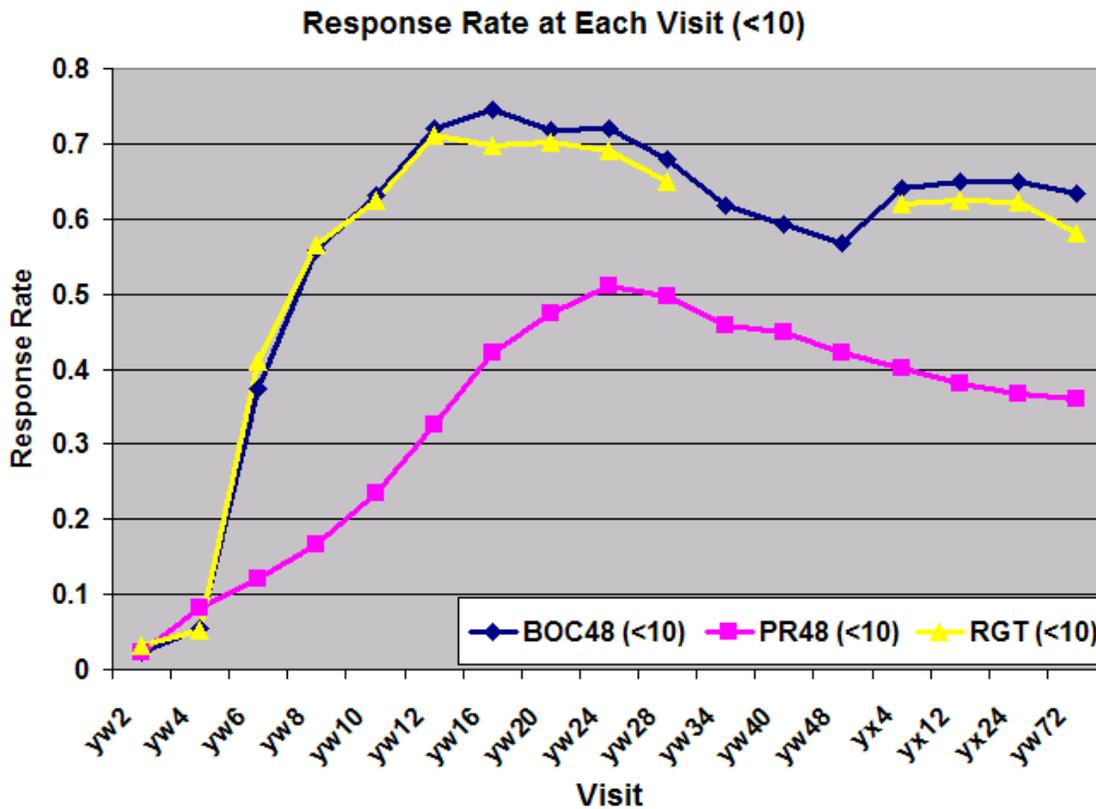
Efficacy Parameter	PR48	RGT	BOC48
SVR at EOF (<10)			

SVR Rate	12/ 52 ( 23.1)	22/ 52 ( 42.3)	29/ 55 ( 52.7)
Diff in SVR	-	18.8	27.8
95% CI for Diff	-	[ 0.9, 36.8]	[ 10.1, 45.5]
CMH P_value	-	0.0440	0.0035
-----			
SVR_EOF (<25) [140, ]			
SVR Rate	12/ 52 ( 23.1)	22/ 52 ( 42.3)	29/ 55 ( 52.7)
Diff in SVR	-	18.8	27.8
95% CI for Diff	-	[ 0.9, 36.8]	[ 10.1, 45.5]
CMH P_value	-	0.0440	0.0035
-----			
SVR_EOT (<10) [EOT ± 14]			
SVR Rate	15/ 52 ( 28.8)	26/ 52 ( 50.0)	36/ 55 ( 65.5)
Diff in SVR	-	21.2	35.3
95% CI for Diff	-	[ 2.6, 39.8]	[ 17.4, 53.3]
CMH P_value	-	0.0440	0.0035
-----			
SVR_X4 (<10) [17, 48]			
SVR Rate	10/ 52 ( 19.2)	22/ 52 ( 42.3)	29/ 55 ( 52.7)
Diff in SVR	-	22.8	31.7
95% CI for Diff	-	[ 5.3, 40.3]	[ 14.4, 49.0]
CMH P_value	-	0.0440	0.0035
-----			
SVR_X12 (<10) [70, 140]			
SVR Rate	11/ 52 ( 21.2)	21/ 52 ( 40.4)	29/ 55 ( 52.7)
Diff in SVR	-	18.8	29.7
95% CI for Diff	-	[ 1.2, 36.5]	[ 12.2, 47.3]
CMH P_value	-	0.0440	0.0035
-----			
SVR24 (<10) [140, ]			
SVR Rate	11/ 52 ( 21.2)	22/ 52 ( 42.3)	28/ 55 ( 50.9)
Diff in SVR	-	20.8	29.7
95% CI for Diff	-	[ 3.0, 38.6]	[ 12.2, 47.3]
CMH P_value	-	0.0440	0.0035
-----			
SVR24N (<10) [140, 196]			
SVR Rate	11/ 52 ( 21.2)	22/ 52 ( 42.3)	28/ 55 ( 50.9)
Diff in SVR	-	20.8	29.7
95% CI for Diff	-	[ 3.0, 38.6]	[ 12.2, 47.3]
CMH P_value	-	0.0440	0.0035
-----			
SVR_X36 (<10) [224, 280]			
SVR Rate	1/ 52 ( 1.9)	10/ 52 ( 19.2)	0/ 55 ( 0.0)
Diff in SVR	-	16.2	-1.9
95% CI for Diff	-	[ 4.2, 28.2]	[ -8.2, 4.3]
CMH P_value	-	0.0440	0.0035
-----			
SVR_W72 (<10) [462, 546]			
SVR Rate	11/ 52 ( 21.2)	20/ 52 ( 38.5)	27/ 55 ( 49.1)
Diff in SVR	-	16.8	25.9
95% CI for Diff	-	[ -0.8, 34.4]	[ 8.5, 43.4]
CMH P_value	-	0.0440	0.0035
-----			

**Table 28:** The Relapse Rate Results for Study P05216 (FAS)<sup>1</sup>

Efficacy Parameter	PR48	RGT	BOC48
EOT<10 as responding and >10 during the Follow-up (at EOF):			
Relapser Rate (<10)	39 /176 (22.2)	24 /257 (9.34)	24 /265 (9.06)
Relapser Rate in Cohort 1	37 /162 (22.8)	21 /232 (9.05)	18 /230 (7.83)
Relapser Rate in Cohort 2	2 / 14 (14.3)	3 / 25 (12.0)	6 / 35 (17.1)
<b>EOT&lt;10 as responding and &gt;25 during the Follow-up (at EOF):</b>			
Relapser Rate (<25)	39 /176 (22.2)	24 /257 (9.34)	24 /265 (9.06)
Relapser Rate in Cohort 1	37 /162 (22.8)	21 /232 (9.05)	18 /230 (7.83)
Relapser Rate in Cohort 2	2 / 14 (14.3)	3 / 25 (12.0)	6 / 35 (17.1)
EOT<25 as responding and >25 during the Follow-up (at EOF):			
Relapser Rate (<25)	53 /190 (27.9)	32 /265 (12.1)	31 /273 (11.4)
Relapser Rate in Cohort 1	49 /174 (28.2)	28 /239 (11.7)	24 /237 (10.1)
Relapser Rate in Cohort 2	4 / 16 (25.0)	4 / 26 (15.4)	7 / 36 (19.4)

<sup>1</sup>: Only subjects who had undetectable at EOT and had observation at EOF were included.



**Figure 9:** Proportion of Subjects Achieving Undetectable HCV-RNA by Study Visit and by Arm for Study P05216

## ➤ Comparison between RGT Arm vs. BOC48 Arm

The purpose of comparison of RGT arm vs. BOC48 arm is to demonstrate that regimens in RGT arm design are OK for both early and late responders. The sponsor concluded that the RGT arm represents a clear advantage over standard of care and the 48-week fixed-duration arm by offering a substantially shorter treatment duration for a large patient population and minimizing boceprevir exposure for all patients. FDA stat reviewer's analysis, however, did not quite support this conclusion for later responders.

In RGT arm, subjects who have undetectable HCV-RNA at all assays from TW8 through TW24 (early responders) are eligible for the shorter treatment duration of 28 weeks (**4 weeks lead-in PR + 24 weeks of triple therapy**) and those with detectable HCV-RNA at any assay from TW8 up to TW24 (later responders) are eligible for the longer treatment duration of 48 weeks (**4 weeks lead-in PR + 24 weeks of triple therapy + 20 weeks of PR**).

The questions to be answered from these comparisons are:

- **Comparison of the early responders** is a comparison of SVR for those subjects with early response who received shorter treatment duration in the RGT arm with matched subjects in the BOC48 arm who received a 48-week fixed duration of treatment. The goal of this analysis is to assess if a shorter treatment duration (28 weeks) is as efficacious as a 48-week fixed treatment duration, or say, *is the extra 20 weeks of triple therapy after 4 weeks lead-in PR plus 24 weeks of triple therapy necessary for early responders in treatment-naïve population.*
- **Comparison of the late responders** is a comparison of SVR for those subjects with later response who received longer treatment duration in the RGT arm with matched subjects in the BOC48 arm who received a 48-week fixed duration of treatment. The goal of this analysis is to assess if triple therapy is needed for 44 weeks, or say, *if PR may be continued without boceprevir for the last 20 weeks for the late responders who receive 48 weeks of treatment.*

In order to do the fair comparisons, early/late responders with correct treatment duration have to be correctly selected. The numbers of subjects in Arm 2 and Arm 3 by the TW8 through TW24 status are similar as it should be since both Arms are identical at those time period (Table 29). As you can see, there were 14 subjects who had all Negative between TW8 through TW24 as early responders, however, they got longer treatment duration as they assigned in Group B incorrectly. One subject who is a later responder was assigned to Group A incorrectly for shorter treatment duration. There 15 subjects were included in the sponsor's early/late responder comparison between Arm 2 and 3. The reviewer thinks they should be excluded.

If these 15 subjects were excluded from the early/late responder comparison between Arm 2 and 3, SVR difference for early responders is 0.6% with 95% CI of [-3.8, 5.2], and -9.2% with 95% CI of [-24.4, 6.3] for late responders in the cohort 1 and 2 combined analysis (Table 30). This -9.2% difference is a big numeric difference although it is not statistically significant. This trial was not

designed to detect the difference. Also, the sample sizes for late responder comparison are limited to about 70 subjects per arm.

The profiles of early and late responders for both arms are listed in Table 31 and Figure 10 and 11. For early responders, the two arms are identical. For late responders, the difference between Arm 2 and 3 began at TW28 where the treatment began to be different between two arms.

In the sponsor's analysis, the SVR rate difference for late responders was about -3% (Table 23), where the 14 subjects were included in the analysis.

**Table 29:** The Number of Subjects Group A, B, and C in Arm 2 and 3 for Study P05216

Parameter	Category	Arm 2 (RGT)				Arm 3 (BOC48)			
		A	B	Other (C)	Overall	A	B	Other (C)	Overall
TW8-TW24 Category	Undetectable (^POS)	161	14	52	227	161		62	223
	Detectable (Some POS)	1	68	72	141		73	70	143
		162	82	124	368	161	73	132	366

<sup>1</sup>: Early responders are subjects who had no POS between TW8 through TW24.

<sup>2</sup>: Late responders are subjects who had some POS between TW8 through TW24, and NEG at TW24.

**Table 30:** The Virologic Response (SVR) of Early and Late Responders in Study P05216

EOF<10	Virologic Response	Arm 2 (RGT) EOF (<10) n/N (%)	Arm 3 (BOC48) EOF (<10) n/N (%)	Δ EOF (Arm 2-Arm 3) [95% CI of two 1-sided]
Cohort 1 + Cohort 2	Overall	233/268 (63.3)	242/366 (66.1)	-2.8 [-9.8, 4.1]
	Early Responders <sup>1</sup>	156/161 (96.9)	155/161 (96.3)	0.6 [-3.8, 5.2]
	Late Responders <sup>2</sup>	45/68 (66.2)	55/73 (75.3)	-9.2 [-24.4, 6.3]
Cohort 1	Early Responders <sup>1</sup>	143/146 (97.9)	137/142 (96.5)	1.5 [-2.8, 6.2]
	Late Responders <sup>2</sup>	38/56 (67.9)	48/65 (73.8)	-6.0 [-22.5, 10.7]
Cohort 2	Early Responders <sup>1</sup>	13/15 (86.7)	18/19 (94.7)	-8.1 [-37.0, 14.8]
	Late Responders <sup>2</sup>	7/12 (58.5)	7/8 (87.5)	-29.2 [-65.1, 16.1]

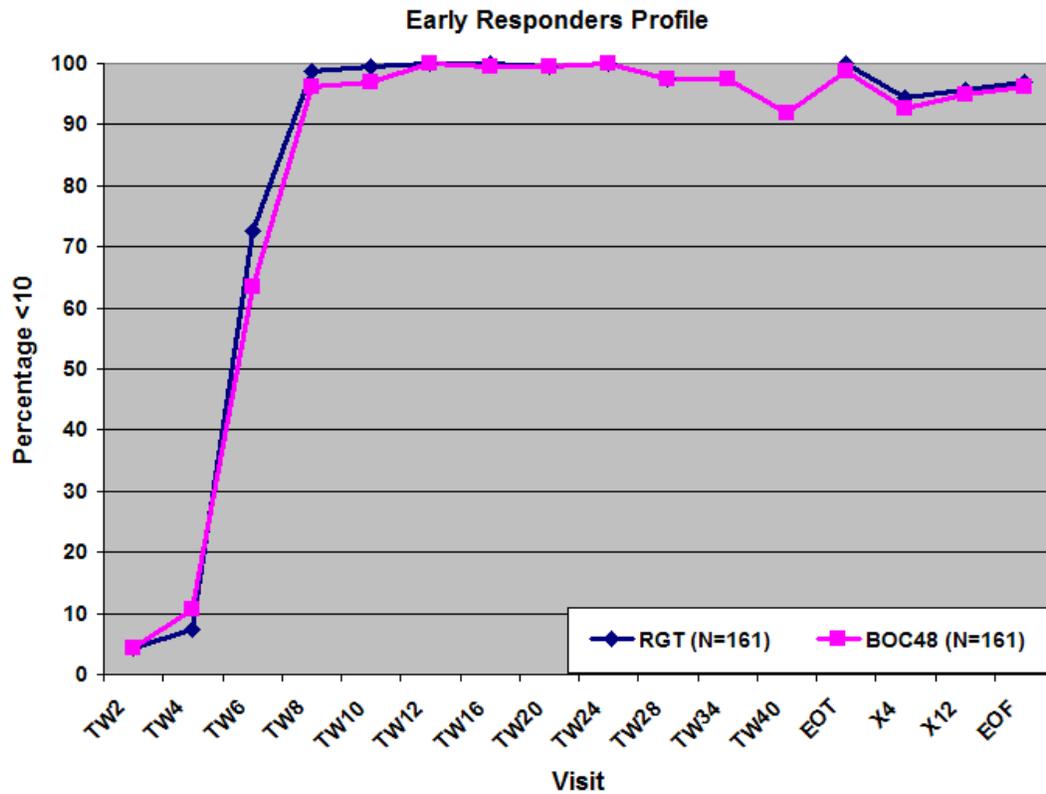
<sup>1</sup>: Early Responders: Undetectable HCV RNA TW 8 through TW24 (In RGT arm, early responders were assigned to shorter treatment duration in Group A. In BOC48 arm, early responders received more than 31 weeks of treatment).

<sup>2</sup>: Late Responders: Detectable HCV RNA TW8, but undetectable by TW24 (In RGT arm, late responders were assigned to longer treatment duration in Group B. In BOC48 arm, late responders received more than 31 weeks of treatment).

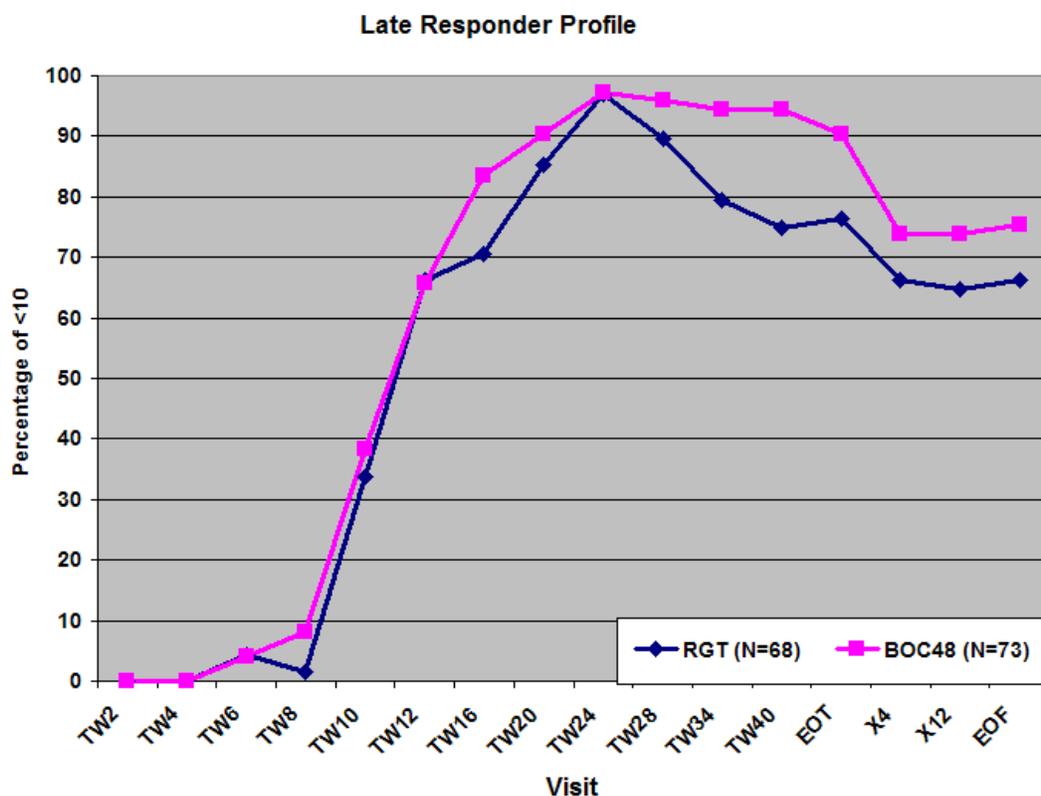
Subjects were discontinued for futility at week 24 in all treatment arms if HCV RNA was detectable.

**Table 31:** The Profiles of Response Rate (<10) for Early and Late Responders in Arm 2 and 3 for Study P05216.

Overall	Early Responders				Late Responders			
	RGT (N=161)		BOC48 (N=161)		RGT (N=68)		BOC48 (N=73)	
	<10 #	%	<10 #	%	<10 #	%	<10 #	%
TW2	7	4.35	7	4.35	0	0	0	0
TW4	12	7.45	17	10.56	0	0	0	0
TW6	117	72.67	102	63.35	3	4.41	3	4.11
TW8	159	98.76	155	96.27	1	1.47	6	8.22
TW10	160	99.38	156	96.89	23	33.82	28	38.36
TW12	161	100	161	100	45	66.18	48	65.75
TW16	161	100	160	99.38	48	70.59	61	83.56
TW20	160	99.38	160	99.38	58	85.29	66	90.41
TW24	161	100	161	100	66	97.06	71	97.26
TW28	157	97.52	157	97.52	61	89.71	70	95.89
TW34			157	97.52	54	79.41	69	94.52
TW40			148	91.93	51	75	69	94.52
TW48			143	88.82	45	66.18	65	89.04
EOT	161	100	159	98.76	52	76.47	66	90.41
X4	152	94.41	149	92.55	45	66.18	54	73.97
X12	154	95.65	153	95.03	44	64.71	54	73.97
EOF	156	96.9	155	96.3	45	66.2	55	75.3



**Figure 10:** Proportion of Early Responders in Arm 2 and 3 Achieving Undetectable HCV-RNA by Study Visit for Study P05216



**Figure 11:** Proportion of Late Responders in Arm 2 and 3 Achieving Undetectable HCV-RNA by Study Visit for Study P05216

The SVR differences in cohort 1 are 1.5% with 95% CI of [-2.8, 6.2] and -6.0% with 95% CI of [-22.5, 10.7] for early and late responders respectively.

The SVR differences in cohort 2 are -8.1% with 95% CI of [-37.0, 14.8] and -29.2% with 95% CI of [-65.1, 16.1] for early and late responders respectively. Again, both are not statistically significant even though the differences seem big.

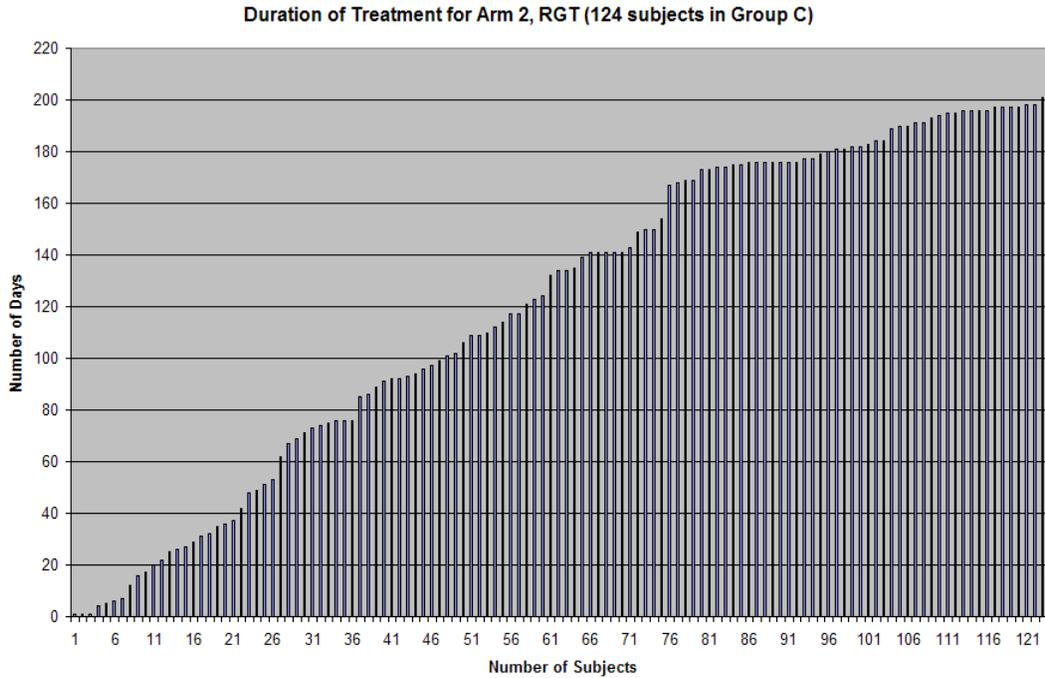
These results may suggest that, for late responders, the treatment regimen in the RGT arm (4 weeks lead-in PR + 24 weeks of BOC/PR + 20 weeks of PR) was not good enough comparing to BOC48 arm where subjects got 4 weeks lead-in PR + 44 weeks of BOC/PR.

For early responders in black population, BOC48 regimen may be a better choice instead of shorter treatment duration used in RGT arm for early responders.

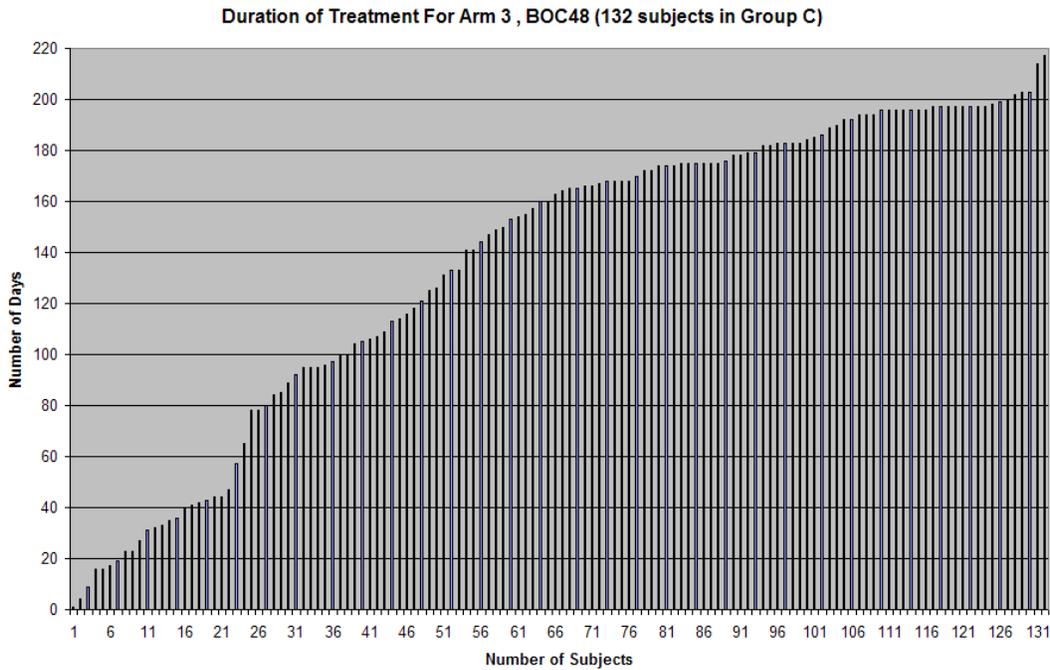
As you can see in Table 29, there were 124 and 132 subjects in Group C for Arm 2 and 3 respectively. The treatment duration ranges of these subjects were [1, 219] and [1, 217] for Arm 2 and 3 respectively (Figure 12 and 13). The SVRs (<10) for these subjects were 14.5% and 24.2% for Arm 2 and 3 respectively (Table 32).

**Table 32:** The SVR (<10) Summary for Subjects in Group C of Arm 2 and 3 for Study P05216

Arm	EOF Status, n/N (%)		
	EOF (<10)=NEG	EOF (<10)=POS	EOF (<10)=Missing
Arm 2 (RGT)	18/124 (14.5%)	74/124 (59.7%)	32/124 (25.8%)
Arm 3 (BOC48)	32/132 (24.2%)	78/132 (59.1%)	22/132 (16.7%)



**Figure 12:** The Treatment Duration of Subjects in Group C for Arm 2 for Study P05216



**Figure 13:** The Treatment Duration of Subjects in Group C for Arm 3 for Study P05216

➤ **Some additional analyses Purposed in the Label for the Comparison between RGT Arm vs. BOC48 Arm**

There are some additional statistical analyses used in the proposed label (which may or may not in the final label).

The number of subjects by the TW8 status (POS, NEG) in Arm 2 and 3 are similar, ie, there were more subjects with NEG at TW8 than that in Arm 1 (Table 33).

**Table 33:** The Number of Subjects in Arm 1, 2, and 3 by TW8 Status for Study P05216

TW8 Status	Arm 1 (PR48)	Arm 2 (RGT)				Arm 3 (BOC48)			
		A	B	Other (C)	Overall	A	B	Other (C)	Overall
Undetectable	<b>60</b>	160	15	33	<b>208</b>	155	6	<b>43</b>	<b>204</b>
Detectable	<b>271</b>		66	63	<b>129</b>		66	<b>65</b>	<b>131</b>
Missing	<b>32</b>	2	1	28	<b>31</b>	6	1	<b>24</b>	<b>31</b>
<b>Sum</b>	<b>363</b>	<b>162</b>	<b>82</b>	<b>124</b>	<b>368</b>	<b>161</b>	<b>73</b>	<b>132</b>	<b>366</b>

The SVRs at EOT and EOF and relapse rates by <10 and <25 for early and late responders in Arm 2 and 3 are listed in Table 34 and 35.

If using the sponsor’s definitions in terms of early and late responders (including those 15 subjects), the results of same analysis are listed in Table 36 for reference.

**Table 34:** The SVRs at EOT and EOF and Relapse Rates for Early and Late Responders in Arm 2 and 3 in Study P05216 using <10 IU/mL as Cut-off Value

Efficacy Parameter	RGT	BOC48	Total
<u>Cohort 1 + 2</u>			
SVR (<10) at EOF			
Late	45 / 68 (66.2)	55 / 73 (75.3)	100 /141 (70.9)
Early	156 /161 (96.9)	155 /161 (96.3)	311 /322 (96.6)
SVR (<10) at EOT			
Late	52 / 68 (76.5)	66 / 73 (90.4)	118 /141 (83.7)
Early	161 /161 ( 100)	159 /161 (98.8)	320 /322 (99.4)
Relapser Rate (≥10)			
Late	7 / 52 (13.5)	9 / 64 (14.1)	16 /116 (13.8)
Early	4 /160 (2.50)	2 /157 (1.27)	6 /317 (1.89)
<u>Cohort 1</u>			
SVR (<10) at EOF			
Late	38 / 56 (67.9)	48 / 65 (73.8)	86 /121 (71.1)

Undetectable	143 /146 (97.9)	137 /142 (96.5)	280 /288 (97.2)
SVR (<10) at EOT			
Late	45 / 56 (80.4)	58 / 65 (89.2)	103 /121 (85.1)
Early	146 /146 ( 100)	140 /142 (98.6)	286 /288 (99.3)
Relapser Rate (≥10)			
Late	7 / 45 (15.6)	9 / 57 (15.8)	16 /102 (15.7)
Early	2 /145 (1.38)	1 /138 (0.72)	3 /283 (1.06)
-----			
<u>Cohort 2</u>			
SVR (<10) at EOF			
Late	7 / 12 (58.3)	7 / 8 (87.5)	14 / 20 (70.0)
Early	13 / 15 (86.7)	18 / 19 (94.7)	31 / 34 (91.2)
SVR (<10) at EOT			
Late	7 / 12 (58.3)	8 / 8 ( 100)	15 / 20 (75.0)
Early	15 / 15 ( 100)	19 / 19 ( 100)	34 / 34 ( 100)
Relapser Rate (≥10)			
Late	. / 7 (0.00)	. / 7 (0.00)	. / . ( . )
Early	2 / 15 (13.3)	1 / 19 (5.26)	3 / 34 (8.82)
-----			

**Table 35:** The SVRs at EOT and EOF and Relapse Rates for Early and Late Responders in Arm 2 and 3 in Study P05216 using <25 IU/mL as Cut-off Value

Efficacy Parameter	RGT	BOC48	Total
-----			
<u>Cohort 1 + 2</u>			
SVR (<25) at EOF			
Late	45 / 68 (66.2)	55 / 73 (75.3)	100 /141 (70.9)
Early	156 /161 (96.9)	155 /161 (96.3)	311 /322 (96.6)
SVR (<25) at EOT			
Late	54 / 68 (79.4)	67 / 73 (91.8)	121 /141 (85.8)
Early	161 /161 ( 100)	159 /161 (98.8)	320 /322 (99.4)
Relapser Rate (≥25) (EOT<10) <sup>1</sup>			
Late	7 / 52 (13.5)	9 / 64 (14.1)	16 /116 (13.8)
Early	4 /160 (2.50)	2 /157 (1.27)	6 /317 (1.89)
-----			
<u>Cohort 1</u>			
SVR (<25) at EOF			
Late	38 / 56 (67.9)	48 / 65 (73.8)	86 /121 (71.1)
Undetectable	143 /146 (97.9)	137 /142 (96.5)	280 /288 (97.2)
SVR (<25) at EOT			
Late	47 / 56 (83.9)	59 / 65 (90.8)	106 /121 (87.6)
Early	146 /146 ( 100)	140 /142 (98.6)	286 /288 (99.3)
Relapser Rate (≥25) (EOT<10)			

Late	7 / 45 (15.6)	9 / 57 (15.8)	16 / 102 (15.7)
Early	2 / 145 (1.38)	1 / 138 (0.72)	3 / 283 (1.06)
<hr/>			
<u>Cohort 2</u>			
SVR (<25) at EOF			
Late	7 / 12 (58.3)	7 / 8 (87.5)	14 / 20 (70.0)
Early	13 / 15 (86.7)	18 / 19 (94.7)	31 / 34 (91.2)
SVR (<25) at EOT			
Late	7 / 12 (58.3)	8 / 8 ( 100)	15 / 20 (75.0)
Early	15 / 15 ( 100)	19 / 19 ( 100)	34 / 34 ( 100)
Relapser Rate (≥25) (EOT<10)			
Late	. / 7 (0.00)	. / 7 (0.00)	. / . ( . )
Early	2 / 15 (13.3)	1 / 19 (5.26)	3 / 34 (8.82)

<sup>1</sup>: Relapse rate: using <10 at EOT visit to count responders, not <25 at EOT.

**Table 36:** The SVRs at EOT and EOF and Relapse Rates for Sponsor's Early and Late Responders in Arm 2 and 3 in Study P05216 using <10 IU/mL as Cut-off Value

Efficacy Parameter	RGT	BOC48	Total
<hr/>			
<u>Cohort 1 + 2</u>			
SVR (<10) at EOF			
Early <sup>1</sup>	156 / 162 (96.3)	155 / 161 (96.3)	311 / 323 (96.3)
Late <sup>2</sup>	59 / 82 (72.0)	55 / 73 (75.3)	114 / 155 (73.5)
SVR (<10) at EOT			
early	162 / 162 ( 100)	159 / 161 (98.8)	321 / 323 (99.4)
late	66 / 82 (80.5)	66 / 73 (90.4)	132 / 155 (85.2)
Relapser Rate (≥10)			
early	5 / 161 (3.11)	2 / 157 (1.27)	7 / 318 (2.20)
late	7 / 66 (10.6)	9 / 64 (14.1)	16 / 130 (12.3)
<hr/>			
<u>Cohort 1</u>			
SVR (<10) at EOF			
early	143 / 147 (97.3)	137 / 142 (96.5)	280 / 289 (96.9)
late	52 / 70 (74.3)	48 / 65 (73.8)	100 / 135 (74.1)
SVR (<10) at EOT			
early	147 / 147 ( 100)	140 / 142 (98.6)	287 / 289 (99.3)
late	59 / 70 (84.3)	58 / 65 (89.2)	117 / 135 (86.7)
Relapser Rate (≥10)			
early	3 / 146 (2.05)	1 / 138 (0.72)	4 / 284 (1.41)
late	7 / 59 (11.9)	9 / 57 (15.8)	16 / 116 (13.8)
<hr/>			
<u>Cohort 2</u>			
SVR (<10) at EOF			

early	13 / 15 (86.7)	18 / 19 (94.7)	31 / 34 (91.2)
late	7 / 12 (58.3)	7 / 8 (87.5)	14 / 20 (70.0)
SVR (<10) at EOT			
early	15 / 15 ( 100)	19 / 19 ( 100)	34 / 34 ( 100)
late	7 / 12 (58.3)	8 / 8 ( 100)	15 / 20 (75.0)
Relapser Rate (≥10)			
early	2 / 15 (13.3)	1 / 19 (5.26)	3 / 34 (8.82)
late	. / 7 (0.00)	. / 7 (0.00)	. / . ( . )

<sup>1</sup>: Early: No Positive between TW8 to TW24 (Early Responders)

<sup>2</sup>: Late: some Positive between TW8 and TW24 (Late Responders)

These are the definitions used by the Sponsor's analyses

### 3.2.4.3 Treatment-failure Study (P05101)

Overall, the stat reviewer replicated the sponsor's results for the primary efficacy endpoint. There are some disagreements in terms of comparison between two boceprevir arms.

Since only about 9 (2%) of subjects dropped out FAS population and this will not change the conclusion of FAS results. mITT analysis results will not be displayed here.

#### ➤ Primary Efficacy Analysis Results

SVR rates in subjects who received boceprevir treatment were 59% and 66% in RGT and BOC48 arms, respectively, vs. 21% in the control arm [P-value<0.0001 for each boceprevir arm vs. control] (Table 37). The high SVR rates were primarily driven by higher response rate at EOT (70% to 77% in RGT and BOC48 arms vs. 31% PR48 control), plus relapse rates were lower in the RGT and BOC48 arms (12% to 15%) than in the PR48 control arm (32%) as shown in Table 38. The response rate at each visit was listed in Figure 14.

**Table 37:** The Primary Efficacy Endpoint (SVR24) Results for Study P05101 (FAS)

Efficacy Parameter	PR48	RGT	BOC48
SVR at EOF (<10)			
SVR Rate	17/ 80 ( 21.3)	95/162 ( 58.6)	107/161 ( 66.5)
Diff in SVR	-	37.3	45.2
95% CI for Diff	-	[ 25.8, 48.8]	[ 33.7, 56.6]
CMH P_value	-	<0.0001	<0.0001
SVR EOF (<25) [140, ]			
SVR Rate	18/ 80 ( 22.5)	96/162 ( 59.3)	107/161 ( 66.5)
Diff in SVR	-	36.6	43.9

95% CI for Diff	-	[ 25.0, 48.2]	[ 32.3, 55.5]
CMH P_value	-	<0.0001	<0.0001
-----			
SVR_EOT (<10) [EOT+/-14]			
SVR Rate	25/ 80 ( 31.3)	114/162 ( 70.4)	124/161 ( 77.0)
Diff in SVR	-	38.9	45.6
95% CI for Diff	-	[ 27.0, 50.9]	[ 34.0, 57.3]
CMH P_value	-	<0.0001	<0.0001
SVR_X4 (<10) [17, 48]			
SVR Rate	16/ 80 ( 20.0)	101/162 ( 62.3)	107/161 ( 66.5)
Diff in SVR	-	42.3	46.4
95% CI for Diff	-	[ 30.9, 53.7]	[ 35.1, 57.8]
CMH P_value	-	<0.0001	<0.0001
SVR_X12 (<10) [70, 140]			
SVR Rate	16/ 80 ( 20.0)	97/162 ( 59.9)	105/161 ( 65.2)
Diff in SVR	-	39.8	45.2
95% CI for Diff	-	[ 28.4, 51.2]	[ 33.8, 56.6]
CMH P_value	-	<0.0001	<0.0001
SVR24 (<10) [140, ]			
SVR Rate	17/ 80 ( 21.3)	94/162 ( 58.0)	106/161 ( 65.8)
Diff in SVR	-	36.7	44.5
95% CI for Diff	-	[ 25.2, 48.2]	[ 33.0, 56.0]
CMH P_value	-	<0.0001	<0.0001
SVR24N (<10) [140, 196]			
SVR Rate	17/ 80 ( 21.3)	94/162 ( 58.0)	106/161 ( 65.8)
Diff in SVR	-	36.6	44.5
95% CI for Diff	-	[ 25.1, 48.2]	[ 33.0, 56.0]
CMH P_value	-	<0.0001	<0.0001
SVR_X36 (<10) [224, 280]			
SVR Rate	0/ 80 ( 0.0)	66/162 ( 40.7)	8/161 ( 5.0)
Diff in SVR	-	40.7	4.9
95% CI for Diff	-	[ 32.7, 48.7]	[ 0.0, 9.9]
CMH P_value	-	<0.0001	<0.0001
SVR_W72 (<10) [462, 546]			
SVR Rate	17/ 80 ( 21.3)	93/162 ( 57.4)	105/161 ( 65.2)
Diff in SVR	-	36.1	43.9
95% CI for Diff	-	[ 24.6, 47.6]	[ 32.4, 55.4]
CMH P_value	-	<0.0001	<0.0001
-----			

**Table 38:** The Relapse Rate Results for Study P05101 (FAS)<sup>1</sup>

Efficacy Parameter	PR48	RGT	BOC48
EOT<10 as responding and ≥10 during the Follow-up (at EOF):			
Relapser Rate (≥10)	8 / 25 (32.0)	17 /111 (15.3)	14 /121 (11.6)

Relapser Rate in Non-Black	8 / 24 (33.3)	17 /100 (17.0)	14 /111 (12.6)
Relapser Rate in Black	. / 1 (0.00)	. / 11 (0.00)	. / 10 (0.00)

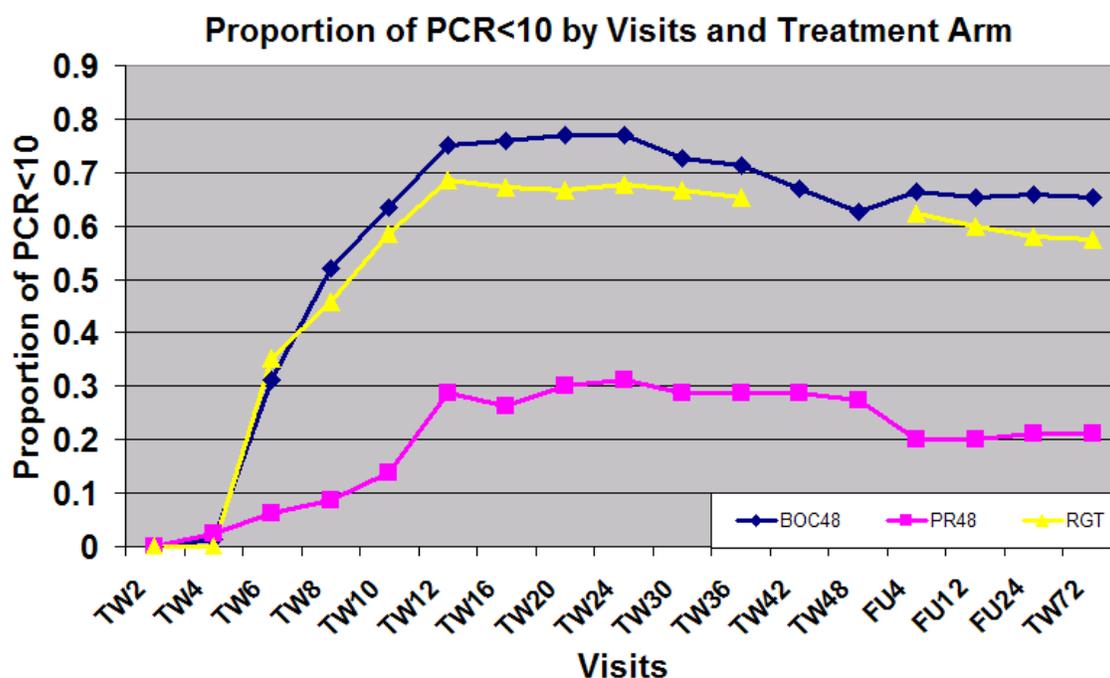
**EOT < 10 as responding and ≥ 25 during the Follow-up (at EOF):**

Relapser Rate (≥25)	7 / 25 (28.0)	16 /111 (14.4)	14 /121 (11.6)
Relapser Rate in Non_Black	7 / 24 (29.2)	16 /100 (16.0)	14 /111 (12.6)
Relapser Rate in Black	. / 1 (0.00)	. / 11 (0.00)	. / 10 (0.00)

**EOT<25 as responding and >25 during the Follow-up (at EOF):**

Relapser Rate (≥25)	11 / 29 (37.9)	25 /121 (20.7)	19 /126 (15.1)
Relapser Rate in Non_Black	11 / 28 (39.3)	24 /109 (22.0)	18 /115 (15.7)
Relapser Rate in Black	. / 1 (0.00)	1 / 12 (8.33)	1 / 11 (9.09)

<sup>1</sup>: Only subjects who had undetectable at EOT and had observation at EOF were included.



**Figure 14:** Proportion of Subjects Achieving Undetectable HCV-RNA by Study Visit and by Arm for Study P05101

➤ **Comparison between RGT Arm vs. BOC48 Arm**

The sponsor concluded that the difference in SVR (RGT vs. BOC48) was not statistically significant although SVR rates appeared numerically higher in the BOC48 arm than the RGT arm (Table 39 below). Despite identical therapy for the first 36 weeks, a higher proportion of BOC48 subjects vs. RGT subjects achieved undetectable HCV-RNA during that time (Similar Figure 14 above), and may be due to differences in responses in the subgroup of subjects with cirrhosis. While receiving triple therapy, in the subgroup of cirrhotics, 2/17 (12%) in arm 2 (RGT) and 15/22

(68%) [[The numbers should be 14/22 \(64%\), checked by the stat reviewer](#)] in arm 3 (BOC48) had an undetectable HCV RNA at Week 8 and reached Week 36. Another note, 27% (44/162) [[one note from the reviewer is that one subject was suppressed after EOT visit was counted here as suppressed](#)] of RGT subjects vs. 17% (27/161) of BOC subjects never achieved undetectable HCV RNA. This suggests an underlying difference in responsiveness, not fully accounted for by randomization.

**Table 39:** The Overall Comparison between Arm 2 and 3 in Study P05101

Cut-off Value for SVR	Arm 2 (RGT) n/N (%)	Arm 3 (BOC48) n/N (%)	$\Delta$ EOF (Arm 2-Arm 3) [95% CI of two 1-sided]
SVR (<10)	95/162 (58.6)	107/161 (66.5)	-7.8 [-18.3, 2.9]
SVR (<25)	96/162 (59.3)	107/161 (66.5)	-7.2 [-17.7, 3.5]

The purpose of comparison in early and late responders between RGT arm and BOC48 arm in Study P05101 is to demonstrate that regimens in RGT arm design are OK for both early and late responders. The sponsor concluded that both arms are comparable for both early and late responders. FDA stat reviewer's analysis did support this conclusion although there are some difference in terms of the classification of early and late responder in RGT Arm.

In RGT arm, subjects who have undetectable HCV-RNA at TW8 (early responders) are eligible for the shorter treatment duration of 36 weeks (**4 weeks lead-in PR + 32 weeks of triple therapy**) and those with detectable HCV-RNA at TW8 (later responders) are eligible for the longer treatment duration of 48 weeks (**4 weeks lead-in PR + 32 weeks of triple therapy + 12 weeks of PR**).

The questions to be answered from these comparisons are:

- **Comparison of the early responders** is a comparison of SVR for those subjects with early response who received shorter treatment duration in the RGT arm with matched subjects in the BOC48 arm who received a 48-week fixed duration of treatment. The goal of this analysis is to assess if a shorter treatment duration (36 weeks) is as efficacious as a 48-week fixed treatment duration, or say, [is the extra 12 weeks of triple therapy after 4 weeks lead-in PR plus 32 weeks of triple therapy necessary for early responders in previous treatment-failure population.](#)
- **Comparison of the late responders** is a comparison of SVR for those subjects with later response who received longer treatment duration in the RGT arm. The goal of this analysis is to assess if triple therapy is needed for 44 weeks, [or if PR may be continued without boceprevir for the last 12 weeks for the late responders who receive 48 weeks of treatment.](#)

In order to do the fair comparisons, early/late responders with correct treatment duration have to be correctly selected. The numbers of subjects in Arm 2 and Arm 3 by the TW8 status are similar as it should be since both Arms are identical at those time period (Table 40). As you can see, there were 44 (2+6+36) subjects in RGT arm who should be excluded from the analysis due to the reasons as following:

- There were two subjects (ID=011129 and 010061) with TW8=POS and got RGT36 as they should not be. Both were <25 detectable at TW8 and both NEG at EOT, 011129 stay NEG, while 010061 became POS from FUX4 (it is a relapser.)
- There were six subjects with TW8=NEG and got OTHER assignment (Group C) instead of Group A. In details, subject (ID=013036) became POS at TW10 and stay POS, subjects (ID=013066) became POS at FUX12 subject (ID=012015) became POS at FUX24, and three subjects (ID=012074, 011037, and 010062) stay NEG all the way.
- There were 36 subjects with TW8=POS and got OTHER assignment (Group C) instead of Group B.

These 44 subjects in Arm 2 were included in the sponsor’s early/late responder comparison between Arm 2 and 3. The reviewer thinks they should be excluded.

**Table 40:** The Number of Subjects Group A, B, and C in Arm 2 and 3 for Study P05101

Parameter	Category	Arm 2 (RGT)				Arm 3 (BOC48)			
		A	B	Other (C)	Overall	A	B	Other (C)	Overall
TW8 Status	Undetectable <sup>1</sup>	68	0	6	74	70		14	84
	Detectable <sup>2</sup>	2	34	36	72		40	30	70
	Missing	1	1	14	16	3		4	7
		71	35	56	162	73	40	48	161

<sup>1</sup>: Subjects with undetectable at TW8 is the early responders.

<sup>2</sup>: Subjects with detectable at TW8 is the late responders.

If these 44 subjects in Arm 2 were excluded from the early/late responder comparison between Arm 2 and 3, SVR difference for early responders is -7.4% with 95% CI of [-17.5, 1.1], and 6.9% with 95% CI of [-14.0, 26.7] for late responders (Table 41). The direction of numeric differences for early and late responders between RGT Arm and BOC48 Arm is opposite. The profiles of early and late responders for both arms are listed in Table 42 and Figure 15 and 16. For early responders, the difference between Arm 2 and 3 began at 12 weeks of follow-up period, while at EOT for late responders. There is no good explanation for this and it could be random. Keep in mind that the sample sizes for early responder comparison are limited to about 70 subjects per arm and about 35 subjects per arm for late responders.

In the sponsor’s analysis, the SVR rate difference for early responders was about -1.6%, and -2.6% for late responders (Table 24), where the 44 subjects in Arm 2 were included in the analyses.

The SVR differences for early and late responders between RGT Arm and BOC48 Arm for in Non-Black and Black subgroups are also listed in Table 41. The sample sizes are too small to make any determination.

These results may suggest that, for both early and late responders, the treatment regimens in the RGT Arm were good enough comparing to BOC48 arm.

**Table 41:** The Virologic Response (SVR) of Early and Late Responders in Study P05101<sup>3</sup>

EOF<10	Virologic Response	Arm 2 (RGT) EOF (<10) n/N (%)	Arm 3 (BOC48) EOF (<10) n/N (%)	Δ EOF (Arm 2-Arm 3) [95% CI of two 1-sided]
Overall	Overall	88/102 (86.3)	97/110 (88.2)	
	Early Responders <sup>1</sup>	61/68 (89.7)	68/70 (97.1)	-7.4 [-17.5, 1.1]
	Late Responders <sup>2</sup>	27/34 (79.4)	29/40 (72.5)	6.9 [-14.0, 26.7]
Non-Black	Early Responders <sup>1</sup>	58/64 (90.6)	63/65 (96.9)	
	Late Responders <sup>2</sup>	20/27 (74.1)	25/34 (73.5)	
Black	Early Responders <sup>1</sup>	3/4 (75.0)	5/5 (100)	
	Late Responders <sup>2</sup>	7/7 (100)	4/6 (66.7)	

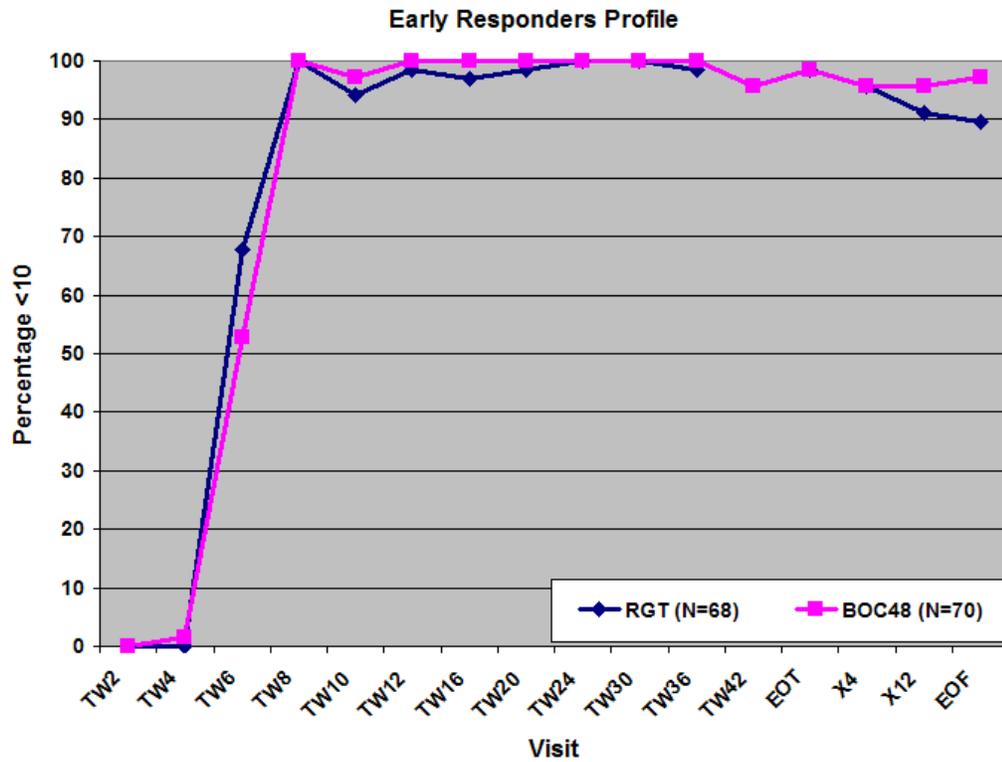
<sup>1</sup>: Early Responders: Undetectable HCV RNA TW 8 (In RGT arm, early responders were assigned to shorter treatment duration in Group A. In BOC48 arm, early responders received more than 39 weeks of treatment).

<sup>2</sup>: Late Responders: Detectable HCV RNA TW8, but undetectable by TW12 (In RGT arm, late responders were assigned to longer treatment duration in Group B. In BOC48 arm, late responders received more than 39 weeks of treatment).

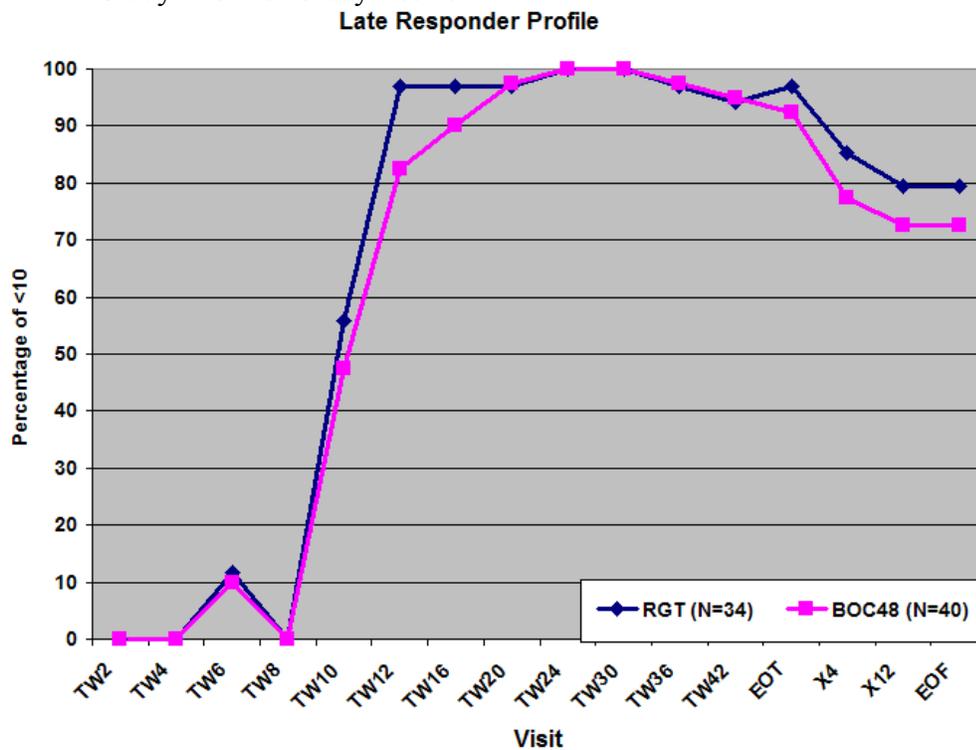
<sup>3</sup>: Subjects were discontinued for futility at TW12 in all treatment arms if HCV RNA was detectable.

**Table 42:** The Profiles of Response Rate (<10) for Early and Late Responders in Arm 2 and 3 for Study P05101.

Overall	Early Responders				Late Responders			
	RGT (N=68)		BOC48 (N=70)		RGT (N=34)		BOC48 (N=40)	
visit	<10 #	%	<10 #	%	<10 #	%	<10 #	%
TW2	0	0	0	0	0	0	0	0
TW4	0	0	1	1.43	0	0	0	0
TW6	46	67.65	37	52.86	4	11.76	4	10
TW8	68	100	70	100	0	0	0	0
TW10	64	94.12	68	97.14	19	55.88	19	47.5
TW12	67	98.53	70	100	33	97.06	33	82.5
TW16	66	97.06	70	100	33	97.06	36	90
TW20	67	98.53	70	100	33	97.06	39	97.5
TW24	68	100	70	100	34	100	40	100
TW30	68	100	70	100	34	100	40	100
TW36	67	98.53	70	100	33	97.06	39	97.5
TW42			67	95.71	32	94.12	38	95
TW48			63	90	32	94.12	35	87.5
EOT	67	98.53	69	98.57	33	97.06	37	92.5
X4	65	95.59	67	95.71	29	85.29	31	77.5
X12	62	91.18	67	95.71	27	79.41	29	72.5
EOF	61	89.71	68	97.14	27	79.41	29	72.5



**Figure 15:** Proportion of Early Responders in Arm 2 and 3 Achieving Undetectable HCV-RNA by Study Visit for Study P05101

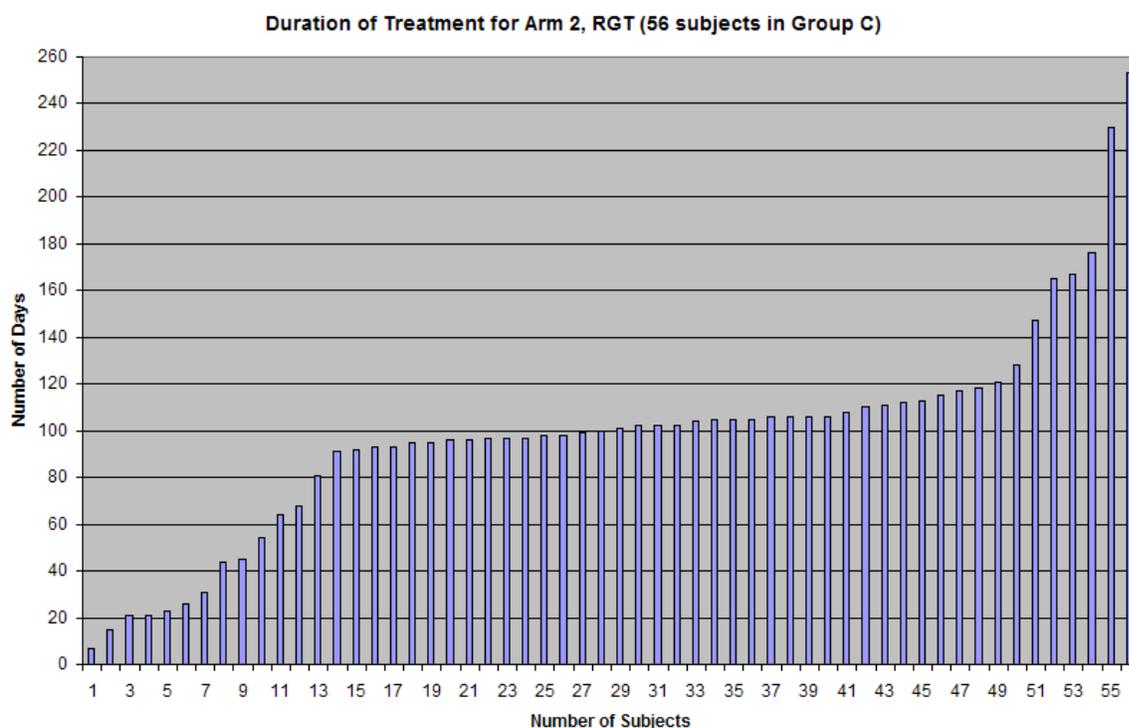


**Figure 16:** Proportion of Late Responders in Arm 2 and 3 Achieving Undetectable HCV-RNA by Study Visit for Study P05101

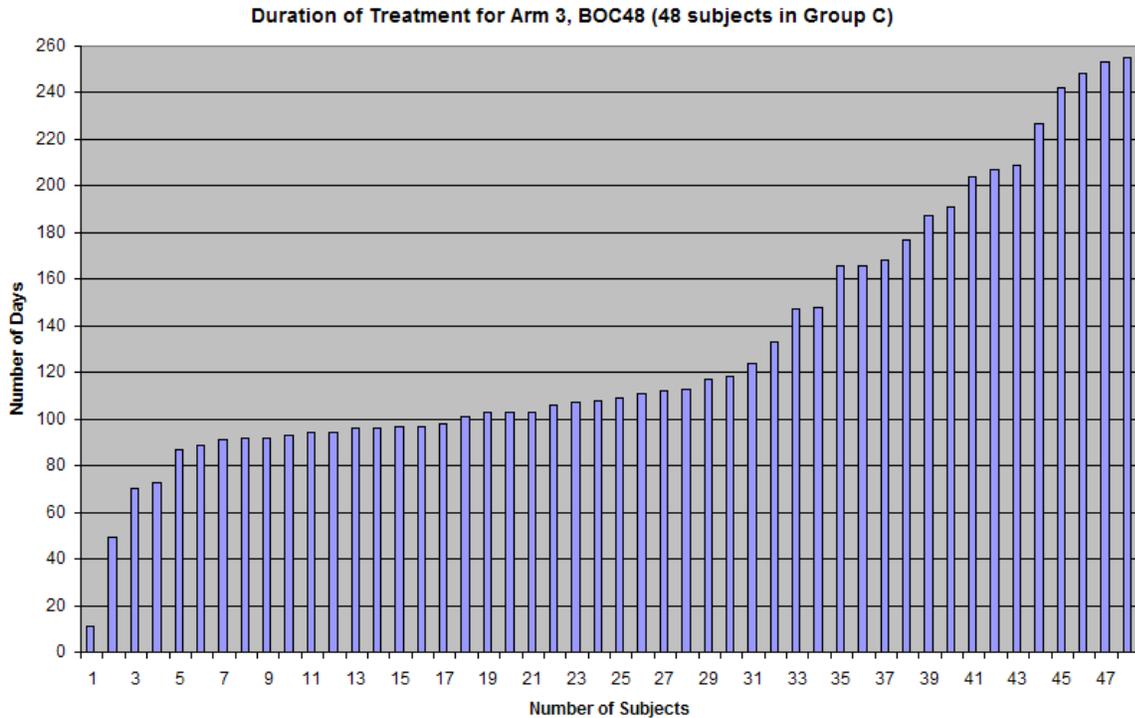
As you can see in Table 40, there were 56 and 48 subjects in Group C for Arm 2 and 3 respectively. The treatment duration ranges of these subjects were [11, 255] and [7, 253] for Arm 2 and 3 respectively (Figure 17 and 18). The SVRs (<10) status for these subjects were listed in Table 43. This 8% difference between Arm 2 and 3 is almost what observed in overall comparison between Arm 2 and 3 shown in Table 39.

**Table 43:** The SVR (<10) Summary for Subjects in Group C of Arm 2 and 3 for Study P05101

Arm	EOF Status, n/N (%)		
	EOF (<10)=NEG	EOF (<10)=POS	EOF (<10)=Missing
Arm 2 (RGT)	4/56 (7.1%)	38/56 (67.9%)	14/56 (25.0%)
Arm 3 (BOC48)	7/48 (14.6%)	36/48 (75.0%)	5/48 (10.4%)



**Figure 17:** The Treatment Duration of Subjects in Group C for Arm 2 for Study P05101



**Figure 18:** The Treatment Duration of Subjects in Group C for Arm 3 for Study P05101

➤ **Using the Status of Subjects at TW8 through TW12 to Define Early/Late Responders for the Comparison between RGT Arm vs. BOC48 Arm**

The analyses above only used the TW8 status (NEG or POS) to classify early/late responders for the comparison between Arm 2 and 3. If we use the similar concept used in the P05216, ie, there was no POS at TW8 through TW12 as early responders, and there were some POS at TW8 through TW12 as late responders. The numbers of subjects in each group are listed in the Table 44 below. The analysis results shown in Table 45 which are similar to what we observed using TW8 status in Table 41.

The reason is that there are only a few subjects were changed due to this. Specifically, there were two subjects (ID=011010 and 013005) had NEG at TW8 and TW12, but POS at TW10 and they were assigned to Group A during the trial in RGT arm. In BOC48 arm, three subjects (ID=013035, 012023, and 010007) were NEG at TW8 and TW12, but POS at TW10. First two were classified into Group A since their duration of treatment were 336 and 227 days, and the last subject (ID=010007) was classified into Group C since its duration of treatment was 209 days.

**Table 44:** The Number of Subjects Group A, B, and C in Arm 2 and 3 if Using the Status at TW8 through TW12 for Study P05101

TW8-TW12 Category	Arm 1 (PR48)	Arm 2 (RGT)				Arm 3 (BOC48)			
		A	B	Other (C)	Overall	A	B	Other (C)	Overall
Undetectable (^POS) <sup>1</sup>	10	66	1	16	83	71		13	84
Detectable (Some POS) <sup>2</sup>	70	5	34	40	79	2	40	35	77
	80	71	35	46	162	73	40	48	161

<sup>1</sup>: Undetectable is that there is no POS during the visits of TW8, TW10, and TW12 (as early responders).

<sup>2</sup>: Detectable is that there is some POS during the visits of TW8, TW10, and TW12 (as late responders).

Subjects with POS at TW12 will be discontinued from the treatment (futility rule).

**Table 45:** The Virologic Response (SVR) of Early and Late Responders Defined by TW8 through TW12 Status in Study P05101<sup>3</sup>

Category by TW8 through TW12	Response, n/N (%)		
	Arm 2 (RGT) N=162	Arm 3 (BOC48) N=161	Δ EOF (Arm 2-Arm 3) [95% CI of two 1-sided]
Undetectable (^POS) == Early Responder and received corresponding duration of treatment	61/66 (92.4)	69/71 (97.2)	-4.8 [-14.2, 3.2]
Detectable (Some POS) == Late Responder and received corresponding duration of	27/34 (79.4)	29/40 (72.5)	6.9 [-14.0, 26.7]

➤ **Some additional analyses Purposed in the Label for the Comparison between RGT Arm vs. BOC48 Arm**

There are some additional statistical analyses used in the proposed label (which may or may not in the final label).

The number of subjects by the TW8 status (POS, NEG) in Arm 2 and 3 are similar, ie, there were more subjects with NEG at TW8 than that in Arm 1 (Table 46). The comparison between Arm 2 and 3 here is what the sponsor did by including those 44 subjects in Arm 2 in the analyses.

**Table 46:** The Number of Subjects in Arm 1, 2, and 3 by TW8 Status for Study P05101

EOF <10	Response, n/N (%)			
	Arm 1 (PR48) N=80	Arm 2 (RGT) N=162	Arm 3 (BOC48) N=161	Δ EOF (Arm 2-Arm 3) [95% CI of two 1-sided]
Undetectable (<10)	7/7 (100)	<b>64/74 (86.5)</b>	<b>74/84 (88.1)</b>	<b>-1.6 [-12.8, 9.2]</b>
Detectable (>10)	8/65 (12.3)	<b>29/72 (40.3)</b>	<b>30/70 (42.9)</b>	<b>-2.6 [-18.8, 13.9]</b>
Missing	2/8 (25.0)	2/16 (12.5)	3/7 (42.9)	

The SVRs at EOT and EOF and relapse rates by <10 and <25 for early and late responders in Arm 2 and 3 by excluding those 44 subjects in Arm 2 are listed in Table 47 and 48. If including those 44 subjects, the results are listed in Table 49 and 50 for reference.

**Table 47:** The SVRs at EOT and EOF and Relapse Rates for Early and Late Responders in Arm 2 and 3 in Study P05101 using <10 IU/mL as Cut-off Value

-----	-----	-----	-----	-----
Efficacy Parameter	RGT	BOC48	Total	
-----	-----	-----	-----	-----
SVR (<10) at EOF				
n	88/102 (86.3)	97/110 (88.2)	185/212 (87.3)	
early	61 / 68 ( <b>89.7</b> )	68 / 70 ( <b>97.1</b> )	129 /138 (93.5)	
late	27 / 34 ( <b>79.4</b> )	29 / 40 ( <b>72.5</b> )	56 / 74 (75.7)	
SVR (<10) at EOT				
n	100/ 102 (98.0)	106/110 (96.4)	206/212 (97.2)	
early	67 / 68 (98.5)	69 / 70 (98.6)	136 /138 (98.6)	
late	33 / 34 (97.1)	37 / 40 (92.5)	70 / 74 (94.6)	
Relapser Rate (≥10)				
n	12/ 99 (12.1)	7/104 (6.73)	19/203 (9.36)	
early	6 / 66 ( <b>9.09</b> )	. / 68 ( <b>0.00</b> )	6 /134 (4.48)	
late	6 / 33 (18.2)	7 / 36 (19.4)	13 / 69 (18.8)	
-----	-----	-----	-----	-----
Black Subjects only				
SVR (<10) at EOF				
n	10/ 11 (90.9)	9/ 11 (81.8)	19/ 22 (86.4)	
early	3 / 4 (75.0)	5 / 5 ( 100)	8 / 9 (88.9)	
late	7 / 7 ( 100)	4 / 6 (66.7)	11 / 13 (84.6)	
SVR (<10) at EOT				
n	11/ . ( 100)	9/ 11 (81.8)	20/ . ( . )	
early	4 / 4 ( 100)	5 / 5 (100)	9 / 9 ( 100)	
late	7 / 7 ( 100)	4 / 6 (66.7)	11 / 13 (84.6)	
Relapser Rate (≥10)				
n	./ .( . )	./ .( . )	./ .( . )	
early	. / 3 (0.00)	. / 5 (0.00)	. / . ( . )	
late	. / 7 (0.00)	. / 4 (0.00)	. / . ( . )	
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Non-Black Subjects only

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SVR (<10) at EOF			
n	78/ 91 (85.7)	88/ 99 (88.9)	166/190 (87.4)
early	58 / 64 (90.6)	63 / 65 (96.9)	121 /129 (93.8)
late	20 / 27 (74.1)	25 / 34 (73.5)	45 / 61 (73.8)
SVR (<10) at EOT			
n	89/ 91 (97.8)	97/ 99 (98.0)	186/190 (97.9)
early	63 / 64 (98.4)	64 / 65 (98.5)	127 /129 (98.4)
late	26 / 27 (96.3)	33 / 34 (97.1)	59 / 61 (96.7)
Relapser Rate (≥10)			
n	12/ 89 (13.5)	7/ 95 (7.37)	19/184 (10.3)
early	6 / 63 (9.52)	. / 63 (0.00)	6 /126 (4.76)
late	6 / 26 (23.1)	7 / 32 (21.9)	13 / 58 (22.4)
-----			

**Table 48:** The SVRs at EOT and EOF and Relapse Rates for Early and Late Responders in Arm 2 and 3 in Study P05101 using <25 IU/mL as Cut-off Value

Efficacy Parameter	RGT	BOC48	Total
-----			
SVR (<25) at EOF			
n	89/102 (87.3)	97/110 (88.2)	186/212 (87.7)
early	62 / 68 (91.2)	68 / 70 (97.1)	130 /138 (94.2)
late	27 / 34 (79.4)	29 / 40 (72.5)	56 / 74 (75.7)
SVR (<25) at EOT			
n	101/102 (99.0)	106/110 (96.4)	207/212 (97.6)
early	68 / 68 ( 100)	69 / 70 (98.6)	137 /138 (99.3)
late	33 / 34 (97.1)	37 / 40 (92.5)	70 / 74 (94.6)
Relapser Rate (<10 at EOT) (≥25 at EOF)			
n	11/ 99 (11.1)	7/104 (6.73)	18/203 (8.87)
early	5 / 66 (7.58)	. / 68 (0.00)	5 /134 (3.73)
late	6 / 33 (18.2)	7 / 36 (19.4)	13 / 69 (18.8)
-----			
Black Subjects only			
-----			
SVR (<25) at EOF			
n	10/ 11 (90.9)	9/ 11 (81.8)	19/ 22 (86.4)
early	3 / 4 (75.0)	5 / 5 ( 100)	8 / 9 (88.9)
late	7 / 7 ( 100)	4 / 6 (66.7)	11 / 13 (84.6)
SVR (<25) at EOT			
n	11/ . ( 100)	9/ 11 (81.8)	20/ . ( . )
early	4 / 4 ( 100)	5 / 5 ( 100)	9 / 9 ( 100)
late	7 / 7 ( 100)	4 / 6 (66.7)	11 / 13 (84.6)
Relapser Rate (<10 at EOT) (≥25 at EOF)			
n	./ . ( . )	./ . ( . )	./ . ( . )
early	. / 3 (0.00)	. / 5 (0.00)	. / . ( . )
late	. / 7 (0.00)	. / 4 (0.00)	. / . ( . )
-----			

Non-Black Subjects only

-----				
SVR (<25) at EOF				
n	79/ 91 (86.8)	88/ 99 (88.9)	167/190 (87.9)	
early	59 / 64 (92.2)	63 / 65 (96.9)	122 /129 (94.6)	
late	20 / 27 (74.1)	25 / 34 (73.5)	45 / 61 (73.8)	
SVR (<25) at EOT				
n	90/ 91 (98.9)	97/ 99 (98.0)	187/190 (98.4)	
early	64 / 64 ( 100)	64 / 65 (98.5)	128 /129 (99.2)	
late	26 / 27 (96.3)	33 / 34 (97.1)	59 / 61 (96.7)	
Relapser Rate (<10 at EOT) (≥25 at EOF)				
n	11/ 89 (12.4)	7/ 95 (7.37)	18/184 (9.78)	
early	5 / 63 (7.94)	. / 63 (0.00)	5 /126 (3.97)	
late	6 / 26 (23.1)	7 / 32 (21.9)	13 / 58 (22.4)	
-----				

**Table 49:** The SVRs at EOT and EOF and Relapse Rates for Sponsor’s Early and Late Responders in Arm 2 and 3 in Study P05101 using <10 IU/mL as Cut-off Value

Efficacy Parameter Status at TW8	PR48	RGT	BOC48
-----			
SVR (<10) at EOF			
n	17/ 80 (21.3)	95/162 (58.6)	107/161 (66.5)
Undetectable	7 / 7 ( 100)	64 / 74 (86.5)	74 / 84 (88.1)
Detectable	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)
SVR (<10) at EOT			
n	25/ 80 (31.3)	114/162 (70.4)	124/161 (77.0)
Undetectable	7 / 7 ( 100)	72 / 74 (97.3)	81 / 84 (96.4)
Detectable	16 / 65 (24.6)	40 / 72 (55.6)	40 / 70 (57.1)
Missing	2 / 8 (25.0)	2 / 16 (12.5)	3 / 7 (42.9)
Relapser Rate (≥10)			
n	8/ 25 (32.0)	17/111 (15.3)	14/121 (11.6)
Undetectable	. / 7 (0.00)	8 / 71 (11.3)	6 / 80 (7.50)
Detectable	8 / 16 (50.0)	9 / 38 (23.7)	8 / 38 (21.1)
Missing	. / 2 (0.00)	. / 2 (0.00)	. / 3 (0.00)
-----			
Black Subjects only			
-----			
SVR (<10) at EOF			
n	1/ 12 (8.33)	11/ 18 (61.1)	10/ 19 (52.6)
Undetectable	. / . ( . )	4 / 5 (80.0)	6 / 6 ( 100)
Detectable	1 / 10 (10.0)	7 / 10 (70.0)	4 / 10 (40.0)
Missing	. / 2 (0.00)	. / 3 (0.00)	. / 3 (0.00)
SVR (<10) at EOT			
n	1/ 12 (8.33)	13/ 18 (72.2)	10/ 19 (52.6)
Undetectable	. / . ( . )	5 / 5 ( 100)	6 / 6 ( 100)
Detectable	1 / 10 (10.0)	8 / 10 (80.0)	4 / 10 (40.0)
Missing	. / 2 (0.00)	. / 3 (0.00)	. / 3 (0.00)

Relapser Rate ( $\geq 10$ )				
n	./ .( . )	./ .( . )	./ .( . )	
Undetectable	. / . ( . )	. / 4 (0.00)	. / 6 (0.00)	
Detectable	. / 1 (0.00)	. / 7 (0.00)	. / 4 (0.00)	
-----				
Non-Black Subjects only				
-----				
SVR (<10) at EOF				
n	16/ 68 (23.5)	84/144 (58.3)	97/142 (68.3)	
Undetectable	7 / 7 ( 100)	60 / 69 (87.0)	68 / 78 (87.2)	
Detectable	7 / 55 (12.7)	22 / 62 (35.5)	26 / 60 (43.3)	
Missing	2 / 6 (33.3)	2 / 13 (15.4)	3 / 4 (75.0)	
SVR (<10) at EOT				
n	24/ 68 (35.3)	101/144 (70.1)	114/142 (80.3)	
Undetectable	7 / 7 ( 100)	67 / 69 (97.1)	75 / 78 (96.2)	
Detectable	15 / 55 (27.3)	32 / 62 (51.6)	36 / 60 (60.0)	
Missing	2 / 6 (33.3)	2 / 13 (15.4)	3 / 4 (75.0)	
Relapser Rate ( $\geq 10$ )				
n	8/ 24 (33.3)	17/100 (17.0)	14/111 (12.6)	
Undetectable	. / 7 (0.00)	8 / 67 (11.9)	6 / 74 (8.11)	
Detectable	8 / 15 (53.3)	9 / 31 (29.0)	8 / 34 (23.5)	
Missing	. / 2 (0.00)	. / 2 (0.00)	. / 3 (0.00)	
-----				

**Table 50:** The SVRs at EOT and EOF and Relapse Rates for Sponsor’s Early and Late Responders in Arm 2 and 3 in Study P05101 using <25 IU/mL as Cut-off Value

Efficacy Parameter Status at TW8	PR48	RGT	BOC48
-----			
SVR (<25) at EOF			
n	18/ 80 (22.5)	96/162 (59.3)	107/161 (66.5)
Undetectable	7 / 7 ( 100)	65 / 74 (87.8)	74 / 84 (88.1)
Detectable	9 / 65 (13.8)	29 / 72 (40.3)	30 / 70 (42.9)
Missing	2 / 8 (25.0)	2 / 16 (12.5)	3 / 7 (42.9)
SVR (<25) at EOT			
n	32/ 80 (40.0)	127/162 (78.4)	130/161 (80.7)
Undetectable	7 / 7 ( 100)	73 / 74 (98.6)	81 / 84 (96.4)
Detectable	22 / 65 (33.8)	50 / 72 (69.4)	46 / 70 (65.7)
Missing	3 / 8 (37.5)	4 / 16 (25.0)	3 / 7 (42.9)
Relapser Rate (<10 at EOT and $\geq 25$ at EOF)			
n	7/ 25 (28.0)	16/111 (14.4)	14/121 (11.6)
Undetectable	. / 7 (0.00)	7 / 71 (9.86)	6 / 80 (7.50)
Detectable	7 / 16 (43.8)	9 / 38 (23.7)	8 / 38 (21.1)
Missing	. / 2 (0.00)	. / 2 (0.00)	. / 3 (0.00)
-----			

Black Subjects only

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SVR (<25) at EOF			
n	1 / 12 (8.33)	11 / 18 (61.1)	10 / 19 (52.6)
Undetectable	. / . ( . )	4 / 5 (80.0)	6 / 6 ( 100)
Detectable	1 / 10 (10.0)	7 / 10 (70.0)	4 / 10 (40.0)
Missing	. / 2 (0.00)	. / 3 (0.00)	. / 3 (0.00)
SVR (<25) at EOT			
n	2 / 12 (16.7)	14 / 18 (77.8)	12 / 19 (63.2)
Undetectable	. / . ( . )	5 / 5 ( 100)	6 / 6 ( 100)
Detectable	1 / 10 (10.0)	9 / 10 (90.0)	6 / 10 (60.0)
Missing	1 / 2 (50.0)	. / 3 (0.00)	. / 3 (0.00)
Relapser Rate (<10 at EOT and ≥25 at EOF)			
n	./ 1 ( . )	./ 11 ( . )	./ 10 ( . )
Undetectable	. / . ( . )	. / 4 (0.00)	. / 6 (0.00)
Detectable	. / 1 (0.00)	. / 7 (0.00)	. / 4 (0.00)

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Non-Black Subjects only

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SVR (<25) at EOF			
n	17 / 68 (25.0)	85 / 144 (59.0)	97 / 142 (68.3)
Undetectable	7 / 7 ( 100)	61 / 69 (88.4)	68 / 78 (87.2)
Detectable	8 / 55 (14.5)	22 / 62 (35.5)	26 / 60 (43.3)
Missing	2 / 6 (33.3)	2 / 13 (15.4)	3 / 4 (75.0)
SVR (<25) at EOT			
n	30 / 68 (44.1)	113 / 144 (78.5)	118 / 142 (83.1)
Undetectable	7 / 7 ( 100)	68 / 69 (98.6)	75 / 78 (96.2)
Detectable	21 / 55 (38.2)	41 / 62 (66.1)	40 / 60 (66.7)
Missing	2 / 6 (33.3)	4 / 13 (30.8)	3 / 4 (75.0)
Relapser Rate (<10 at EOT and ≥25 at EOF)			
n	7 / 24 (29.2)	16 / 100 (16.0)	14 / 111 (12.6)
Undetectable	. / 7 (0.00)	7 / 67 (10.4)	6 / 74 (8.11)
Detectable	7 / 15 (46.7)	9 / 31 (29.0)	8 / 34 (23.5)
Missing	. / 2 (0.00)	. / 2 (0.00)	. / 3 (0.00)

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### 3.3 Evaluation of Safety

#### 3.3.1 Virologic Breakthrough (BT) and Incomplete Virologic Response (IVR)

According to the microbiological reviewer and the protocols of P05216 and P05101, the following definitions will be used for summarizing BT and IVR:

**Breakthrough (BT)** is undetectable HCV RNA (<10) on treatment and a subsequent on treatment HCV RNA value >1,000 IU/mL, which was used by the sponsor.

**Breakthrough-FDA (BT\_FDA)** is undetectable HCV RNA (<10) on-treatment and a subsequent on-treatment HCV RNA value  $\geq$  25 IU/mL, which was preferred by FDA.

**Incomplete Virologic Response (IVR)** is defined as on-treatment increase greater than or equal to 1-log<sub>10</sub> IU/mL from on-treatment nadir. Ie, if a subject reached NEG on-treatment, its HCV RNA viral load have to  $\geq$ 100 IU/mL after NEG on-treatment in order to meet the IVR definition.

The summary of virologic breakthrough and incomplete virologic response for study P05216 and P05101 are listed in Table 51 and 52 respectively. Please refer to the microbiologic review for details.

**Table 51:** The Summary of Virologic Breakthrough and Incomplete Virologic Response for Study P05216

Category	Source	Arm 1 (PR48) N=363	Arm 2 (RGT) N=368	Arm 3 (BOC48) N=366
Break-through	Sponsor reported BT	8	14	8
	BT identified by Stat reviewer	<b>8 + 2 more</b>	<b>14 + 5 more</b>	<b>8 + 2 more</b>
	FDA's BT definition by Stat reviewer	<b>8 + 2 more + 1 additional</b>	<b>14 + 5 more + 12 additional</b>	<b>8 + 2 more + 11 additional</b>
Incomplete Virologic Response (IVR)	Sponsor's IVR	14	21	23
	Sponsor's IVR by Experts	<b>14 + 7 more</b>	<b>21 + 3 more</b>	<b>23 + 3 more</b>
	IVR identified by Stat reviewer	<b>14 + 7 more + 25 additional</b>	<b>21 + 3 more + 32 additional</b>	<b>23 + 3 more + 23 additional</b>

**Table 52:** The Summary of Virologic Breakthrough and Incomplete Virologic Response for Study P05101

Category	Source	Arm 1 (PR48) N=80	Arm 2 (RGT) N=162	Arm 3 (BOC48) N=161
Break-through	Sponsor reported BT		2	3
	BT identified by Stat reviewer		2	2
	FDA's BT definition by Stat reviewer		2 + 3 more	2 + 2 more
Incomplete Virologic Response (IVR)	Sponsor's IVR	<b>1 (011113)</b>	<b>4</b>	<b>2</b>
	Sponsor's IVR by Experts	<b>1 (011113)</b>	<b>4+3 more</b>	<b>2 + 2 more</b>
	IVR by Stat reviewer	<b>Different 1 (012043)</b>	<b>4+3 more + 10 additional</b>	<b>2 + 2 more + 8 additional</b>

### 3.4 Benefit: Risk Assessment (Optional)

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

No significant difference in SVR was observed for gender, age, or location (US vs. non-US) within the boceprevir treatment arms and within the control arm for both studies. There are some numeric differences in SVR observed in race category.

In both studies, SVR was higher in subjects with baseline HCV RNA  $\leq$  800,000 IU/mL than in those with baseline HCV RNA  $>$  800,000 IU/mL, in subjects with HCV-1 subtype 1b than in those with HCV-1 subtype 1a, in subjects with a baseline platelet count  $\geq$  150,000/ $\mu$ L than those with platelet count  $<$ 150,000/ $\mu$ L, in subjects with a lower Metavir fibrosis score (0, 1, and 2 combined) than in those with higher Metavir fibrosis (3 or 4 combined), and in subjects without cirrhosis at baseline than in those with cirrhosis.

Because the studies were not designed to detect these subgroup differences and the limitation of sample size within subgroup, be cautious in terms of the differences observed here.

### 4.1 Gender, Race, Age, and Geographic Region

#### ❖ Study P05216

For study P05216, Cohort 2 was Black subjects only with independent randomization from Cohort 1 of Non-Black. It counts about 15% of sample size. There is a numerical difference (11%) in SVR between the RGT arm (42%) and the BOC48 arm (53%), while there is only a  $<$ 2% difference in SVR between the RGT arm (67%) and the BOC48 arm (68%) in Non-Black subjects (Table 53).

The difference (7%) in Female group between the RGT arm and BOC48 arm is larger than that in Male group (1%).

In study P05216, US subjects counted about 65% (709/1097) of sample size. The SVR rates between two boceprevir arms within US (5% difference) and international (0% difference) subgroups are comparable.

The subgroup analyses for gender, age and geographic region within Cohort 1 and 2 are listed in Table 54 and 55 respectively. The trend in Cohort 1 is similar to the overall. The sample size in Cohort 2 is too small to make any determination.

#### ❖ Study P05101

For study P05101, Black subjects which counted about 12% of sample size were not randomized independent as it in P05216. The SVR rate difference for Non-Black between RGT arm and BOC48 arm is about 10% and is similar to the overall (Table 56). The SVR rate in RGT arm is better than that in the BOC48 arm in Black subgroup which may due to the very small sample size.

In study P05101, US subjects counted about 58% (232/403) of sample size. The SVR rates between two boceprevir arms within US (3% difference) are comparable, while the SVR rate difference within international is 14% (RGT=56%, and BOC48=70%).

The subgroup analyses for gender, age and geographic region within Non-Black and Black are listed in Table 57 and 58 respectively. The trend in Non-Black group is similar to the overall. The sample size in Black is too small to make any determination.

The subgroup analysis results using <25 IU/mL were also listed here in Table 59 and 60 for reference.

**Table 53:** The Summary Subgroup Analyses of SVR<sub>24</sub> (<10 IU/mL) for Study P05216 (FAS)

Efficacy Parameter	PR48	RGT	BOC48
As Randomized and Dosed (FAS)			
N	137/363 (37.7)	233/368 (63.3)	242/366 (66.1)
Race Group			
BLACK	12 / 52 (23.1)	22 / 52 (42.3)	29 / 55 (52.7)
NON-BLACK	125 /311 (40.2)	211 /316 (66.8)	213 /311 (68.5)
AMERICAN INDIAN	. / 1 (0.00)	. / 1 (0.00)	3 / 4 (75.0)
ASIAN	6 / 9 (66.7)	3 / 4 (75.0)	5 / 8 (62.5)
MULTIRACIAL	2 / 5 (40.0)	2 / 5 (40.0)	2 / 4 (50.0)
NATIVE HAWAIIAN	. / . ( . )	2 / 2 ( 100)	. / . ( . )
WHITE	117 /296 (39.5)	204 /304 (67.1)	203 /295 (68.8)
Gender			
F	65 /157 (41.4)	84 /139 (60.4)	97 /145 (66.9)
M	72 /206 (35.0)	149 /229 (65.1)	145 /221 (65.6)
Age Group			
<=40 yr	35 / 67 (52.2)	37 / 51 (72.5)	41 / 59 (69.5)
>40 yr	102 /296 (34.5)	196 /317 (61.8)	201 /307 (65.5)
Region			
EU	44 / 99 (44.4)	54 / 79 (68.4)	56 / 86 (65.1)
LA	4 / 10 (40.0)	10 / 12 (83.3)	8 / 10 (80.0)
NA	89 /254 (35.0)	169 /277 (61.0)	178 /270 (65.9)
Location (US vs. International)			
US	76 /225 (33.8)	153 /245 (62.4)	160 /239 (66.9)
International	61 /138 (44.2)	80 /123 (65.0)	82 /127 (64.6)

**Table 54:** The Summary Subgroup Analyses of SVR<sub>24</sub> (<10 IU/mL) in Cohort 1 for Study P05216 (FAS)

Efficacy Parameter	PR48	RGT	BOC48
Race Group			
NON-BLACK	125 / 311 (40.2)	211 / 316 (66.8)	213 / 311 (68.5)
Gender			
F	62 / 140 (44.3)	77 / 116 (66.4)	86 / 123 (69.9)
M	63 / 171 (36.8)	134 / 200 (67.0)	127 / 188 (67.6)
Age Group			
<=40 yr	30 / 60 (50.0)	36 / 48 (75.0)	38 / 55 (69.1)
>40 yr	95 / 251 (37.8)	175 / 268 (65.3)	175 / 256 (68.4)
Region			
EU	43 / 98 (43.9)	54 / 78 (69.2)	56 / 83 (67.5)
LA	4 / 10 (40.0)	10 / 12 (83.3)	8 / 10 (80.0)
NA	78 / 203 (38.4)	147 / 226 (65.0)	149 / 218 (68.3)
Location (US vs. International)			
US	65 / 174 (37.4)	131 / 195 (67.2)	132 / 188 (70.2)
International	60 / 137 (43.8)	80 / 121 (66.1)	81 / 123 (65.9)

**Table 55:** The Summary Subgroup Analyses of SVR<sub>24</sub> (<10 IU/mL) in Cohort 2 for Study P05216 (FAS)

Efficacy Parameter	PR48	RGT	BOC48
Race Group			
BLACK	12 / 52 (23.1)	22 / 52 (42.3)	29 / 55 (52.7)
Gender			
F	3 / 17 (17.6)	7 / 23 (30.4)	11 / 22 (50.0)
M	9 / 35 (25.7)	15 / 29 (51.7)	18 / 33 (54.5)
Age Group			
<=40 yr	5 / 7 (71.4)	1 / 3 (33.3)	3 / 4 (75.0)
>40 yr	7 / 45 (15.6)	21 / 49 (42.9)	26 / 51 (51.0)
Region			
EU	1 / 1 (100)	. / 1 (0.00)	. / 3 (0.00)
NA	11 / 51 (21.6)	22 / 51 (43.1)	29 / 52 (55.8)
Location (US vs. International)			
US	11 / 51 (21.6)	22 / 50 (44.0)	28 / 51 (54.9)
International	1 / 1 (100)	. / 2 (0.00)	1 / 4 (25.0)

**Table 56:** The Summary Subgroup Analyses of SVR<sub>24</sub> (<10 IU/mL) for Study P05101 (FAS)

Efficacy Parameter	PR48	RGT	BOC48
As Randomized and Dosed (FAS)			
N	17 / 80 (21.3)	95 / 162 (58.6)	107 / 161 (66.5)
Race Group			
BLACK	1 / 12 (8.33)	11 / 18 (61.1)	10 / 19 (52.6)
NON-BLACK	16 / 68 (23.5)	84 / 144 (58.3)	97 / 142 (68.3)
ASIAN	. / . ( . )	. / 1 (0.00)	5 / 5 ( 100)
MULTIRACIAL	. / . ( . )	. / 1 (0.00)	1 / 1 ( 100)
NATIVE HAWAIIAN	. / 1 (0.00)	. / . ( . )	. / 1 (0.00)
WHITE	16 / 67 (23.9)	84 / 142 (59.2)	91 / 135 (67.4)
Gender			
F	4 / 22 (18.2)	36 / 64 (56.3)	32 / 49 (65.3)
M	13 / 58 (22.4)	59 / 98 (60.2)	75 / 112 (67.0)
Age Group			
<=53 yr	8 / 40 (20.0)	53 / 89 (59.6)	52 / 82 (63.4)
>53 yr	9 / 40 (22.5)	42 / 73 (57.5)	55 / 79 (69.6)
Region			
EU	8 / 29 (27.6)	24 / 46 (52.2)	28 / 42 (66.7)
LA	. / . ( . )	. / 1 (0.00)	. / . ( . )
NA	9 / 51 (17.6)	71 / 115 (61.7)	79 / 119 (66.4)
Location (US vs. International)			
US	8 / 43 (18.6)	56 / 92 (60.9)	62 / 97 (63.9)
International	9 / 37 (24.3)	39 / 70 (55.7)	45 / 64 (70.3)

**Table 57:** The Summary Subgroup Analyses of SVR<sub>24</sub> (<10 IU/mL) in Non-Black for Study P05101 (FAS)

Efficacy Parameter	PR48	RGT	BOC48
Race Group			
NON-BLACK	16 / 68 (23.5)	84 / 144 (58.3)	97 / 142 (68.3)
Gender			
F	4 / 19 (21.1)	32 / 56 (57.1)	27 / 39 (69.2)
M	12 / 49 (24.5)	52 / 88 (59.1)	70 / 103 (68.0)
Age Group			
<=53 yr	7 / 36 (19.4)	49 / 82 (59.8)	48 / 72 (66.7)
>53 yr	9 / 32 (28.1)	35 / 62 (56.5)	49 / 70 (70.0)
Region			
EU	8 / 29 (27.6)	24 / 46 (52.2)	27 / 40 (67.5)
LA	. / . ( . )	. / 1 (0.00)	. / . ( . )
NA	8 / 39 (20.5)	60 / 97 (61.9)	70 / 102 (68.6)

Location (US vs. International)			
US	7 / 31 (22.6)	45 / 74 (60.8)	53 / 80 (66.3)
International	9 / 37 (24.3)	39 / 70 (55.7)	44 / 62 (71.0)

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**Table 58:** The Summary Subgroup Analyses of SVR<sub>24</sub> (<10 IU/mL) in Black for Study P05101 (FAS)

Efficacy Parameter	PR48	RGT	BOC48
Race Group			
BLACK	1 / 12 (8.33)	11 / 18 (61.1)	10 / 19 (52.6)
Gender			
F	. / 3 (0.00)	4 / 8 (50.0)	5 / 10 (50.0)
M	1 / 9 (11.1)	7 / 10 (70.0)	5 / 9 (55.6)
Age Group			
<=53 yr	1 / 4 (25.0)	4 / 7 (57.1)	4 / 10 (40.0)
>53 yr	. / 8 (0.00)	7 / 11 (63.6)	6 / 9 (66.7)
Region			
EU	. / . ( . )	. / . ( . )	1 / 2 (50.0)
NA	1 / 12 (8.33)	11 / 18 (61.1)	9 / 17 (52.9)
Location (US vs. International)			
US	1 / 12 (8.33)	11 / 18 (61.1)	9 / 17 (52.9)
International	. / . ( . )	. / . ( . )	1 / 2 (50.0)

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**Table 59:** The Summary Subgroup Analyses of SVR<sub>24</sub> (<25 IU/mL) for Study P05216 (FAS)

Efficacy Parameter	PR48	RGT	BOC48
As Randomized and Dosed (FAS)			
N	138/363 (38.0)	233/368 (63.3)	242/366 (66.1)
Race Group			
BLACK	12 / 52 (23.1)	22 / 52 (42.3)	29 / 55 (52.7)
NON-BLACK	126 /311 (40.5)	211 /316 (66.8)	213 /311 (68.5)
AMERICAN INDIAN	. / 1 (0.00)	. / 1 (0.00)	3 / 4 (75.0)
ASIAN	6 / 9 (66.7)	3 / 4 (75.0)	5 / 8 (62.5)
MULTIRACIAL	2 / 5 (40.0)	2 / 5 (40.0)	2 / 4 (50.0)
NATIVE HAWAIIAN	. / . ( . )	2 / 2 ( 100)	. / . ( . )
WHITE	118 /296 (39.9)	204 /304 (67.1)	203 /295 (68.8)
Gender			
F	65 /157 (41.4)	84 /139 (60.4)	97 /145 (66.9)
M	73 /206 (35.4)	149 /229 (65.1)	145 /221 (65.6)
Age Group			

<=40 yr	35 / 67 (52.2)	37 / 51 (72.5)	41 / 59 (69.5)
>40 yr	103 / 296 (34.8)	196 / 317 (61.8)	201 / 307 (65.5)
Region			
EU	44 / 99 (44.4)	54 / 79 (68.4)	56 / 86 (65.1)
LA	4 / 10 (40.0)	10 / 12 (83.3)	8 / 10 (80.0)
NA	90 / 254 (35.4)	169 / 277 (61.0)	178 / 270 (65.9)
Location (US vs. International)			
US	77 / 225 (34.2)	153 / 245 (62.4)	160 / 239 (66.9)
International	61 / 138 (44.2)	80 / 123 (65.0)	82 / 127 (64.6)
-----			
Non-Black Subjects only			
-----			
Race Group			
NON-BLACK	126 / 311 (40.5)	211 / 316 (66.8)	213 / 311 (68.5)
Gender			
F	62 / 140 (44.3)	77 / 116 (66.4)	86 / 123 (69.9)
M	64 / 171 (37.4)	134 / 200 (67.0)	127 / 188 (67.6)
Age Group			
<=40 yr	30 / 60 (50.0)	36 / 48 (75.0)	38 / 55 (69.1)
>40 yr	96 / 251 (38.2)	175 / 268 (65.3)	175 / 256 (68.4)
Region			
EU	43 / 98 (43.9)	54 / 78 (69.2)	56 / 83 (67.5)
LA	4 / 10 (40.0)	10 / 12 (83.3)	8 / 10 (80.0)
NA	79 / 203 (38.9)	147 / 226 (65.0)	149 / 218 (68.3)
Location (US vs. International)			
US	66 / 174 (37.9)	131 / 195 (67.2)	132 / 188 (70.2)
International	60 / 137 (43.8)	80 / 121 (66.1)	81 / 123 (65.9)
-----			
Black Subjects only			
-----			
Race			
BLACK OR AFRICA	12 / 52 (23.1)	22 / 52 (42.3)	29 / 55 (52.7)
Gender			
F	3 / 17 (17.6)	7 / 23 (30.4)	11 / 22 (50.0)
M	9 / 35 (25.7)	15 / 29 (51.7)	18 / 33 (54.5)
Age Group			
<=40 yr	5 / 7 (71.4)	1 / 3 (33.3)	3 / 4 (75.0)
>40 yr	7 / 45 (15.6)	21 / 49 (42.9)	26 / 51 (51.0)
Region			
EU	1 / 1 ( 100)	. / 1 (0.00)	. / 3 (0.00)
NA	11 / 51 (21.6)	22 / 51 (43.1)	29 / 52 (55.8)
Location (US vs. International)			
US	11 / 51 (21.6)	22 / 50 (44.0)	28 / 51 (54.9)
International	1 / 1 ( 100)	. / 2 (0.00)	1 / 4 (25.0)
-----			

**Table 60:** The Summary Subgroup Analyses of SVR<sub>24</sub> (<25 IU/mL) for Study P05101 (FAS)

Efficacy Parameter	PR48	RGT	BOC48
As Randomized and Dosed (FAS)			
N	18 / 80 (22.5)	96 / 162 (59.3)	107 / 161 (66.5)
Race Group			
BLACK	1 / 12 (8.33)	11 / 18 (61.1)	10 / 19 (52.6)
NON-BLACK	17 / 68 (25.0)	85 / 144 (59.0)	97 / 142 (68.3)
ASIAN	. / . ( . )	. / 1 (0.00)	5 / 5 ( 100)
MULTIRACIAL	. / . ( . )	. / 1 (0.00)	1 / 1 ( 100)
NATIVE HAWAIIAN	. / 1 (0.00)	. / . ( . )	. / 1 (0.00)
WHITE	17 / 67 (25.4)	85 / 142 (59.9)	91 / 135 (67.4)
Gender			
F	4 / 22 (18.2)	37 / 64 (57.8)	32 / 49 (65.3)
M	14 / 58 (24.1)	59 / 98 (60.2)	75 / 112 (67.0)
Age Group			
<=53 yr	8 / 40 (20.0)	54 / 89 (60.7)	52 / 82 (63.4)
>53 yr	10 / 40 (25.0)	42 / 73 (57.5)	55 / 79 (69.6)
Region			
EU	8 / 29 (27.6)	24 / 46 (52.2)	28 / 42 (66.7)
LA	. / . ( . )	. / 1 (0.00)	. / . ( . )
NA	10 / 51 (19.6)	72 / 115 (62.6)	79 / 119 (66.4)
Location (US vs. International)			
US	9 / 43 (20.9)	56 / 92 (60.9)	62 / 97 (63.9)
International	9 / 37 (24.3)	40 / 70 (57.1)	45 / 64 (70.3)
Non-Black Subjects only			
Race Group			
NON-BLACK	17 / 68 (25.0)	85 / 144 (59.0)	97 / 142 (68.3)
Gender			
F	4 / 19 (21.1)	33 / 56 (58.9)	27 / 39 (69.2)
M	13 / 49 (26.5)	52 / 88 (59.1)	70 / 103 (68.0)
Age Group			
<=53 yr	7 / 36 (19.4)	50 / 82 (61.0)	48 / 72 (66.7)
>53 yr	10 / 32 (31.3)	35 / 62 (56.5)	49 / 70 (70.0)
Region			
EU	8 / 29 (27.6)	24 / 46 (52.2)	27 / 40 (67.5)
LA	. / . ( . )	. / 1 (0.00)	. / . ( . )
NA	9 / 39 (23.1)	61 / 97 (62.9)	70 / 102 (68.6)
Location (US vs. International)			
US	8 / 31 (25.8)	45 / 74 (60.8)	53 / 80 (66.3)
International	9 / 37 (24.3)	40 / 70 (57.1)	44 / 62 (71.0)
Black Subjects only			

-----			
Race Group			
BLACK	1 / 12 (8.33)	11 / 18 (61.1)	10 / 19 (52.6)
Gender			
F	. / 3 (0.00)	4 / 8 (50.0)	5 / 10 (50.0)
M	1 / 9 (11.1)	7 / 10 (70.0)	5 / 9 (55.6)
Age Group			
<=53 yr	1 / 4 (25.0)	4 / 7 (57.1)	4 / 10 (40.0)
>53 yr	. / 8 (0.00)	7 / 11 (63.6)	6 / 9 (66.7)
Region			
EU	. / . ( . )	. / . ( . )	1 / 2 (50.0)
NA	1 / 12 (8.33)	11 / 18 (61.1)	9 / 17 (52.9)
Location (US vs. International)			
US	1 / 12 (8.33)	11 / 18 (61.1)	9 / 17 (52.9)
International	. / . ( . )	. / . ( . )	1 / 2 (50.0)
-----			

## 4.2 Other Special/Subgroup Populations

The subgroup analysis for some baseline covariates and some important variables available during the course of the trial will be presented below for two studies separately.

### 4.2.1 Other Baseline Covariates

In both studies, SVR was higher in subjects with baseline HCV RNA  $\leq$  800,000 IU/mL than in those with baseline HCV RNA  $>$  800,000 IU/mL, in subjects with HCV genotype 1 subtype 1b than in those with genotype 1 subtype 1a, in subjects with a baseline platelet count  $\geq$  150,000/ $\mu$ L than those with platelet count  $<$ 150,000/ $\mu$ L, in subjects with a lower Metavir fibrosis score (0, 1, and 2 combined) than in those with higher Metavir fibrosis (3 or 4 combined), and in subjects without cirrhosis at baseline than in those with cirrhosis (Table 61 and 62).

The interaction test for baseline viral load ( $\leq$  and  $>$ 800,000) between Arm 2 and Arm 3 is not significant for both studies. For baseline cirrhosis, there may be a slight indication of the interaction of status of cirrhosis and treatment group (Arm 2 or 3) in study P05101, but it is not able to determine since the number of subjects having cirrhosis at baseline are very small.

For study P05101, previous relapsers (or called some negative) had higher SVR rates in both boceprevir arms than non-responders (or called never negative), and subjects who previously took Peg2A in its previous HCV treatment is about 47% (189/403) in total FAS population, and

they seems had a little bit lower SVR rates for both boceprevir arms than those who took Peg2B in their previous HCV treatment.

The subgroup analysis results in Cohort 1 and 2 in study P05216 using <10 IU/mL were listed here in Table 63 and 64, and the subgroup analysis results using <25 IU/mL for both P05216 and P05101 were listed here in Table 65 and 66 for reference.

**Table 61:** The Baseline Covariates Subgroup Analyses of SVR24 (<10 IU/mL) for Study P05216 (FAS)

Efficacy Parameter	PR48	RGT	BOC48
As Randomized and Dosed (FAS)			
N	137/363 (37.7)	233/368 (63.3)	242/366 (66.1)
Weight Group			
<75 Kg	67 /146 (45.9)	82 /131 (62.6)	83 /131 (63.4)
>=75 Kg	70 /217 (32.3)	151 /237 (63.7)	159 /235 (67.7)
BMI			
25-30	49 /148 (33.1)	129 /173 (74.6)	90 /138 (65.2)
<=25	60 /129 (46.5)	59 /101 (58.4)	83 /123 (67.5)
>30	28 / 86 (32.6)	45 / 94 (47.9)	69 /105 (65.7)
Baseline Platelets Count			
<150,000/uL	8 / 27 (29.6)	18 / 33 (54.5)	20 / 38 (52.6)
>=150,000/uL	129 /336 (38.4)	215 /335 (64.2)	222 /328 (67.7)
Baseline ALT Status			
Elevated at BSL	98 /269 (36.4)	187 /293 (63.8)	192 /281 (68.3)
Normal at BSL	39 / 94 (41.5)	46 / 75 (61.3)	50 / 85 (58.8)
Baseline HCV Viral Category (IU/mL)			
<=400,000	21 / 26 (80.8)	25 / 32 (78.1)	22 / 25 (88.0)
>400,000	116 /337 (34.4)	208 /336 (61.9)	220 /341 (64.5)
Baseline HCV Viral Category (IU/mL)			
<=800,000	35 / 55 (63.6)	41 / 54 (75.9)	45 / 53 (84.9)
>800,000	102 /308 (33.1)	192 /314 (61.1)	197 /313 (62.9)
Baseline Statin Use			
N	134 /360 (37.2)	227 /359 (63.2)	236 /359 (65.7)
Y	3 / 3 ( 100)	6 / 9 (66.7)	6 / 7 (85.7)
Baseline Steatosis Score			
.	5 / 11 (45.5)	6 / 15 (40.0)	9 / 11 (81.8)
0	57 /128 (44.5)	75 /107 (70.1)	70 /108 (64.8)
1	59 /170 (34.7)	123 /187 (65.8)	125 /190 (65.8)
2	15 / 50 (30.0)	26 / 53 (49.1)	37 / 54 (68.5)
3	1 / 4 (25.0)	3 / 6 (50.0)	1 / 3 (33.3)

Baseline Steatosis Score Group				
=0	57 /128 (44.5)	75 /107 (70.1)	70 /108 (64.8)	
>0	75 /224 (33.5)	152 /246 (61.8)	163 /247 (66.0)	
Metavir Fibrosis Score				
.	5 / 11 (45.5)	6 / 15 (40.0)	9 / 11 (81.8)	
0	8 / 17 (47.1)	17 / 20 (85.0)	6 / 10 (60.0)	
1	96 /246 (39.0)	159 /238 (66.8)	166 /246 (67.5)	
2	19 / 65 (29.2)	37 / 61 (60.7)	39 / 57 (68.4)	
3	3 / 11 (27.3)	9 / 18 (50.0)	12 / 18 (66.7)	
4	6 / 13 (46.2)	5 / 16 (31.3)	10 / 24 (41.7)	
Metavir Fibrosis Score Group				
0/1/2	123 /328 (37.5)	213 /319 (66.8)	211 /313 (67.4)	
3/4	9 / 24 (37.5)	14 / 34 (41.2)	22 / 42 (52.4)	
Liver Cirrhosis at Baseline				
N	126 /339 (37.2)	222 /337 (65.9)	223 /331 (67.4)	
Y	6 / 13 (46.2)	5 / 16 (31.3)	10 / 24 (41.7)	
Opioid Replacement Therapy				
N	137 /362 (37.8)	231 /365 (63.3)	239 /358 (66.8)	
Y	. / 1 (0.00)	2 / 3 (66.7)	3 / 8 (37.5)	
HCV-1 Subtype (b) (4)				
1	25 / 60 (41.7)	39 / 55 (70.9)	29 / 42 (69.0)	
1a	61 /177 (34.5)	109 /182 (59.9)	119 /188 (63.3)	
1b	51 /126 (40.5)	85 /131 (64.9)	94 /136 (69.1)	
HCV-1 Subtype (b) (4)				
1	24 / 60 (40.0)	38 / 55 (69.1)	31 / 46 (67.4)	
1a	62 /177 (35.0)	106 /179 (59.2)	118 /187 (63.1)	
1b	51 /126 (40.5)	89 /134 (66.4)	93 /133 (69.9)	
HCV-1 Subtype (b) (4)				
1a	78 /228 (34.2)	139 /234 (59.4)	147 /237 (62.0)	
1b	48 /121 (39.7)	88 /124 (71.0)	85 /117 (72.6)	
6e	. / . ( . )	1 / 1 ( 100)	. / . ( . )	
6h	1 / 1 ( 100)	. / . ( . )	. / . ( . )	
6n	1 / 1 ( 100)	. / . ( . )	1 / 1 ( 100)	

**Table 62:** The Baseline Covariates Subgroup Analyses of SVR24 (<10 IU/mL) for Study P05101 (FAS)

Efficacy Parameter	PR48	RGT	BOC48
As Randomized and Dosed (FAS)			
N	17/ 80 (21.3)	95/162 (58.6)	107/161 (66.5)
Weight Group			
<75 Kg	4 / 17 (23.5)	20 / 42 (47.6)	34 / 44 (77.3)
>=75 K	13 / 63 (20.6)	75 /120 (62.5)	73 /117 (62.4)

BMI			
25-30	11 / 42 (26.2)	41 / 68 (60.3)	44 / 66 (66.7)
<=25	4 / 20 (20.0)	21 / 35 (60.0)	30 / 44 (68.2)
>30	2 / 18 (11.1)	33 / 59 (55.9)	33 / 51 (64.7)
Baseline Platelets Count			
<=150,000/ul	2 / 10 (20.0)	8 / 21 (38.1)	13 / 19 (68.4)
150,000-200,000	4 / 16 (25.0)	20 / 37 (54.1)	27 / 45 (60.0)
>200,000/ul	11 / 54 (20.4)	67 /104 (64.4)	67 / 97 (69.1)
Baseline ALT Status			
Elevated at BSL	9 / 55 (16.4)	58 /109 (53.2)	77 /115 (67.0)
Normal at BSL	8 / 25 (32.0)	37 / 53 (69.8)	30 / 46 (65.2)
Baseline HCV Viral Category (IU/mL)			
<=400,000	3 / 6 (50.0)	7 / 7 ( 100)	5 / 7 (71.4)
>400,000	14 / 74 (18.9)	88 /155 (56.8)	102 /154 (66.2)
Baseline HCV Viral Category (IU/mL)			
<=800,000	6 / 15 (40.0)	12 / 15 (80.0)	16 / 20 (80.0)
>800,000	11 / 65 (16.9)	83 /147 (56.5)	91 /141 (64.5)
Baseline Statin Use			
N	16 / 76 (21.1)	88 /154 (57.1)	105 /159 (66.0)
Y	1 / 4 (25.0)	7 / 8 (87.5)	2 / 2 ( 100)
Baseline Steatosis Score			
.	1 / 4 (25.0)	4 / 13 (30.8)	5 / 11 (45.5)
0	5 / 23 (21.7)	24 / 36 (66.7)	31 / 45 (68.9)
1	10 / 39 (25.6)	48 / 81 (59.3)	54 / 74 (73.0)
2	1 / 12 (8.33)	17 / 25 (68.0)	16 / 30 (53.3)
3	. / 1 (0.00)	2 / 7 (28.6)	1 / 1 ( 100)
4	. / 1 (0.00)	. / . ( . )	. / . ( . )
Baseline Steatosis Score Group			
=0	5 / 23 (21.7)	24 / 36 (66.7)	31 / 45 (68.9)
>0	11 / 53 (20.8)	67 /113 (59.3)	71 /105 (67.6)
Metavir Fibrosis Score			
.	1 / 4 (25.0)	4 / 13 (30.8)	5 / 11 (45.5)
0	3 / 5 (60.0)	6 / 8 (75.0)	3 / 5 (60.0)
1	9 / 43 (20.9)	52 / 79 (65.8)	55 / 78 (70.5)
2	2 / 13 (15.4)	19 / 30 (63.3)	23 / 36 (63.9)
3	2 / 5 (40.0)	8 / 15 (53.3)	4 / 9 (44.4)
4	. / 10 (0.00)	6 / 17 (35.3)	17 / 22 (77.3)
Metavir Fibrosis Score Group			
0/1/2	14 / 61 (23.0)	77 /117 (65.8)	81 /119 (68.1)
3/4	2 / 15 (13.3)	14 / 32 (43.8)	21 / 31 (67.7)
Liver Cirrhosis at Baseline			
N	16 / 66 (24.2)	85 /132 (64.4)	85 /128 (66.4)
Y	. / 10 (0.00)	6 / 17 (35.3)	17 / 22 (77.3)
Opioid Replacement Therapy			
N	17 / 80 (21.3)	94 /161 (58.4)	103 /157 (65.6)
Y	. / . ( . )	1 / 1 ( 100)	4 / 4 ( 100)

HCV-1 Subtype	(b) (4)			
1		. / 5 (0.00)	10 / 14 (71.4)	8 / 14 (57.1)
1a		8 / 38 (21.1)	37 / 74 (50.0)	48 / 77 (62.3)
1b		9 / 37 (24.3)	48 / 74 (64.9)	51 / 70 (72.9)
HCV-1 Subtype	(b) (4)			
1		. / 6 (0.00)	9 / 13 (69.2)	11 / 17 (64.7)
1a		9 / 38 (23.7)	37 / 74 (50.0)	47 / 77 (61.0)
1b		8 / 36 (22.2)	49 / 75 (65.3)	49 / 67 (73.1)
HCV-1 Subtype	(b) (4)			
1a		11 / 46 (23.9)	51 / 96 (53.1)	62 / 97 (63.9)
1b		6 / 34 (17.6)	44 / 66 (66.7)	43 / 61 (70.5)
6l		. / . ( . )	. / . ( . )	1 / 1 ( 100)
Previous Peg Treatment Type				
PEG2A		10 / 42 (23.8)	44 / 79 (55.7)	42 / 68 (61.8)
PEG2B		7 / 38 (18.4)	51 / 83 (61.4)	65 / 93 (69.9)
Previous Trt Response	(b) (4)			
Never Negative		3 / 30 (10.0)	24 / 59 (40.7)	31 / 59 (52.5)
Some Negative		14 / 50 (28.0)	71 / 103 (68.9)	76 / 102 (74.5)
Previous Trt Response (CRF)				
NON-RESPONDER		4 / 41 (9.76)	31 / 75 (41.3)	38 / 72 (52.8)
RELAPSER		13 / 39 (33.3)	64 / 86 (74.4)	69 / 89 (77.5)
Previous Trt Response (Combined)				
Never Negative		2 / 29 (6.90)	23 / 57 (40.4)	30 / 58 (51.7)
Some Negative		15 / 51 (29.4)	72 / 105 (68.6)	77 / 103 (74.8)

**Table 63:** The Baseline Covariates Subgroup Analyses of SVR24 (<10 IU/mL) in Cohort 1 for Study P05216 (FAS)

Efficacy Parameter	PR48	RGT	BOC48
As Randomized and Dosed (FAS)			
N	125/311 (40.2)	211/316 (66.8)	213/311 (68.5)
Weight Group			
<75 Kg	65 /137 (47.4)	78 /120 (65.0)	79 /121 (65.3)
>=75 K	60 /174 (34.5)	133 /196 (67.9)	134 /190 (70.5)
BMI			
25-30	44 /121 (36.4)	113 /152 (74.3)	81 /120 (67.5)
<=25	56 /121 (46.3)	56 / 92 (60.9)	80 /116 (69.0)
>30	25 / 69 (36.2)	42 / 72 (58.3)	52 / 75 (69.3)
Baseline Platelets Count			
<150,000/ul	8 / 25 (32.0)	16 / 30 (53.3)	17 / 34 (50.0)
>=150,000/ul	117 /286 (40.9)	195 /286 (68.2)	196 /277 (70.8)

Baseline ALT Status				
Elevated at BSL	93 / 233 (39.9)	166 / 252 (65.9)	175 / 247 (70.9)	
Normal at BSL	32 / 78 (41.0)	45 / 64 (70.3)	38 / 64 (59.4)	
Baseline HCV Viral Category (IU/mL)				
<=400,000	21 / 26 (80.8)	23 / 29 (79.3)	20 / 23 (87.0)	
>400,000	104 / 285 (36.5)	188 / 287 (65.5)	193 / 288 (67.0)	
Baseline HCV Viral Category (IU/mL)				
<=800,000	33 / 53 (62.3)	37 / 48 (77.1)	42 / 49 (85.7)	
>800,000	92 / 258 (35.7)	174 / 268 (64.9)	171 / 262 (65.3)	
Baseline Statin Use				
N	123 / 309 (39.8)	206 / 308 (66.9)	210 / 308 (68.2)	
Y	2 / 2 (100)	5 / 8 (62.5)	3 / 3 (100)	
Baseline Steatosis Score				
.	5 / 11 (45.5)	4 / 11 (36.4)	9 / 10 (90.0)	
0	51 / 108 (47.2)	68 / 92 (73.9)	66 / 93 (71.0)	
1	53 / 144 (36.8)	113 / 161 (70.2)	105 / 158 (66.5)	
2	15 / 45 (33.3)	23 / 47 (48.9)	32 / 47 (68.1)	
3	1 / 3 (33.3)	3 / 5 (60.0)	1 / 3 (33.3)	
Baseline Steatosis Score Group				
=0	51 / 108 (47.2)	68 / 92 (73.9)	66 / 93 (71.0)	
>0	69 / 192 (35.9)	139 / 213 (65.3)	138 / 208 (66.3)	
Metavir Fibrosis Score				
.	5 / 11 (45.5)	4 / 11 (36.4)	9 / 10 (90.0)	
0	8 / 16 (50.0)	15 / 17 (88.2)	5 / 9 (55.6)	
1	84 / 206 (40.8)	147 / 212 (69.3)	147 / 208 (70.7)	
2	19 / 55 (34.5)	32 / 50 (64.0)	34 / 48 (70.8)	
3	3 / 10 (30.0)	8 / 13 (61.5)	9 / 14 (64.3)	
4	6 / 13 (46.2)	5 / 13 (38.5)	9 / 22 (40.9)	
Metavir Fibrosis Score Group				
0/1/2	111 / 277 (40.1)	194 / 279 (69.5)	186 / 265 (70.2)	
3/4	9 / 23 (39.1)	13 / 26 (50.0)	18 / 36 (50.0)	
Liver Cirrhosis at Baseline				
N	114 / 287 (39.7)	202 / 292 (69.2)	195 / 279 (69.9)	
Y	6 / 13 (46.2)	5 / 13 (38.5)	9 / 22 (40.9)	
Opioid Replacement Therapy				
N	125 / 310 (40.3)	209 / 313 (66.8)	210 / 305 (68.9)	
Y	. / 1 (0.00)	2 / 3 (66.7)	3 / 6 (50.0)	
HCV-1 Subtype (b) (4)				
1	24 / 52 (46.2)	38 / 52 (73.1)	28 / 37 (75.7)	
1a	53 / 145 (36.6)	94 / 146 (64.4)	102 / 154 (66.2)	
1b	48 / 114 (42.1)	79 / 118 (66.9)	83 / 120 (69.2)	
HCV-1 Subtype (b) (4)				
1	23 / 53 (43.4)	37 / 52 (71.2)	30 / 41 (73.2)	
1a	54 / 144 (37.5)	91 / 144 (63.2)	101 / 153 (66.0)	

1b	48 /114 (42.1)	83 /120 (69.2)	82 /117 (70.1)
HCV-1 Subtype ( (b) (4) )			
1a	69 /187 (36.9)	123 /195 (63.1)	130 /197 (66.0)
1b	46 /112 (41.1)	82 /111 (73.9)	74 /104 (71.2)
6e	. / . ( . )	1 / 1 ( 100)	. / . ( . )
6h	1 / 1 ( 100)	. / . ( . )	. / . ( . )
6n	1 / 1 ( 100)	. / . ( . )	1 / 1 ( 100)

**Table 64:** The Baseline Covariates Subgroup Analyses of SVR24 (<10 IU/mL) in Cohort 2 for Study P05216 (FAS)

Efficacy Parameter	PR48	RGT	BOC48
As Randomized and Dosed (FAS)			
N	12/ 52 (23.1)	22/ 52 (42.3)	29/ 55 (52.7)
Weight Group			
<75 Kg	2 / 9 (22.2)	4 / 11 (36.4)	4 / 10 (40.0)
>=75 K	10 / 43 (23.3)	18 / 41 (43.9)	25 / 45 (55.6)
BMI			
25-30	5 / 27 (18.5)	16 / 21 (76.2)	9 / 18 (50.0)
<=25	4 / 8 (50.0)	3 / 9 (33.3)	3 / 7 (42.9)
>30	3 / 17 (17.6)	3 / 22 (13.6)	17 / 30 (56.7)
Baseline Platelets Count			
<150,000/ul	. / 2 (0.00)	2 / 3 (66.7)	3 / 4 (75.0)
>=150,000/ul	12 / 50 (24.0)	20 / 49 (40.8)	26 / 51 (51.0)
Baseline ALT Status			
Elevated at BSL	5 / 36 (13.9)	21 / 41 (51.2)	17 / 34 (50.0)
Normal at BSL	7 / 16 (43.8)	1 / 11 (9.09)	12 / 21 (57.1)
Baseline HCV Viral Category (IU/mL)			
<=400,000	. / . ( . )	2 / 3 (66.7)	2 / 2 ( 100)
>400,000	12 / 52 (23.1)	20 / 49 (40.8)	27 / 53 (50.9)
Baseline HCV Viral Category (IU/mL)			
<=800,000	2 / 2 ( 100)	4 / 6 (66.7)	3 / 4 (75.0)
>800,000	10 / 50 (20.0)	18 / 46 (39.1)	26 / 51 (51.0)
Baseline Statin Use			
N	11 / 51 (21.6)	21 / 51 (41.2)	26 / 51 (51.0)
Y	1 / 1 ( 100)	1 / 1 ( 100)	3 / 4 (75.0)
Baseline Steatosis Score			
.	. / . ( . )	2 / 4 (50.0)	. / 1 (0.00)
0	6 / 20 (30.0)	7 / 15 (46.7)	4 / 15 (26.7)
1	6 / 26 (23.1)	10 / 26 (38.5)	20 / 32 (62.5)
2	. / 5 (0.00)	3 / 6 (50.0)	5 / 7 (71.4)
3	. / 1 (0.00)	. / 1 (0.00)	. / . ( . )
Baseline Steatosis Score Group			

=0	6 / 20 (30.0)	7 / 15 (46.7)	4 / 15 (26.7)
>0	6 / 32 (18.8)	13 / 33 (39.4)	25 / 39 (64.1)
Metavir Fibrosis Score			
.	. / . ( . )	2 / 4 (50.0)	. / 1 (0.00)
0	. / 1 (0.00)	2 / 3 (66.7)	1 / 1 ( 100)
1	12 / 40 (30.0)	12 / 26 (46.2)	19 / 38 (50.0)
2	. / 10 (0.00)	5 / 11 (45.5)	5 / 9 (55.6)
3	. / 1 (0.00)	1 / 5 (20.0)	3 / 4 (75.0)
4	. / . ( . )	. / 3 (0.00)	1 / 2 (50.0)
Metavir Fibrosis Score Group			
0/1/2	12 / 51 (23.5)	19 / 40 (47.5)	25 / 48 (52.1)
3/4	. / 1 (0.00)	1 / 8 (12.5)	4 / 6 (66.7)
Liver Cirrhosis at Baseline			
N	12 / 52 (23.1)	20 / 45 (44.4)	28 / 52 (53.8)
Y	. / . ( . )	. / 3 (0.00)	1 / 2 (50.0)
Opioid Replacement Therapy			
N	12 / 52 (23.1)	22 / 52 (42.3)	29 / 53 (54.7)
Y	. / . ( . )	. / . ( . )	. / 2 (0.00)
HCV-1 Subtype (b) (4)			
1	1 / 8 (12.5)	1 / 3 (33.3)	1 / 5 (20.0)
1a	8 / 32 (25.0)	15 / 36 (41.7)	17 / 34 (50.0)
1b	3 / 12 (25.0)	6 / 13 (46.2)	11 / 16 (68.8)
HCV-1 Subtype (b) (4)			
1	1 / 7 (14.3)	1 / 3 (33.3)	1 / 5 (20.0)
1a	8 / 33 (24.2)	15 / 35 (42.9)	17 / 34 (50.0)
1b	3 / 12 (25.0)	6 / 14 (42.9)	11 / 16 (68.8)
HCV-1 Subtype (b) (4)			
1a	9 / 41 (22.0)	16 / 39 (41.0)	17 / 40 (42.5)
1b	2 / 9 (22.2)	6 / 13 (46.2)	11 / 13 (84.6)

**Table 65:** The Baseline Covariates Subgroup Analyses of SVR24 (<25 IU/mL) for Study P05216 (FAS)

Efficacy Parameter	PR48	RGT	BOC48
As Randomized and Dosed (FAS)			
N	138/363 (38.0)	233/368 (63.3)	242/366 (66.1)
Weight Group			
<75 Kg	67 /146 (45.9)	82 /131 (62.6)	83 /131 (63.4)
>=75 K	71 /217 (32.7)	151 /237 (63.7)	159 /235 (67.7)

BMI				
25-30	49 /148 (33.1)	129 /173 (74.6)	90 /138 (65.2)	
<=25	60 /129 (46.5)	59 /101 (58.4)	83 /123 (67.5)	
>30	29 / 86 (33.7)	45 / 94 (47.9)	69 /105 (65.7)	
Baseline Platelets Count				
<150,000/ul	9 / 27 (33.3)	18 / 33 (54.5)	20 / 38 (52.6)	
>=150,000/ul	129 /336 (38.4)	215 /335 (64.2)	222 /328 (67.7)	
Baseline ALT Status				
Elevated at BSL	99 /269 (36.8)	187 /293 (63.8)	192 /281 (68.3)	
Normal at BSL	39 / 94 (41.5)	46 / 75 (61.3)	50 / 85 (58.8)	
Baseline HCV Viral Category (IU/mL)				
<=400,000	21 / 26 (80.8)	25 / 32 (78.1)	22 / 25 (88.0)	
>400,000	117 /337 (34.7)	208 /336 (61.9)	220 /341 (64.5)	
Baseline HCV Viral Category (IU/mL)				
<=800,000	36 / 55 (65.5)	41 / 54 (75.9)	45 / 53 (84.9)	
>800,000	102 /308 (33.1)	192 /314 (61.1)	197 /313 (62.9)	
Baseline Statin Use				
N	135 /360 (37.5)	227 /359 (63.2)	236 /359 (65.7)	
Y	3 / 3 ( 100)	6 / 9 (66.7)	6 / 7 (85.7)	
Baseline Steatosis Score				
.	5 / 11 (45.5)	6 / 15 (40.0)	9 / 11 (81.8)	
0	57 /128 (44.5)	75 /107 (70.1)	70 /108 (64.8)	
1	59 /170 (34.7)	123 /187 (65.8)	125 /190 (65.8)	
2	16 / 50 (32.0)	26 / 53 (49.1)	37 / 54 (68.5)	
3	1 / 4 (25.0)	3 / 6 (50.0)	1 / 3 (33.3)	
Baseline Steatosis Score Group				
=0	57 /128 (44.5)	75 /107 (70.1)	70 /108 (64.8)	
>0	76 /224 (33.9)	152 /246 (61.8)	163 /247 (66.0)	
Metavir Fibrosis Score				
.	5 / 11 (45.5)	6 / 15 (40.0)	9 / 11 (81.8)	
0	8 / 17 (47.1)	17 / 20 (85.0)	6 / 10 (60.0)	
1	96 /246 (39.0)	159 /238 (66.8)	166 /246 (67.5)	
2	20 / 65 (30.8)	37 / 61 (60.7)	39 / 57 (68.4)	
3	3 / 11 (27.3)	9 / 18 (50.0)	12 / 18 (66.7)	
4	6 / 13 (46.2)	5 / 16 (31.3)	10 / 24 (41.7)	
Metavir Fibrosis Score Group				
0/1/2	124 /328 (37.8)	213 /319 (66.8)	211 /313 (67.4)	
3/4	9 / 24 (37.5)	14 / 34 (41.2)	22 / 42 (52.4)	
Liver Cirrhosis at Baseline				
N	127 /339 (37.5)	222 /337 (65.9)	223 /331 (67.4)	
Y	6 / 13 (46.2)	5 / 16 (31.3)	10 / 24 (41.7)	
Opioid Replacement Therapy				
N	138 /362 (38.1)	231 /365 (63.3)	239 /358 (66.8)	
Y	. / 1 (0.00)	2 / 3 (66.7)	3 / 8 (37.5)	

HCV-1 Subtype	(b) (4)			
1		25 / 60 (41.7)	39 / 55 (70.9)	29 / 42 (69.0)
1a		62 /177 (35.0)	109 /182 (59.9)	119 /188 (63.3)
1b		51 /126 (40.5)	85 /131 (64.9)	94 /136 (69.1)
HCV-1 Subtype	(b) (4)			
1		24 / 60 (40.0)	38 / 55 (69.1)	31 / 46 (67.4)
1a		63 /177 (35.6)	106 /179 (59.2)	118 /187 (63.1)
1b		51 /126 (40.5)	89 /134 (66.4)	93 /133 (69.9)
HCV-1 Subtype	(b) (4)			
1a		79 /228 (34.6)	139 /234 (59.4)	147 /237 (62.0)
1b		48 /121 (39.7)	88 /124 (71.0)	85 /117 (72.6)
6e		. / . ( . )	1 / 1 ( 100)	. / . ( . )
6h		1 / 1 ( 100)	. / . ( . )	. / . ( . )
6n		1 / 1 ( 100)	. / . ( . )	1 / 1 ( 100)

**Table 66: The Baseline Covariates Subgroup Analyses of SVR24 (<25 IU/mL) for Study P05101 (FAS)**

Efficacy Parameter	PR48	RGT	BOC48
As Randomized and Dosed (FAS)			
N	18/ 80 (22.5)	96/162 (59.3)	107/161 (66.5)
Weight Group			
<75 Kg	4 / 17 (23.5)	21 / 42 (50.0)	34 / 44 (77.3)
>=75 K	14 / 63 (22.2)	75 /120 (62.5)	73 /117 (62.4)
BMI			
25-30	11 / 42 (26.2)	42 / 68 (61.8)	44 / 66 (66.7)
<=25	4 / 20 (20.0)	21 / 35 (60.0)	30 / 44 (68.2)
>30	3 / 18 (16.7)	33 / 59 (55.9)	33 / 51 (64.7)
Baseline Platelets Count			
150,000-200,000	5 / 16 (31.3)	20 / 37 (54.1)	27 / 45 (60.0)
<=150,000/ul	2 / 10 (20.0)	8 / 21 (38.1)	13 / 19 (68.4)
>200,000/ul	11 / 54 (20.4)	68 /104 (65.4)	67 / 97 (69.1)
Baseline ALT Status			
Elevated at BSL	10 / 55 (18.2)	59 /109 (54.1)	77 /115 (67.0)
Normal at BSL	8 / 25 (32.0)	37 / 53 (69.8)	30 / 46 (65.2)
Baseline HCV Viral Category (IU/mL)			
<=400,000	3 / 6 (50.0)	7 / 7 ( 100)	5 / 7 (71.4)
>400,000	15 / 74 (20.3)	89 /155 (57.4)	102 /154 (66.2)
Baseline HCV Viral Category (IU/mL)			
<=800,000	6 / 15 (40.0)	13 / 15 (86.7)	16 / 20 (80.0)
>800,000	12 / 65 (18.5)	83 /147 (56.5)	91 /141 (64.5)
Baseline Statin Use			

N	17 / 76 (22.4)	89 /154 (57.8)	105 /159 (66.0)
Y	1 / 4 (25.0)	7 / 8 (87.5)	2 / 2 ( 100)
Baseline Steatosis Score			
.	1 / 4 (25.0)	4 / 13 (30.8)	5 / 11 (45.5)
0	6 / 23 (26.1)	24 / 36 (66.7)	31 / 45 (68.9)
1	10 / 39 (25.6)	48 / 81 (59.3)	54 / 74 (73.0)
2	1 / 12 (8.33)	17 / 25 (68.0)	16 / 30 (53.3)
3	. / 1 (0.00)	3 / 7 (42.9)	1 / 1 ( 100)
4	. / 1 (0.00)	. / . ( . )	. / . ( . )
Baseline Steatosis Score Group			
=0	6 / 23 (26.1)	24 / 36 (66.7)	31 / 45 (68.9)
>0	11 / 53 (20.8)	68 /113 (60.2)	71 /105 (67.6)
Metavir Fibrosis Score			
.	1 / 4 (25.0)	4 / 13 (30.8)	5 / 11 (45.5)
0	3 / 5 (60.0)	6 / 8 (75.0)	3 / 5 (60.0)
1	9 / 43 (20.9)	52 / 79 (65.8)	55 / 78 (70.5)
2	2 / 13 (15.4)	20 / 30 (66.7)	23 / 36 (63.9)
3	3 / 5 (60.0)	8 / 15 (53.3)	4 / 9 (44.4)
4	. / 10 (0.00)	6 / 17 (35.3)	17 / 22 (77.3)
Metavir Fibrosis Score Group			
0/1/2	14 / 61 (23.0)	78 /117 (66.7)	81 /119 (68.1)
3/4	3 / 15 (20.0)	14 / 32 (43.8)	21 / 31 (67.7)
Liver Cirrhosis at Baseline			
N	17 / 66 (25.8)	86 /132 (65.2)	85 /128 (66.4)
Y	. / 10 (0.00)	6 / 17 (35.3)	17 / 22 (77.3)
Opioid Replacement Therapy			
N	18 / 80 (22.5)	95 /161 (59.0)	103 /157 (65.6)
Y	. / . ( . )	1 / 1 ( 100)	4 / 4 ( 100)
HCV-1 Subtype (b) (4)			
1	. / 5 (0.00)	10 / 14 (71.4)	8 / 14 (57.1)
1a	9 / 38 (23.7)	38 / 74 (51.4)	48 / 77 (62.3)
1b	9 / 37 (24.3)	48 / 74 (64.9)	51 / 70 (72.9)
HCV-1 Subtype (b) (4)			
1	. / 6 (0.00)	9 / 13 (69.2)	11 / 17 (64.7)
1a	10 / 38 (26.3)	38 / 74 (51.4)	47 / 77 (61.0)
1b	8 / 36 (22.2)	49 / 75 (65.3)	49 / 67 (73.1)
HCV-1 Subtype (b) (4)			
1a	12 / 46 (26.1)	52 / 96 (54.2)	62 / 97 (63.9)
1b	6 / 34 (17.6)	44 / 66 (66.7)	43 / 61 (70.5)
6l	. / . ( . )	. / . ( . )	1 / 1 ( 100)
Previous Peg Treatment Type			
PEG2A	10 / 42 (23.8)	45 / 79 (57.0)	42 / 68 (61.8)
PEG2B	8 / 38 (21.1)	51 / 83 (61.4)	65 / 93 (69.9)
Previous Trt Response (b) (4)			
Never Negative	3 / 30 (10.0)	24 / 59 (40.7)	31 / 59 (52.5)
Some Negative	15 / 50 (30.0)	72 /103 (69.9)	76 /102 (74.5)

Previous Trt Response (CRF)				
NON-RESPONDER	4 / 41 (9.76)	31 / 75 (41.3)	38 / 72 (52.8)	
RELAPSER	14 / 39 (35.9)	65 / 86 (75.6)	69 / 89 (77.5)	
Previous Trt Response (Combined)				
Never Negative	2 / 29 (6.90)	23 / 57 (40.4)	30 / 58 (51.7)	
Some Negative	16 / 51 (31.4)	73 / 105 (69.5)	77 / 103 (74.8)	

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#### 4.2.2 Some Important Variables Collected During the Trial

The variables discussed here include the TW4 responsiveness, Anemia, EPO usage, Ribavirin dose modification (Table 67 and 68). TW8 responsiveness results were listed in section 3.2.4.

- TW4 Responsiveness:

TW4 responsiveness ( $<1$  or  $\geq 1$ -log<sub>10</sub> decline from baseline) is a very good predictor of the final SVR24. In study P05216, subjects with  $\geq 1$ -log<sub>10</sub> decline at TW4 from baseline had about 40-50% more response rate across three arms than subjects with  $<1$ -log<sub>10</sub> decline at TW4.

In study P05101, the benefits of  $\geq 1$ -log<sub>10</sub> decline at TW4 over  $<1$ -log<sub>10</sub> decline at TW4 are about 40-45 in two boceprevir arms and are similar to what observed study P05216. As pointed out in Table 3, this is highly corrected with the previous treatment response either relapsers or partial responders.

- Anemia occurred during the trial

In both studies, subjects who developed Anemia (HGB $<10$ ) seems had higher SVR24 rate than subjects who did not. Because Anemia status, EPO usage, and Ribavirin dose adjustment are all tangled together, it seems hard to separate them in these two trials.

The interaction test of Anemia status and boceprevir treatment regimen (RGT and BOC48) may have some indication of interaction. Again, there is no determination due the limitation of the sample sizes.

The subgroup analysis results in Cohort 1 and 2 in study P05216 using  $<10$  IU/mL were also listed here in Table 69 and 70, and the subgroup analysis results using  $<25$  IU/mL for both P05216 and P05101 were also listed here in Table 71 and 72 for reference.

**Table 67: Some Important Variables Subgroup Analyses of SVR<sub>24</sub> (<10 IU/mL) for Study P05216 (FAS)**

Efficacy Parameter	PR48	RGT	BOC48
As Randomized and Dosed (FAS)			
N	137/363 (37.7)	233/368 (63.3)	242/366 (66.1)
EPO Usage			
N	89 /276 (32.2)	123 /209 (58.9)	122 /207 (58.9)
Y	48 / 87 (55.2)	110 /159 (69.2)	120 /159 (75.5)
Week 4 Responsiveness			
<1-log <sub>10</sub> Decline	3 / 83 (3.61)	27 / 97 (27.8)	36 / 95 (37.9)
>=1-log <sub>10</sub> Decline	133 /260 (51.2)	203 /252 (80.6)	200 /254 (78.7)
Missing	1 / 20 (5.00)	3 / 19 (15.8)	6 / 17 (35.3)
Anemia (HGB<10) During the Treatment			
NO	77 /246 (31.3)	110 /182 (60.4)	102 /181 (56.4)
YES	60 /108 (55.6)	123 /179 (68.7)	140 /184 (76.1)
Missing	. / 9 (0.00)	. / 7 (0.00)	. / 1 (0.00)
Sex by Anemia			
Female_NO	32 / 84 (38.1)	28 / 52 (53.8)	22 / 47 (46.8)
Female_YES	33 / 68 (48.5)	56 / 83 (67.5)	75 / 98 (76.5)
Male_NO	45 /162 (27.8)	82 /130 (63.1)	80 /134 (59.7)
Male_YES	27 / 40 (67.5)	67 / 96 (69.8)	65 / 86 (75.6)
Missing	. / 9 (0.00)	. / 7 (0.00)	. / 1 (0.00)
EPO by Anemia			
No_NO	73 /232 (31.5)	94 /161 (58.4)	92 /166 (55.4)
No_YES	16 / 35 (45.7)	29 / 41 (70.7)	30 / 40 (75.0)
Yes_NO	4 / 14 (28.6)	16 / 21 (76.2)	10 / 15 (66.7)
Yes_YES	44 / 73 (60.3)	94 /138 (68.1)	110 /144 (76.4)
No_x <sup>1</sup>	. / 9 (0.00)	. / 7 (0.00)	. / 1 (0.00)
Ribavirin Dose Modification (Y/N)			
N	104 /290 (35.9)	167 /256 (65.2)	146 /241 (60.6)
Y	33 / 73 (45.2)	66 /112 (58.9)	96 /125 (76.8)
Ribavirin Dose Modification by Anemia			
No_NO	71 /228 (31.1)	104 /165 (63.0)	91 /163 (55.8)
No_YES	33 / 53 (62.3)	63 / 84 (75.0)	55 / 77 (71.4)
Yes_NO	6 / 18 (33.3)	6 / 17 (35.3)	11 / 18 (61.1)
Yes_YES	27 / 55 (49.1)	60 / 95 (63.2)	85 /107 (79.4)
No_x	. / 9 (0.00)	. / 7 (0.00)	. / 1 (0.00)

**Table 68: Some Important Variables Subgroup Analyses of SVR<sub>24</sub> (<10 IU/mL) for Study P05101 (FAS)**

Efficacy Parameter	PR48	RGT	BOC48
As Randomized and Dosed (FAS)			

N	17 / 80 (21.3)	95 / 162 (58.6)	107 / 161 (66.5)
EPO Usage			
N	11 / 63 (17.5)	42 / 96 (43.8)	56 / 87 (64.4)
Y	6 / 17 (35.3)	53 / 66 (80.3)	51 / 74 (68.9)
Week 4 Responsiveness			
<1-log10 Decline	. / 12 (0.00)	15 / 46 (32.6)	15 / 44 (34.1)
<0.5 log10	. / 4 (0.00)	4 / 13 (30.8)	1 / 8 (12.5)
0.5 - <1 log10	. / 8 (0.00)	11 / 33 (33.3)	14 / 36 (38.9)
>=1-log10 Decline	17 / 67 (25.4)	80 / 110 (72.7)	90 / 114 (78.9)
1 - <1.5 log10	. / 11 (0.00)	15 / 21 (71.4)	15 / 28 (53.6)
1.5 - <2 log10	3 / 17 (17.6)	11 / 20 (55.0)	15 / 15 (100)
2 - <3 log10	3 / 17 (17.6)	18 / 26 (69.2)	30 / 37 (81.1)
3 - <4 log10	5 / 12 (41.7)	18 / 23 (78.3)	12 / 15 (80.0)
4 - <5 log10	5 / 7 (71.4)	14 / 15 (93.3)	15 / 16 (93.8)
>=5 log10	1 / 3 (33.3)	4 / 5 (80.0)	3 / 3 (100)
Missing	. / 1 (0.00)	. / 6 (0.00)	2 / 3 (66.7)
Anemia During the Treatment			
NO	12 / 60 (20.0)	36 / 83 (43.4)	47 / 82 (57.3)
YES	5 / 20 (25.0)	59 / 78 (75.6)	60 / 79 (75.9)
missing	. / . ( . )	. / 1 (0.00)	. / . ( . )
Sex by Anemia			
Female_NO	1 / 12 (8.33)	5 / 18 (27.8)	6 / 15 (40.0)
Female_YES	3 / 10 (30.0)	31 / 45 (68.9)	26 / 34 (76.5)
Male_NO	11 / 48 (22.9)	31 / 65 (47.7)	41 / 67 (61.2)
Male_YES	2 / 10 (20.0)	28 / 33 (84.8)	34 / 45 (75.6)
missing	. / . ( . )	. / 1 (0.00)	. / . ( . )
EPO by Anemia			
No_NO	11 / 57 (19.3)	32 / 78 (41.0)	42 / 73 (57.5)
No_YES	. / 6 (0.00)	10 / 17 (58.8)	14 / 14 (100)
Yes_NO	1 / 3 (33.3)	4 / 5 (80.0)	5 / 9 (55.6)
Yes_YES	5 / 14 (35.7)	49 / 61 (80.3)	46 / 65 (70.8)
No_x	. / . ( . )	. / 1 (0.00)	. / . ( . )
Ribavirin Dose Modification (Y/N)			
N	15 / 72 (20.8)	71 / 126 (56.3)	68 / 107 (63.6)
Y	2 / 8 (25.0)	24 / 36 (66.7)	39 / 54 (72.2)
Ribavirin Dose Modification by Anemia			
No_NO	12 / 59 (20.3)	34 / 78 (43.6)	42 / 74 (56.8)
No_YES	3 / 13 (23.1)	37 / 47 (78.7)	26 / 33 (78.8)
Yes_NO	. / 1 (0.00)	2 / 5 (40.0)	5 / 8 (62.5)
Yes_YES	2 / 7 (28.6)	22 / 31 (71.0)	34 / 46 (73.9)
No_x	. / . ( . )	. / 1 (0.00)	. / . ( . )
Previous Peg Treatment Type			
PEG2A	10 / 42 (23.8)	44 / 79 (55.7)	42 / 68 (61.8)
PEG2B	7 / 38 (18.4)	51 / 83 (61.4)	65 / 93 (69.9)
Previous Trt Response (b) (4)			

Never Negative	3 / 30 (10.0)	24 / 59 (40.7)	31 / 59 (52.5)
Some Negative	14 / 50 (28.0)	71 / 103 (68.9)	76 / 102 (74.5)
Previous Trt Response (CRF)			
NON-RESPONDER	4 / 41 (9.76)	31 / 75 (41.3)	38 / 72 (52.8)
RELAPSER	13 / 39 (33.3)	64 / 86 (74.4)	69 / 89 (77.5)
Previous Trt Response (Combined)			
Never Negative	2 / 29 (6.90)	23 / 57 (40.4)	30 / 58 (51.7)
Some Negative	15 / 51 (29.4)	72 / 105 (68.6)	77 / 103 (74.8)
Week 4 Status by Previous Response Adjusted			
<1-log   Never Neg	. / 7 (0.00)	4 / 21 (19.0)	11 / 28 (39.3)
<1-log   Some Neg	. / 5 (0.00)	11 / 25 (44.0)	4 / 16 (25.0)
>=1-log   Never Neg	2 / 22 (9.09)	19 / 33 (57.6)	19 / 29 (65.5)
>=1-log   Some Neg	15 / 45 (33.3)	61 / 77 (79.2)	71 / 85 (83.5)
Missing   Never Neg	. / . ( . )	. / 3 (0.00)	. / 1 (0.00)
Missing   Some Neg	. / 1 (0.00)	. / 3 (0.00)	2 / 2 ( 100)
Week 4 Status by Previous Response Adjusted (Non-Black)			
<1-log   Never Neg	. / 5 (0.00)	3 / 17 (17.6)	8 / 23 (34.8)
<1-log   Some Neg	. / 3 (0.00)	11 / 22 (50.0)	3 / 13 (23.1)
>=1-log   Never Neg	2 / 19 (10.5)	17 / 30 (56.7)	18 / 25 (72.0)
>=1-log   Some Neg	14 / 40 (35.0)	53 / 69 (76.8)	66 / 79 (83.5)
Missing   Never Neg	. / . ( . )	. / 3 (0.00)	. / . ( . )
Missing   Some Neg	. / 1 (0.00)	. / 3 (0.00)	2 / 2 ( 100)
Week 4 Status by Previous Response Adjusted (Black)			
<1-log   Never Neg	. / 2 (0.00)	1 / 4 (25.0)	3 / 5 (60.0)
<1-log   Some Neg	. / 2 (0.00)	. / 3 (0.00)	1 / 3 (33.3)
>=1-log   Never Neg	. / 3 (0.00)	2 / 3 (66.7)	1 / 4 (25.0)
>=1-log   Some Neg	1 / 5 (20.0)	8 / 8 ( 100)	5 / 6 (83.3)
Missing   Never Neg	. / . ( . )	. / . ( . )	. / 1 (0.00)

**Table 69:** Some Important Variables Subgroup Analyses of SVR<sub>24</sub> (<10 IU/mL) in Cohort 1 for Study P05216 (FAS)

Efficacy Parameter	PR48	RGT	BOC48
As Randomized and Dosed (FAS)			
N	125/311 (40.2)	211/316 (66.8)	213/311 (68.5)
EPO Usage			
N	83 / 237 (35.0)	116 / 185 (62.7)	114 / 184 (62.0)
Y	42 / 74 (56.8)	95 / 131 (72.5)	99 / 127 (78.0)
Week 4 Responsiveness			
<1-log <sub>10</sub> Decline	3 / 62 (4.84)	21 / 73 (28.8)	31 / 79 (39.2)
>=1-log <sub>10</sub> Decline	121 / 234 (51.7)	187 / 228 (82.0)	178 / 218 (81.7)
Missing	1 / 15 (6.67)	3 / 15 (20.0)	4 / 14 (28.6)
Anemia (HGB<10) During the Treatment			
NO	70 / 212 (33.0)	105 / 164 (64.0)	94 / 159 (59.1)

YES	55 / 91 (60.4)	106 /147 (72.1)	119 /151 (78.8)
Missing	. / 8 (0.00)	. / 5 (0.00)	. / 1 (0.00)
Sex by Anemia			
Female_NO	30 / 77 (39.0)	28 / 47 (59.6)	20 / 41 (48.8)
Female_YES	32 / 58 (55.2)	49 / 67 (73.1)	66 / 82 (80.5)
Male_NO	40 /135 (29.6)	77 /117 (65.8)	74 /118 (62.7)
Male_YES	23 / 33 (69.7)	57 / 80 (71.3)	53 / 69 (76.8)
Missing	. / 8 (0.00)	. / 5 (0.00)	. / 1 (0.00)
EPO by Anemia			
No_NO	67 /199 (33.7)	89 /143 (62.2)	87 /148 (58.8)
No_YES	16 / 30 (53.3)	27 / 37 (73.0)	27 / 35 (77.1)
Yes_NO	3 / 13 (23.1)	16 / 21 (76.2)	7 / 11 (63.6)
Yes_YES	39 / 61 (63.9)	79 /110 (71.8)	92 /116 (79.3)
No_x <sup>1</sup>	. / 8 (0.00)	. / 5 (0.00)	. / 1 (0.00)
Ribavirin Dose Modification (Y/N)			
N	97 /249 (39.0)	156 /228 (68.4)	133 /208 (63.9)
Y	28 / 62 (45.2)	55 / 88 (62.5)	80 /103 (77.7)
Ribavirin Dose Modification by Anemia			
No_NO	66 /196 (33.7)	99 /150 (66.0)	85 /144 (59.0)
No_YES	31 / 45 (68.9)	57 / 73 (78.1)	48 / 63 (76.2)
Yes_NO	4 / 16 (25.0)	6 / 14 (42.9)	9 / 15 (60.0)
Yes_YES	24 / 46 (52.2)	49 / 74 (66.2)	71 / 88 (80.7)
No_x	. / 8 (0.00)	. / 5 (0.00)	. / 1 (0.00)

<sup>1</sup>: x stands for missing.

**Table 70:** Some Important Variables Subgroup Analyses of SVR<sub>24</sub> (<10 IU/mL) in Cohort 2 for Study P05216 (FAS)

Efficacy Parameter	PR48	RGT	BOC48
As Randomized and Dosed (FAS)			
N	12/ 52 (23.1)	22/ 52 (42.3)	29/ 55 (52.7)
EPO Usage			
N	6 / 39 (15.4)	7 / 24 (29.2)	8 / 23 (34.8)
Y	6 / 13 (46.2)	15 / 28 (53.6)	21 / 32 (65.6)
Week 4 Responsiveness			
<1-log <sub>10</sub> Decline	. / 21 (0.00)	6 / 24 (25.0)	5 / 16 (31.3)
>=1-log <sub>10</sub> Decline	12 / 26 (46.2)	16 / 24 (66.7)	22 / 36 (61.1)
Missing	. / 5 (0.00)	. / 4 (0.00)	2 / 3 (66.7)
Anemia (HGB<10) During the Treatment			
NO	7 / 34 (20.6)	5 / 18 (27.8)	8 / 22 (36.4)
YES	5 / 17 (29.4)	17 / 32 (53.1)	21 / 33 (63.6)
Missing	. / 1 (0.00)	. / 2 (0.00)	. / . ( . )
Sex by Anemia			
Female_NO	2 / 7 (28.6)	. / 5 (0.00)	2 / 6 (33.3)

Female_YES	1 / 10 (10.0)	7 / 16 (43.8)	9 / 16 (56.3)
Male_NO	5 / 27 (18.5)	5 / 13 (38.5)	6 / 16 (37.5)
Male_YES	4 / 7 (57.1)	10 / 16 (62.5)	12 / 17 (70.6)
Missing	. / 1 (0.00)	. / 2 (0.00)	. / . ( . )
EPO by Anemia			
No_NO	6 / 33 (18.2)	5 / 18 (27.8)	5 / 18 (27.8)
No_YES	. / 5 (0.00)	2 / 4 (50.0)	3 / 5 (60.0)
Yes_NO	1 / 1 ( 100)	. / . ( . )	3 / 4 (75.0)
Yes_YES	5 / 12 (41.7)	15 / 28 (53.6)	18 / 28 (64.3)
No_x <sup>1</sup>	. / 1 (0.00)	. / 2 (0.00)	. / . ( . )
Ribavirin Dose Modification (Y/N)			
N	7 / 41 (17.1)	11 / 28 (39.3)	13 / 33 (39.4)
Y	5 / 11 (45.5)	11 / 24 (45.8)	16 / 22 (72.7)
Ribavirin Dose Modification by Anemia			
No_NO	5 / 32 (15.6)	5 / 15 (33.3)	6 / 19 (31.6)
No_YES	2 / 8 (25.0)	6 / 11 (54.5)	7 / 14 (50.0)
Yes_NO	2 / 2 ( 100)	. / 3 (0.00)	2 / 3 (66.7)
Yes_YES	3 / 9 (33.3)	11 / 21 (52.4)	14 / 19 (73.7)
No_x	. / 1 (0.00)	. / 2 (0.00)	. / . ( . )

-----  
<sup>1</sup>: x stands for missing.

**Table 71:** Some Important Variables Subgroup Analyses of SVR<sub>24</sub> (<25 IU/mL) for Study P05216 (FAS)

----- Efficacy Parameter	PR48	RGT	BOC48
-----	-----	-----	-----
As Randomized and Dosed (FAS)			
N	138/363 (38.0)	233/368 (63.3)	242/366 (66.1)
EPO Usage			
N	90 /276 (32.6)	123 /209 (58.9)	122 /207 (58.9)
Y	48 / 87 (55.2)	110 /159 (69.2)	120 /159 (75.5)
Week 4 Responsiveness			
<1-log <sub>10</sub> Decline	3 / 83 (3.61)	27 / 97 (27.8)	36 / 95 (37.9)
>=1-log <sub>10</sub> Decline	134 /260 (51.5)	203 /252 (80.6)	200 /254 (78.7)
Missing	1 / 20 (5.00)	3 / 19 (15.8)	6 / 17 (35.3)
Anemia (HGB<10) During the Treatment			
NO	77 /246 (31.3)	110 /182 (60.4)	102 /181 (56.4)
YES	61 /108 (56.5)	123 /179 (68.7)	140 /184 (76.1)
Missing	. / 9 (0.00)	. / 7 (0.00)	. / 1 (0.00)
Sex by Anemia			
Female_NO	32 / 84 (38.1)	28 / 52 (53.8)	22 / 47 (46.8)
Female_YES	33 / 68 (48.5)	56 / 83 (67.5)	75 / 98 (76.5)
Male_NO	45 /162 (27.8)	82 /130 (63.1)	80 /134 (59.7)
Male_YES	28 / 40 (70.0)	67 / 96 (69.8)	65 / 86 (75.6)
Missing	. / 9 (0.00)	. / 7 (0.00)	. / 1 (0.00)

EPO by Anemia				
No_NO	73 /232 (31.5)	94 /161 (58.4)	92 /166 (55.4)	
No_YES	17 / 35 (48.6)	29 / 41 (70.7)	30 / 40 (75.0)	
Yes_NO	4 / 14 (28.6)	16 / 21 (76.2)	10 / 15 (66.7)	
Yes_YES	44 / 73 (60.3)	94 /138 (68.1)	110 /144 (76.4)	
No_x <sup>1</sup>	. / 9 (0.00)	. / 7 (0.00)	. / 1 (0.00)	
Ribavirin Dose Modification (Y/N)				
N	105 /290 (36.2)	167 /256 (65.2)	146 /241 (60.6)	
Y	33 / 73 (45.2)	66 /112 (58.9)	96 /125 (76.8)	
Ribavirin Dose Modification by Anemia				
No_NO	71 /228 (31.1)	104 /165 (63.0)	91 /163 (55.8)	
No_YES	34 / 53 (64.2)	63 / 84 (75.0)	55 / 77 (71.4)	
Yes_NO	6 / 18 (33.3)	6 / 17 (35.3)	11 / 18 (61.1)	
Yes_YES	27 / 55 (49.1)	60 / 95 (63.2)	85 /107 (79.4)	
No_x	. / 9 (0.00)	. / 7 (0.00)	. / 1 (0.00)	

**Table 72: Some Important Variables Subgroup Analyses of SVR<sub>24</sub> (<25 IU/mL) for Study P05101 (FAS)**

Efficacy Parameter	PR48	RGT	BOC48
As Randomized and Dosed (FAS)			
N	18/ 80 (22.5)	96/162 (59.3)	107/161 (66.5)
EPO Usage			
N	11 / 63 (17.5)	42 / 96 (43.8)	56 / 87 (64.4)
Y	7 / 17 (41.2)	54 / 66 (81.8)	51 / 74 (68.9)
Week 4 Responsiveness			
<1-log <sub>10</sub> Decline	. / 12 (0.00)	15 / 46 (32.6)	15 / 44 (34.1)
>=1-log <sub>10</sub> Decline	18 / 67 (26.9)	81 /110 (73.6)	90 /114 (78.9)
Missing	. / 1 (0.00)	. / 6 (0.00)	2 / 3 (66.7)
Anemia During the Treatment			
NO	13 / 60 (21.7)	37 / 83 (44.6)	47 / 82 (57.3)
YES	5 / 20 (25.0)	59 / 78 (75.6)	60 / 79 (75.9)
missing	. / . ( . )	. / 1 (0.00)	. / . ( . )
Sex by Anemia			
Female_NO	1 / 12 (8.33)	6 / 18 (33.3)	6 / 15 (40.0)
Female_YES	3 / 10 (30.0)	31 / 45 (68.9)	26 / 34 (76.5)
Male_NO	12 / 48 (25.0)	31 / 65 (47.7)	41 / 67 (61.2)
Male_YES	2 / 10 (20.0)	28 / 33 (84.8)	34 / 45 (75.6)
missing	. / . ( . )	. / 1 (0.00)	. / . ( . )
EPO by Anemia			
No_NO	11 / 57 (19.3)	32 / 78 (41.0)	42 / 73 (57.5)
No_YES	. / 6 (0.00)	10 / 17 (58.8)	14 / 14 ( 100)
Yes_NO	2 / 3 (66.7)	5 / 5 ( 100)	5 / 9 (55.6)
Yes_YES	5 / 14 (35.7)	49 / 61 (80.3)	46 / 65 (70.8)
No_x	. / . ( . )	. / 1 (0.00)	. / . ( . )

Ribavirin Dose Modification (Y/N)			
N	16 / 72 (22.2)	72 / 126 (57.1)	68 / 107 (63.6)
Y	2 / 8 (25.0)	24 / 36 (66.7)	39 / 54 (72.2)
Ribavirin Dose Modification by Anemia			
No_NO	13 / 59 (22.0)	35 / 78 (44.9)	42 / 74 (56.8)
No_YES	3 / 13 (23.1)	37 / 47 (78.7)	26 / 33 (78.8)
Yes_NO	. / 1 (0.00)	2 / 5 (40.0)	5 / 8 (62.5)
Yes_YES	2 / 7 (28.6)	22 / 31 (71.0)	34 / 46 (73.9)
No_x	. / . ( . )	. / 1 (0.00)	. / . ( . )
Previous Peg Treatment Type			
PEG2A	10 / 42 (23.8)	45 / 79 (57.0)	42 / 68 (61.8)
PEG2B	8 / 38 (21.1)	51 / 83 (61.4)	65 / 93 (69.9)
Previous Trt Response (b) (4)			
Never Negative	3 / 30 (10.0)	24 / 59 (40.7)	31 / 59 (52.5)
Some Negative	15 / 50 (30.0)	72 / 103 (69.9)	76 / 102 (74.5)
Previous Trt Response (CRF)			
NON-RESPONDER	4 / 41 (9.76)	31 / 75 (41.3)	38 / 72 (52.8)
RELAPSER	14 / 39 (35.9)	65 / 86 (75.6)	69 / 89 (77.5)
Previous Trt Response (Combined)			
Never Negative	2 / 29 (6.90)	23 / 57 (40.4)	30 / 58 (51.7)
Some Negative	16 / 51 (31.4)	73 / 105 (69.5)	77 / 103 (74.8)
Week 4 Status by Previous Response Adjusted			
<1-log   Never	. / 7 (0.00)	4 / 21 (19.0)	11 / 28 (39.3)
<1-log   Some N	. / 5 (0.00)	11 / 25 (44.0)	4 / 16 (25.0)
>=1-log   Never	2 / 22 (9.09)	19 / 33 (57.6)	19 / 29 (65.5)
>=1-log   Some	16 / 45 (35.6)	62 / 77 (80.5)	71 / 85 (83.5)
Missing   Never	. / . ( . )	. / 3 (0.00)	. / 1 (0.00)
Missing   Some	. / 1 (0.00)	. / 3 (0.00)	2 / 2 ( 100)

## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

Some key statistical issues have already summarized in the executive summary at the beginning of the review. Here will present some additional statistical considerations.

#### 5.1.1 Randomization

As stated in section 3.2.2.1, some errors were detected in the randomization process for both trials. As a result, some subjects were randomized to the wrong stratum. The impact of this on the primary efficacy endpoint analysis using CMH method is ignorable because the benefits of triple therapy are very large comparing to the control PR arm for both trials. Using the exact method without stratification factor adjustment, the exact confidence intervals of the treatment differences for Arm 3 vs. control Arm and Arm 2 vs. control Arm are very close to the CMH results. Results are not listed here.

#### 5.1.2 The Cut-off Days of Treatment Used in Arm 3 for Identify Early/Late

Overall, the sponsor used the cut-off treatment days (31 weeks for treatment-naïve and 39 weeks for previous treatment-failure) in Arm 3 seems OK.

##### 5.1.2.1 Study P05216 (treatment-naïve)

If more than 28 weeks (196 days) of treatment is required for subjects in Arm 3 to be into Group A or B instead of 31 weeks (217 days) used by the sponsor, group A picked up 10 more subjects (all NEG at EOF) and 6 for group B (2 NEG, 2 POS, and 2 missing at EOF) (Table 73). The impact is very limited (See Table 74 for details).

**Table 73:** The Number of Early/Late Responder in Arm 3 Using 28 or 31 Weeks of Treatment for Study P05216

Parameter	Category	>28 Weeks Treatment (BOC48)			>31 Weeks Treatment <sup>1</sup> Arm3Flg (BOC48)		
		A	B	Other (C)	A	B	Other (C)
TW8-TW24 Category	Early Responder	171		52	161		62
	Late Responder		79	64		73	70
		171	79	116	161	73	132

<sup>1</sup>: This is what the sponsor used and variable named Arm3Flg in the submitted dataset.

**Table 74:** The Virologic Response (SVR) of Early and Late Responders in Study P05216

EOF<10 Cohort 1+2	Virologic Response	Arm 2 (RGT) EOF (<10) n/N (%)	Arm 3 (BOC48) EOF (<10) n/N (%)	Δ EOF (Arm 2-Arm 3) [95% CI of two 1-sided]
Old: >217 for BOC48	Early Responders	156/161 (96.9)	155/161 (96.3)	0.6 [-3.8, 5.2]
	Late Responders	45/68 (66.2)	55/73 (75)	-9.2 [-24.4, 6.3]
New: >196 for BOC48	Early Responders	156/161 (96.9)	165/171 (96.6)	0.3
	Late Responders	45/68 (66.2)	57/79 (72.2)	-6.0

### 5.1.2.2 Study P05101 (Previous treatment-failure)

If more than 36 weeks (252 days) of treatment required for subjects in Arm 3 to be into Group A or B instead of 39 weeks (273 days), group A and B picked up 1 more subject each (NEG at EOF for group A and missing at EOF for group B (Table 75). There is almost no change.

**Table 75:** The Number of Early/Late Responder in Arm 3 Using 36 or 39 Weeks of Treatment for Study P05101

Parameter	Category	>36 Weeks Treatment (BOC48)			>39 Weeks Treatment <sup>1</sup> Arm3Flg (BOC48)		
		A	B	Other (C)	A	B	Other (C)
TW8 Category	Undetectable	71		13	70		14
	Detectable		41	29		40	30
	Missing	3		4	3		4

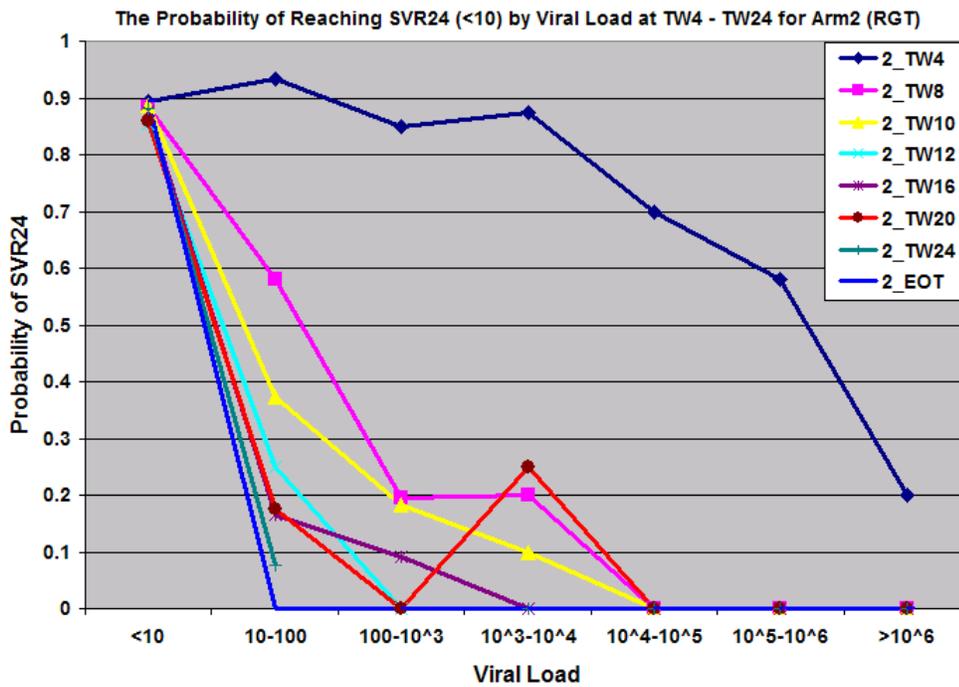
<sup>1</sup>: This is what the sponsor used and variable named Arm3Flg in the submitted dataset.

### 5.1.3 Sample Size

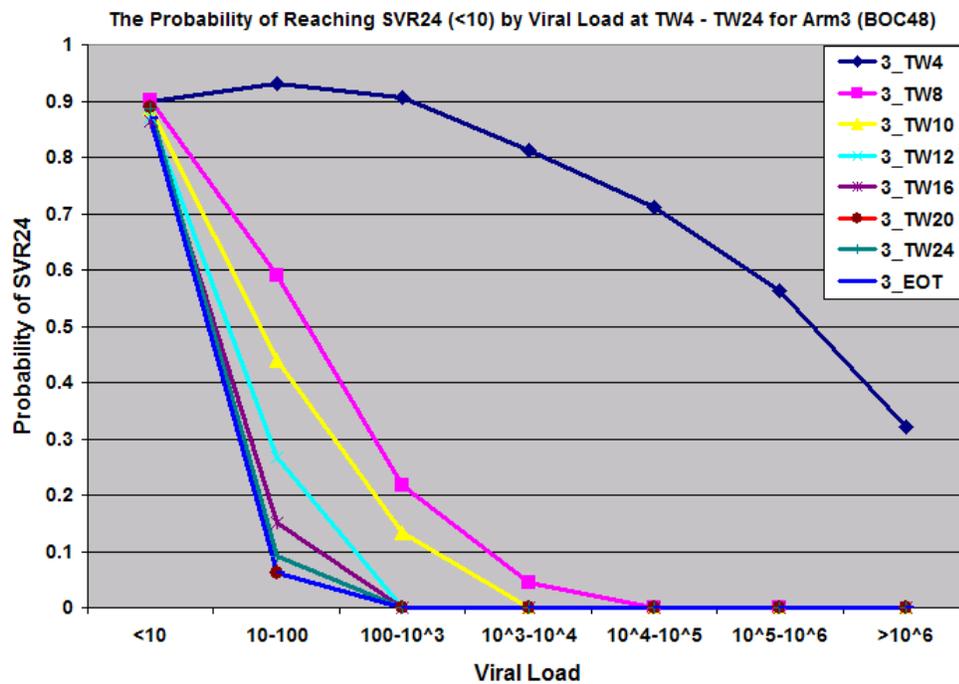
The sample sizes for the early and late responder comparison between Arm 2 and 3 were small. Additionally, the trials were not designed to detect such difference. So, even though some numeric differences between Arm 2 (RGT) and Arm 3 (BOC48), they are not statistically significant and we can not draw any firm conclusion. The same caution should be applied to the subgroup analyses.

### 5.1.4 Futility Rule for Treatment-naïve Subjects

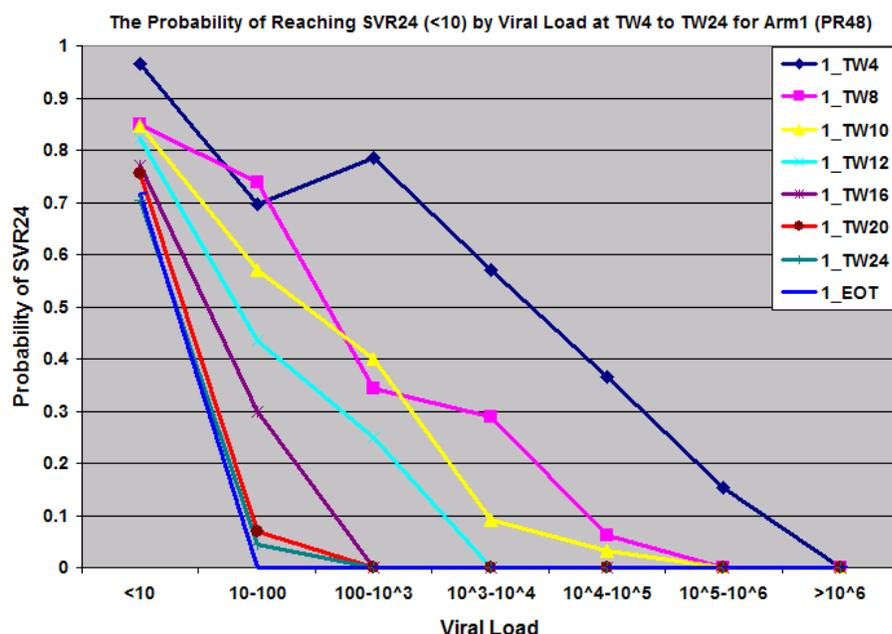
The futility rule used in study P05216 was the detectable at TW24. The chances of reaching SVR<sub>24</sub> (<10) of subjects with HCV-1 viral load >100 IU/mL at both TW12 and TW24 are ZERO for both boceprevir arms (Table 76 and 77 and Figure 19-21). This leads that detectable at TW12 could be used as futility rule instead of at TW24 such that subjects who have no chance to response will get at least 12 weeks less treatment. This is just an observation from data, and please see microbiologic review for more details.



**Figure 19:** The Probability of Reaching SVR24 (<10) by Viral Load at TW4 to TW24 in Arm 2 In study P05216.



**Figure 20:** The Probability of Reaching SVR24 (<10) by Viral Load at TW4 to TW24 in Arm 3 In study P05216.



**Figure 21:** The Probability of Reaching SVR24 (<10) by Viral Load at TW4 to TW24 in Arm 1 In study P05216.

By comparing the TW4 curve in Arm 1 to Arm 2 and 3, the higher response rates for subjects who had high viral load at TW4 were due to the benefits of boceprevir. If no boceprevir, it will be a sort of straight line as seen in Figure 21.

**Table 76:** The Probability of Reaching SVR24 (<10) by Viral Load at TW4 to TW24 by Treatment Arm for Study P05216 (Part 1)

VL	TW8			TW10			TW12		
	PR48	RGT	BOC48	PR48	RGT	BOC48	PR48	RGT	BOC48
<b>&lt;=10</b>	51/60 (85%)	184/208 (88%)	184/204 (90%)	72/85 (85%)	204/230 (89%)	205/231 (89%)	97/118 (82%)	224/262 (85%)	230/264 (87%)
<b>10-100</b>	51/69 (74%)	36/62 (58%)	46/78 (59%)	37/65 (57%)	22/59 (37%)	29/66 (44%)	27/62 (44%)	9/36 (25%)	12/45 (27%)
<b>100-10<sup>3</sup></b>	13/38 (34%)	7/36 (19%)	5/23 (22%)	16/40 (40%)	4/22 (18%)	2/15 (13%)	11/44 (25%)	0/11	0/9
<b>10<sup>3</sup>-10<sup>4</sup></b>	15/52 (29%)	3/15 (20%)	1/22 (5%)	3/33 (9%)	1/10 (10%)	0/7	0/17	0/5	0/9
<b>10<sup>4</sup>-10<sup>5</sup></b>	2/32 (6%)	0/6	0/7	1/30 (3%)	0/7	0/5	0/28	0/5	0/2
<b>10<sup>5</sup>-10<sup>6</sup></b>	0/54	0/7	0/1	0/42	0/6	0/7	0/43	0/7	0/9
<b>&gt;10<sup>6</sup></b>	0/26	0/3		0/22	0/3	0/1	0/19	0/4	0/2
<b>Missing</b>	5/32 (16%)	3/31 (10%)	6/31 (19%)	8/46 (17%)	2/31 (6%)	6/34 (18%)	2/32 (6%)	0/38	0/26
<b>Sum</b>	137/363	233/368	242/366	137/363	233/368	242/366	137/363	233/368	242/366

**Table 77:** The Proportion of Response for Each Range of Viral Load at TW8 to TW24 by Treatment Arm for Study P05216 (Part 2)

VL	TW16			TW20			TW24		
	PR48	RGT	BOC48	PR48	RGT	BOC48	PR48	RGT	BOC48
<=10	118/153 (77%)	225/257 (88%)	236/273 (86%)	130/17 2 (76%)	222/258 (86%)	234/263 (89%)	130/185 (70%)	224/254 (88%)	234/264 (89%)
10-100	15/50 (30%)	5/30 (17%)	3/20 (15%)	3/43 (7%)	3/17 (18%)	1/16 (6%)	1/23 (4%)	1/13 (8%)	1/11 (9%)
100-10 <sup>3</sup>	0/24	1/11 (9%)	0/11	0/12	0/5	0/9	0/13		0/9
10 <sup>3</sup> -10 <sup>4</sup>	0/13	0/5	0/5	0/7	1/4 (25%)	0/7	0/10	0/9	0/6
10 <sup>4</sup> -10 <sup>5</sup>	0/20	0/2	0/7	0/21	0/6	0/4	0/14	0/3	0/1
10 <sup>5</sup> -10 <sup>6</sup>	0/46	0/8	0/7	0/36	0/10	0/8	0/37	0/13	0/11
>10 <sup>6</sup>	0/15	0/4	0/2	0/17	0/3	0/3	0/17	0/2	0/1
Missing	4/42 (10%)	2/51 (4%)	3/41 (7%)	4/55 (7%)	7/65 (11%)	7/56 (23%)	6/64 (9%)	8/74 (11%)	7/63 (11%)
Sum	137/363	233/368	242/366	137/363	233/368	242/366	137/363	233/368	242/366

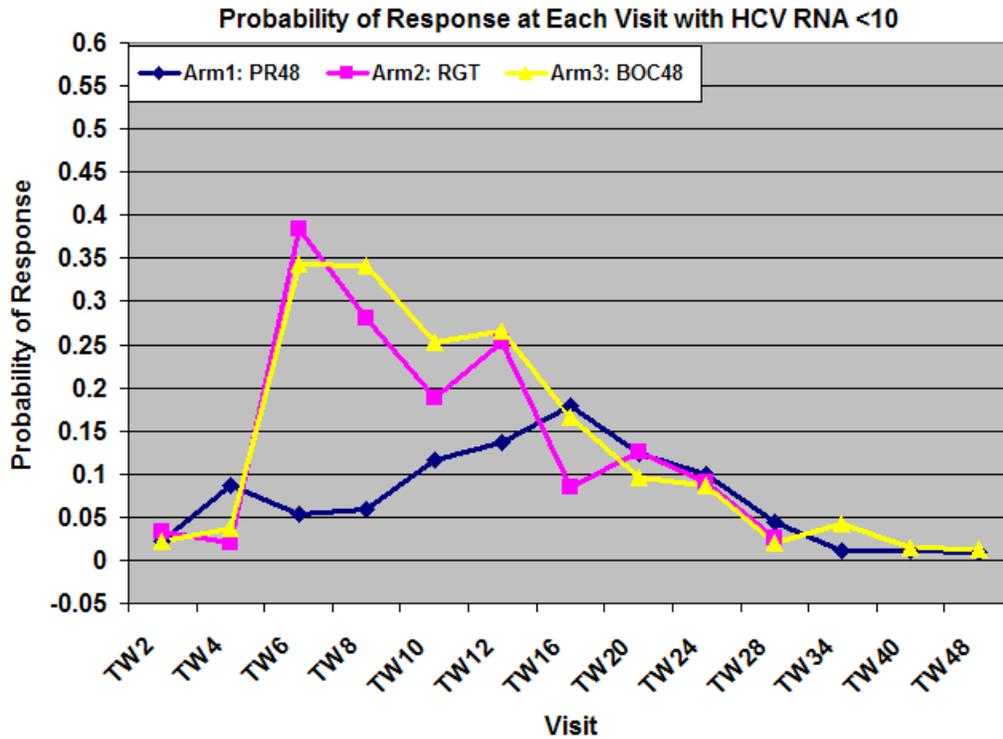
### 5.1.5 Exploratory analyses -- Predictiveness

Some exploratory analyses will be presented here to assist the assessment of the effectiveness of boceprevir. The following analyses are all based on the response rate using <10 as cut-off value.

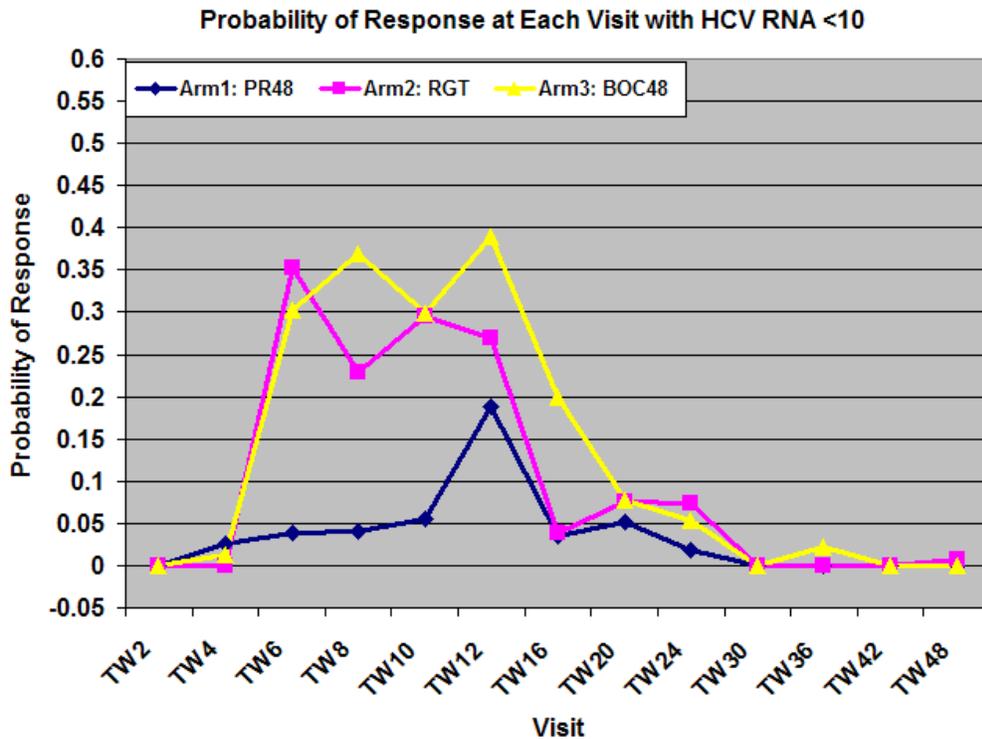
#### 5.1.5.1 The Probability to be suppressed if not suppressed at previous visit

This analysis tries to assess the probability for subjects who will get suppression at current visit if the subjects were not suppressed at previous visit. If the subject were not suppressed and if the subject continues to take the designed regimen by arm, what is the chance that the subject will be suppressed?

For treatment-naïve subjects (P05216), it looks like boceprevir arms have benefits over control arm until TW12 (Figure 22). Ie, if the subject still has not been suppressed at TW12 and the subject decides to continue taking boceprevir treatment regimen, the chance to be suppressed will be no more than 10-15%. For previous treatment-failure subjects (P05101), the critical point is also around TW16 to TW20, ie, if the subject still has not been suppressed at TW16 or TW20, the chance to be suppressed will be no more than 10% if the subject chooses to continue taking boceprevir treatment (Figure 23).



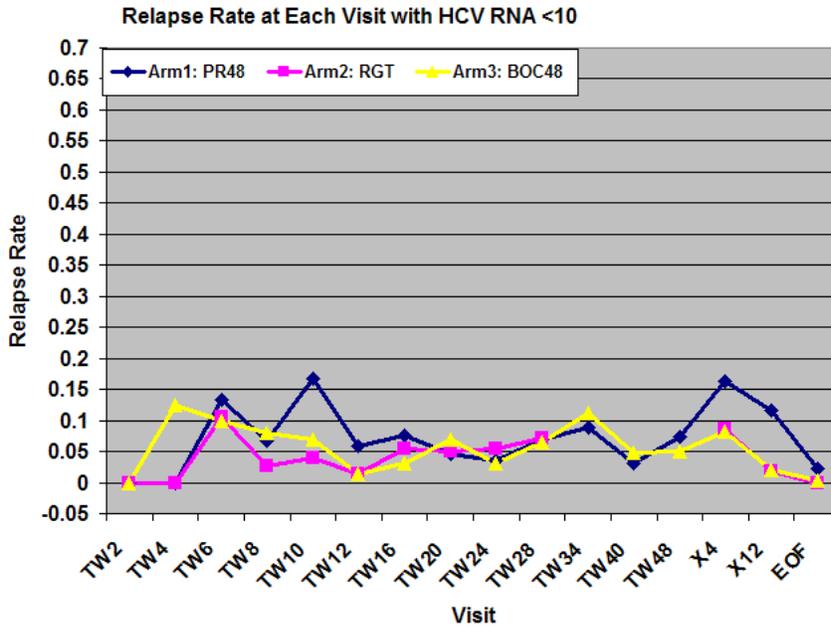
**Figure 22:** The Probability to be Suppressed if not Suppressed at Previous Visit for Study P05216



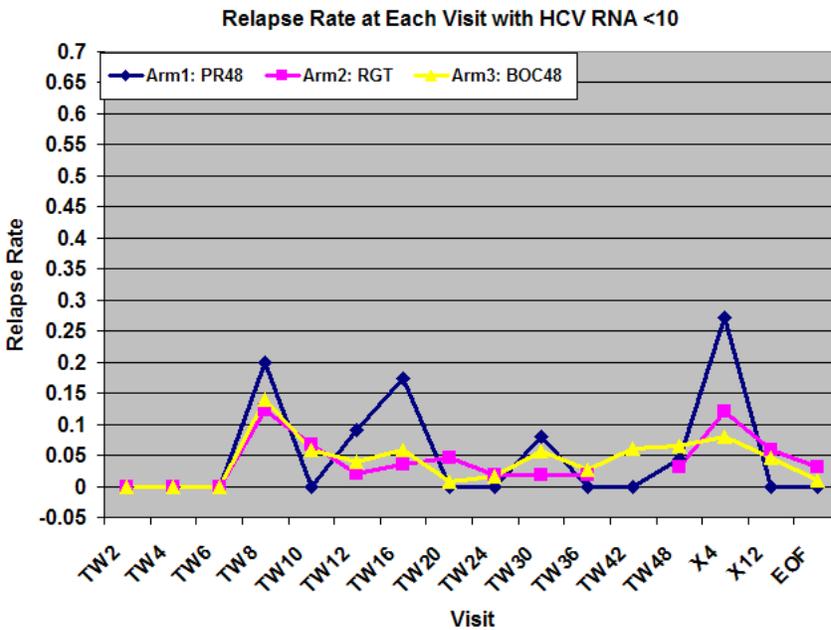
**Figure 23:** The Probability to be suppressed if not suppressed at Previous Visit for Study P05101

### 5.1.5.2 The Probability to be relapsed if suppressed at previous visit

This analysis tries to assess the probability for subjects who will relapse at current visit if the subjects were suppressed at previous visit. For treatment-naïve subjects (P05216), the relapse rate across visits is around 5% for two boceprevir arms (Figure 24) and also around 5% after TW12 for previous treatment-failure subjects (Figure 25). One note is that futility rule for P05101 was detectable at TW12. Before TW12, the relapse rate was a little big high, especially at TW8 for two boceprevir arms.



**Figure 24:** The Probability of Relapsing if Suppressed at Previous Visit for Study P05216



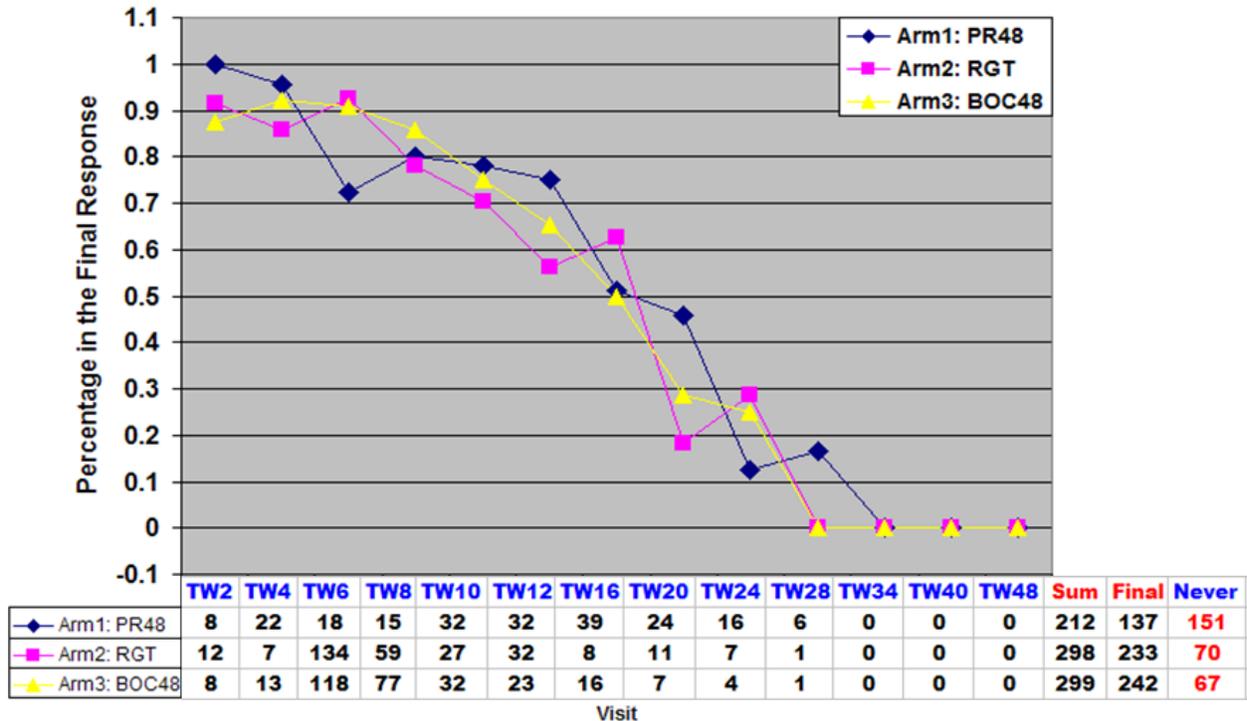
**Figure 25:** The Probability of Relapsing if Suppressed at Previous Visit for Study P05101

### 5.1.5.3 First time suppression

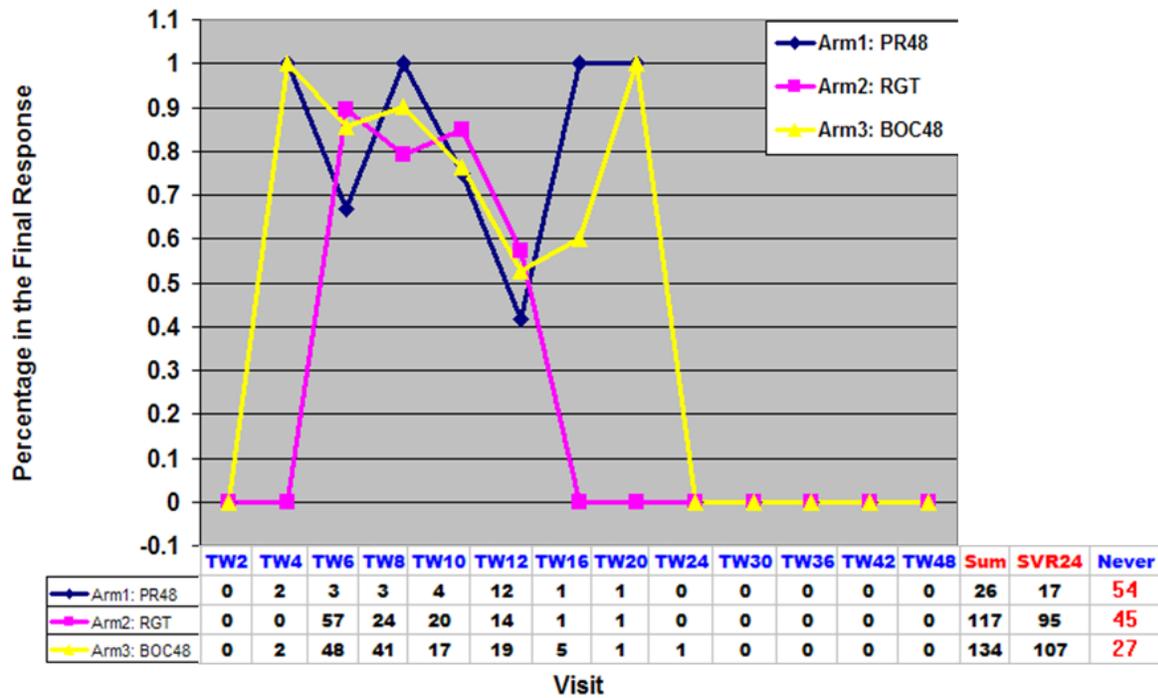
This analysis tries to assess for the subjects who were first suppressed at each visit, what is the proportion of them will sustain the suppression to reach SVR<sub>24</sub> by visit by Arm. The trend is that the earlier suppressed, the higher chance to sustain the suppression to reach SVR<sub>24</sub> for both treatment-naïve and previous treatment-failure subjects.

For treatment-naïve subjects (P05216), if subject's first suppression occurred at TW24, the chance to maintain the suppression to reach SVR<sub>24</sub> is less than 30% for two boceprevir arms (Figure 26). The number of subjects who got their first time suppression by visit and by arm is listed at the bottom of the plot in Figure 26. The percentages of never suppressed were 19% (70/368) for RGT arm and 18.3% (67/366) for BOC48 arm comparing to 41.6% (151/363) in control arm.

For previous treatment-failure subjects (P05101), if subject's first suppression occurred at TW24, the chance to maintain the suppression to reach SVR<sub>24</sub> is almost ZERO for two boceprevir arms (Figure 27). The number of subjects who got their first time suppression by visit and by arm is listed at the bottom of the plot in Figure 27. The percentages of never suppressed were 27.8% (45/162) for RGT arm and 16.8% (27/161) for BOC48 arm comparing to 67.5% (54/80) in control arm.



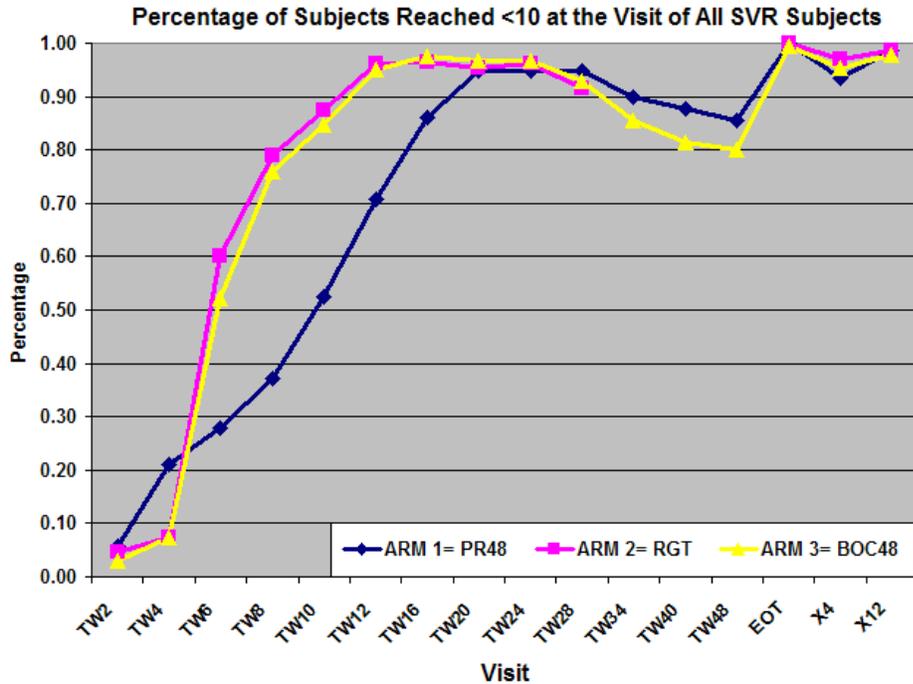
**Figure 26:** The Probability of Relapsing if Suppressed at Previous Visit for Study P05216



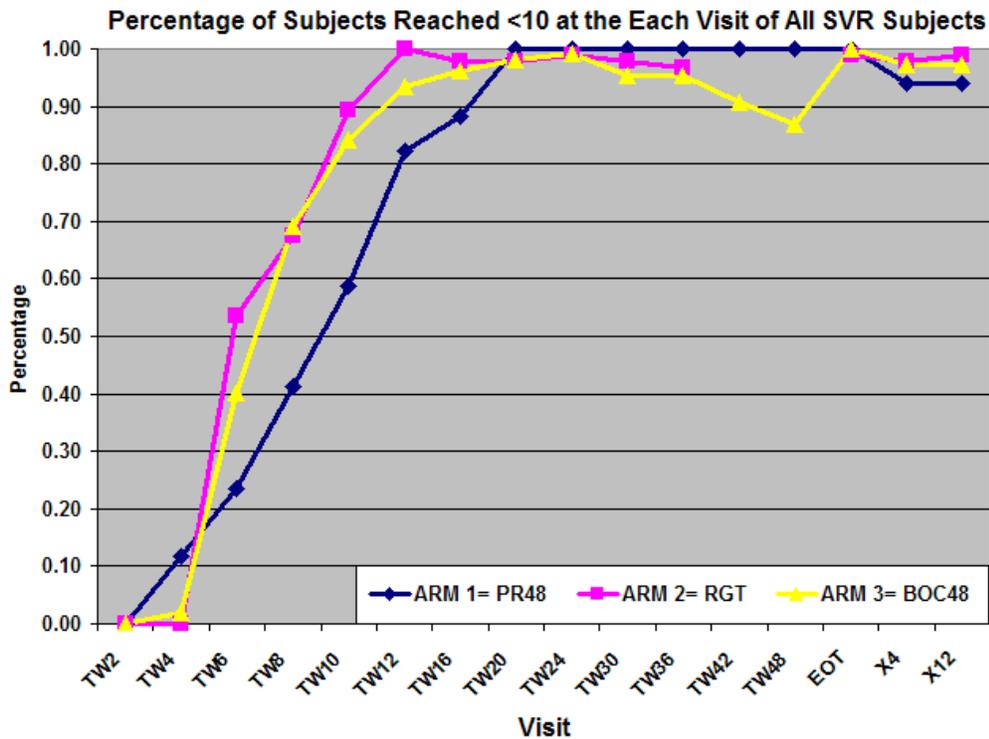
**Figure 27:** The Probability of Relapsing if Suppressed at Previous Visit for Study P05101

#### 5.1.5.4 Percentage of subjects who reached suppression (<10) at each visit for all SVR subjects

This analysis tries to assess the percentage of all reaching SVR<sub>24</sub> subjects (responders) reaching suppression for each visit. For treatment-naïve subjects (P05216), over 95% of responders have already been suppressed at TW12 and maintained at that level (Figure 28), and similar pattern for previous treatment-failure subjects(P05101) (Figure 29).



**Figure 28:** The Percentage of all Responders (SVR<sub>24</sub>) Reaching Suppression at Each Visit for Study P05216



**Figure 29:** The Percentage of all Responders (SVR<sub>24</sub>) Reaching Suppression at Each Visit for Study P05101

## 5.2 Conclusions and Recommendations

These two key phase 3 studies have demonstrated that boceprevir plus PR is efficacious for HCV-1a or HCV-1b infected subjects in both treatment-naïve (SVR rates of 63-66% in BOC contained arms vs. 38% in control arm) and patients previously failed pegylated interferon alfa plus ribavirin therapy (SVR rates of 59-66% in BOC contained arms vs. 21% in control arm) (including relapsers and partial responders only). Both non-black and black population will benefit from the addition of boceprevir to the regimen although the SVR rate of boceprevir contained regimen in black population (SVR rate of 42-53% in treatment-naïve population and 53-61% in previously failed population) is relatively lower compared to non-black population (SVR rate of 67-68% in treatment-naïve population and 59-68% in previously failed population).

The duration of boceprevir treatment for early responders after 4 weeks of lead-in PegIntron/ribavirin can be 24 weeks of triple for treatment-naïve and 32 weeks of triple for previous treatment failure subjects as the RGT arm strategy the sponsor used in the trials (SVR rates of 97% and 96% in RGT arm and BOC48 arm respectively in study P05216, and 90% and 97% in RGT arm and BOC48 arm respectively in study P05101). For later responders, the duration of boceprevir treatment after 4 weeks of lead-in PegIntron/ribavirin for previous treatment failure subjects can be 32 weeks of triple followed by 12 weeks of PR as the RGT arm strategy the sponsor used in the P05101 trial (SVR rates of 79% and 73% in RGT arm and BOC48 arm respectively in study P05101).

For the early responder in Black subjects in treatment-naïve study, the longer boceprevir treatment duration than what in the RGT arm seems have better SVR (SVR rate of 87% [13/15] in the RGT arm and 95% [18/19] in the BOC48 arm in study P05216). There is a numeric difference in the SVR rate of 8% for early responders between RGT arm and BOC48 arm for Black subjects in Cohort 2 of study P05216 although it is not statistically significant. The sample size (<20 subjects per arm) is too small to make any determination.

For the later responders in treatment-naïve population, the duration of boceprevir treatment of 24 weeks plus 20 weeks of PegIntron/ribavirin after 4 weeks of lead-in PegIntron/ribavirin used in the RGT arm of P05216 is not long enough. There is a numeric difference in SVR rate of 9.2% (SVR rate of 66% in the RGT arm and 75% in the BOC48 arm) for late responders between RGT arm and BOC48 arm although it is not statistically significant. The study was not designed with adequate power to detect this difference. The recommended duration could either be the 44 weeks of triple therapy as used in the BOC48 arm in P05216 trial or 32 weeks of triple therapy followed by the 12 weeks of PR as the RGT arm for later responder in study P05101 as suggested by the Pharmacometrics reviewer. There was no data available to make a final statistical choice between the two since the later one was not in the trial.

Another remaining issue is whether or not the previous Null responder should be included in the indication. Please refer to clinical review for details.

## APPENDICES

### References

1. StatXact PROCs User Manual for SAS Users, Version 6, 2004, Cytel.
2. SAS Version 9.2, SAS Inc.
3. Matthews and Altman. Interaction 3: How to examine heterogeneity. *BMJ*, 1996: Vol. 313:P862.

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/s/  
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