EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

7 September 2012
EMA/CHMP/393220/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

ViraferonPeg

peginterferon alfa-2b

Procedure No.: EMEA/H/C/000329/WS/0216

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

2 March 2012
EMA/CHMP/80845/2012

Committee for Medicinal Products for Human Use (CHMP)

CHMP Type II variation assessment report

Invented name PegIntron, ViraferonPeg and Rebetol

Procedure No. EMEA/H/C/xxxx/WS/0216

Marketing authorisation holder (MAH): Schering-Plough Europe

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1. Background information on the procedure

1.1. *Requested Type II variation*

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Schering-Plough Europe submitted to the European Medicines Agency on 30 November 2011 an application for a variation, following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

This application concerns the following medicinal products:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
PegIntron, EMEA/H/C/000280/WS/0216	peginterferon alfa-2b	See Annex A
Rebetol, EMEA/H/C/000246/WS/0216	ribavirin	See Annex A
ViraferonPeg, EMEA/H/C/000329/WS/0216	peginterferon alfa-2b	See Annex A

The following variation was requested:

Variation requested		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication to reflect the triple combination use of peginterferon alfa 2b, ribavirin and boceprevir in the treatment of Hepatitis C. In the labelling of Rebetol the use of "Lot" and "Exp" has been aligned in all languages.

The requested worksharing procedure proposed amendments to the SmPC, Labelling and Package Leaflet.

Appointed Rapporteur for the WS procedure: Kristina Dunder

1.2. *Steps taken for the assessment*

Submission date:	30 November 2011
Start of procedure:	18 December 2011
Rapporteur's preliminary assessment report circulated on:	20 January 2012
Rapporteur's updated assessment report circulated on:	10 February 2012
CHMP opinion:	16 February 2012

Information on Paediatric requirements

Not applicable

2. Scientific discussion

2.1. *Introduction*

The therapeutic goal of treatment for chronic hepatitis C (CHC) is the eradication of the hepatitis C virus (HCV) with a halting/reversal of the disease progression, which is essentially a cure of this disease. Until recently, the standard of care treatment was the combination of peginterferon alpha (PEG) and ribavirin (RBV). Of the six major HCV genotypes, genotype 1 is the least responsive to PEG plus RBV with sustained virological response (SVR) rates of approximately 40% in previously untreated HCV genotype 1 patients. SVR rates are even lower in blacks and in subjects with advanced liver fibrosis/cirrhosis. Merck (Schering-Plough Research Institute) HCV clinical studies showed that in patients not achieving SVR (nonresponders and relapsers) with PEG plus RBV, approximately 25% to 30% of the nonresponders had substantial liver fibrosis with likelihood for further disease progression, thus identifying an unmet medical need to increase response rates for both previously untreated and previous treatment-failure (relapsers/nonresponders) HCV genotype 1 patients.

In response to this unmet medical need, Victrelis (International Nonproprietary Name [INN] boceprevir, SCH 503034, referred to as BOC hereafter) was developed. BOC is a potent, orally administered, serine protease inhibitor, specifically designed to inhibit the HCV nonstructural protein 3 (NS3) protease and, thereby, inhibit viral replication in infected host cells. BOC (Victrelis, EU/1/11/704/001), when added to standard-of-care PEG plus RBV, has been assessed by the EMA/CHMP (positive opinion adopted on 26 May 2011) and approved by the European Commission (Marketing Authorisation granted 18 July 2011) for the treatment of CHC genotype 1 infection in adult patients with compensated liver disease who are previously untreated or who have failed previous therapy.

The Marketing Authorisation Holder (MAH) is submitting data from two pivotal Phase 3 studies: one in naive patients (P05216) and one in previously treated patients (P05101), to support the update of Annexes I and IIIB of the PegIntron/ViraferonPeg (peginterferon alfa-2b) and Rebetol (ribavirin) 200 mg hard capsules product information concerning the use of tritherapy (Pegintron/ViraferonPeg + Rebetol + Victrelis) to treat CHC genotype 1 infected adult patients with compensated liver disease who are previously untreated or naive failed previous therapy. In addition the MAH is submitting data that were also included with the Victrelis MAA from a number of supportive Phase 2/3 trials.

All data submitted within this dossier has previously been submitted to and assessed by the Agency as part of the Victrelis Marketing Authorisation Application (MAA) EMEA/H/C/2332.

The aim of this variation is as such to introduce the tritherapy indication to the product information of Pegintron/ViraferonPeg and Rebetol.

The following sections of the SmPC for PegIntron/ViraferonPeg and Rebetol are amended to cross refer to the boceprevir SmPC, as it is expected that physicians will use the boceprevir SmPC for the use of tritherapy:

- **4.1 Therapeutic indications**
- **4.2 Posology and method of administration**
- **4.3 Contraindications**
- **4.8 Undesirable effects**
- **5.1 Pharmacodynamic properties**

2.2. *Clinical aspects*

The indication for boceprevir is the treatment of chronic hepatitis C (HCV) genotype 1 infection, in combination with peginterferon alpha and ribavirin, in adult patients (18 years and older) with compensated liver disease who are previously untreated or who have failed previous therapy.

Table 1. Tabular Summary of pivotal clinical studies

Study ID	Diagnosis Incl. criteria	Design	Study Posology	Subjs by arm entered/ compl.
P03523 (SPRINT-1) Completed	Treatment-naïve	Phase 2, open-label, two-part study. • Part 1 included five treatment arms with BOC/PR for 28 or 48 weeks, with and without a 4-week lead-in with PR. • Part 2 included exploration of BOC/P/low-dose RBV (400 to 1000 mg/day) for 48 weeks. • Randomization was stratified by race (black vs white) and by cirrhosis vs no cirrhosis (Part 1)	Part 1 BOC 800 mg TID PEG2b 1.5 µg/kg QW RBV 800 to 1400 mg/day Part 2 BOC 800 mg TID PEG2b 1.5 µg/kg QW RBV 400 to 1000 mg/day	Total: 598/595 Part 1: 520 treated Part 2: 75 treated
P05216 (SPRINT-2) Completed 2008-2010	Treatment-naïve	**Phase 3**, double-blind, placebo-controlled study comparing two regimens of boceprevir response-guided therapy (RGT) treatment paradigm of BOC/PR (28/48 wk) and BOC/PR (48 wk) to PR (48 wk). • 2 cohorts: Cohort 1 (white) and Cohort 2 (black) • Randomization to 3 treatment arms (1:1:1) in each cohort. • Stratified by HCV genotype 1a vs 1b and by viral load (≤400,000 IU/mL vs >400,000 IU/mL) within cohort. • 28- or 48-wk treatment duration; 4-week lead-in with PR.	BOC 800 mg TID (or placebo) PEG2b 1.5 µg/kg QW RBV 600 to 1400 mg/day	1099/1097 Cohort 1: 938 nonblack treated subjects Cohort 2: 159 black treated subjects
P03659 (RESPOND-1) Completed	Previous PEG/RBV Treatment Failures	Phase 2, double-blind (for RBV), placebo-controlled study to determine the safe and effective dose range of boceprevir (100 to 800 mg) and PEG2b with or without RBV. • Up to 49-wk treatment duration.	BOC (or placebo) 100, 200, 400, or 800 mg PO TID PEG2b 1.5 µg/kg QW RBV (or placebo) 800 to 1400 mg/day	357/357
P05101 (RESPOND-2) Completed 2008-2010	Previous PEG/RBV Treatment Failures	**Phase 3,** double-blind, placebo-controlled study comparing two regimens of boceprevir response-guided therapy (RGT) treatment paradigm of BOC/PR (36/48 wk) and BOC/PR (48 wk) to PR (48 wk).	BOC 800 mg TID (or placebo) PEG2b 1.5 µg/kg QW RBV 600 to 1400 mg/day	404/403

		• Randomization to 3 treatment arms in a 1:2:2 ratio. • Stratified by previous treatment in qualifying treatment regimen and by HCV genotype 1a vs 1b. • 36- or 48-wk treatment duration; 4-week lead-in with PR.		
Long-Term Follow-up Study				
P05063 Ongoing	Received at least one dose in a previous Phase 1, 2, or 3 BOC trial or NAR Trial	3.5 year long-term follow-up study to confirm durability of virologic response, characterize long-term safety, and characterize natural history of HCV sequence variants.	No drug therapy administered	No planned sample size 604 enrolled as of 04 MAR 2010

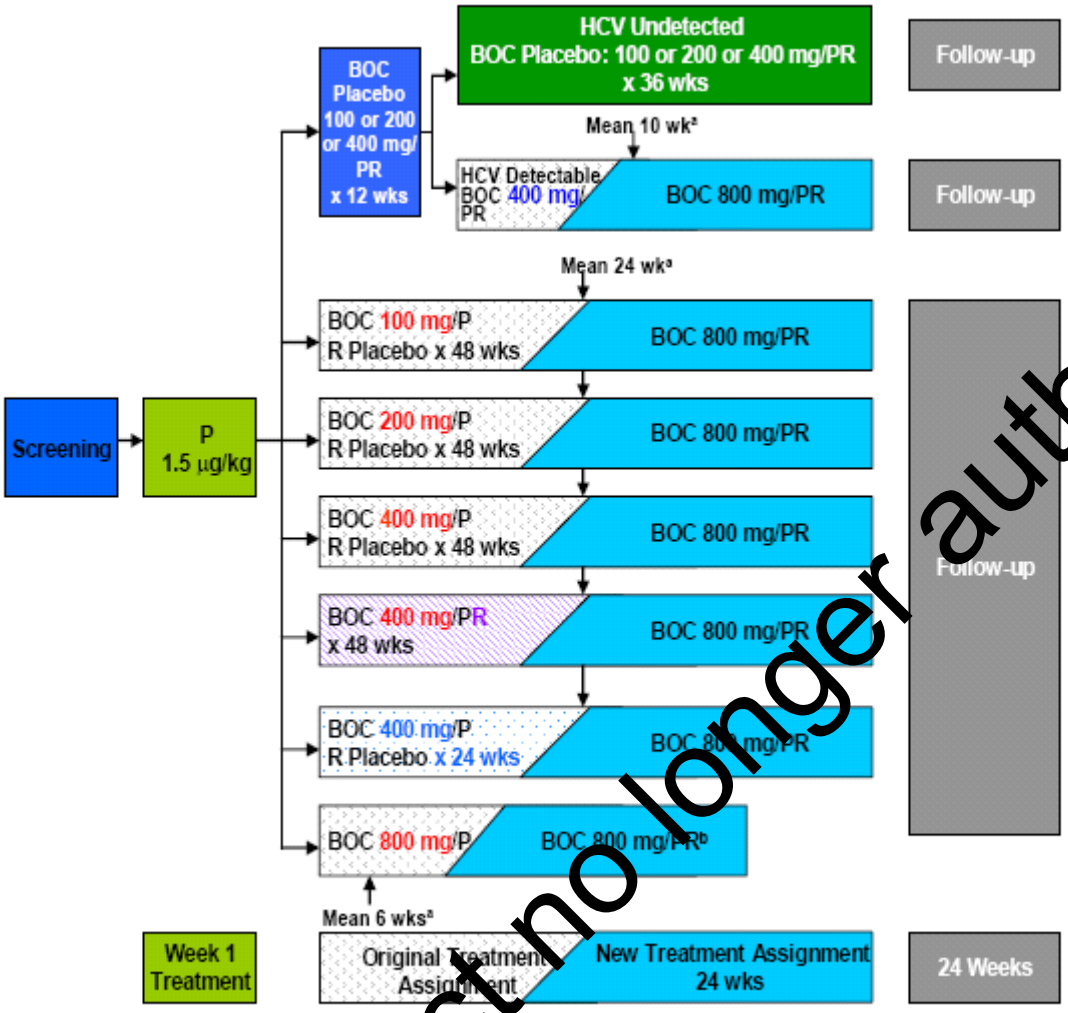
HCV=hepatitis C virus; NAR=narlaprevir; PO=oral, PLB = placebo; RBV = ribavirin; QW=once a week; SC=subcutaneous; SPRI=Schering-Plough Research Institute; TID = three times a day; WBD = weight-based dosing

2.3. *Clinical efficacy*

2.3.1. Dose response studies

Two phase IIb studies were conducted. The first one (September 2005) was conducted in previously treated HCV genotype-1 patients (RESPOND-1); the second one (January 2007) was conducted in naïve HCV genotype 1 patients (SPRINT-1).

P03659/RESPOND-1 was a randomized, placebo-controlled, dose-ranging, multi-site, medical evaluator-blind (BOC) and double-blind (REBETOL [RBV]) study of BOC in combination with PEG 1.5 mg/kg QW SC plus RBV (800 to 1400 mg/day) or RBV placebo in adult, HCV genotype 1 (HCV-1) prior peginterferon alfa/ribavirin nonresponders. The study design is summarized in the figure below.



BOC=boceprevir; HCV=hepatitis C virus; P=peginterferon alfa-2b; R=ribavirin; wks=weeks
[a] Mean duration of boceprevir before subjects rolled over
[b] nonrandomized

Study Conduct

There were two protocol amendments:

The first amendment added an open label group, Arm 7 (15 of 65 were to be African-American), all of whom were to receive PEG 1.5 µg/kg SC for 1 week followed by PEG/BOC 800 mg TID for 24 weeks.

The second amendment

Switch all continuing subjects to BOC 800 plus RBV (with PEG) as follows:

- Arms 2 to 6: For subjects in the BOC 100, 200, and 400-mg arms with significant HCV-RNA decrease (HCV-RNA ≤10,000 IU/ml) at most recent visit, increase BOC dose to 800 mg TID and add weight based RBV. Discontinue all other (non-responding) subjects
- Arm 7: Add RBV to all the subjects in the BOC 800-mg dose (mean treatment duration only 6.5
- weeks)
- Arm 1 (PEG/RBV Control): At "rollover" Week 17 (HCV Positive at Week 13), add 800 mg BOC
- An additional 24 weeks of treatment was indicated for all eligible subjects who continued on triple therapy (PEG + RBV + BOC 800 mg TID)

- All subjects were followed for 24 weeks after the end of treatment (EOT).

This amendment followed a review by the Data Review Advisory Board (DRAB) which identified a low anti-HCV activity of suboptimal Boceprevir doses and the important development of resistance in the groups without ribavirin. Thus, the decision was taken to switch all continuing subjects to tritherapy with boceprevir 800mg TID.

A total of 357 subjects were randomized in the study: 292 were randomized in the initial six arms of the study, and an additional 65 in Arm 7 (PEG + BOC 800 mg TID). After the implementation of Amendment No. 2 and the evaluation of eligible subjects, 143 subjects rolled over into treatment with PEG/RBV/BOC 800 mg TID for an additional 24 weeks.

The majority of subjects in the intent-to-treat (ITT) population were male (62%), between 18 and 65 years of age (mean = 49.5 years), and white (92%), with the exception of the subset of subjects treated with PEG/BOC 800 mg (Arm 7) in which 23% were African American.

Sixty-two percent of subjects were classified as genotype 1a, 35% were genotype 1b, and 3% were considered as "other" (genotype 1 unspecified). Most of the subjects (82-98%) had Baseline HCV-RNA levels of >600,000 IU/mL with a mean of 2.9 x 10^6 IU/mL.

This phase II dose ranging study had a complex 7-arms design to meet the multiple objectives of:

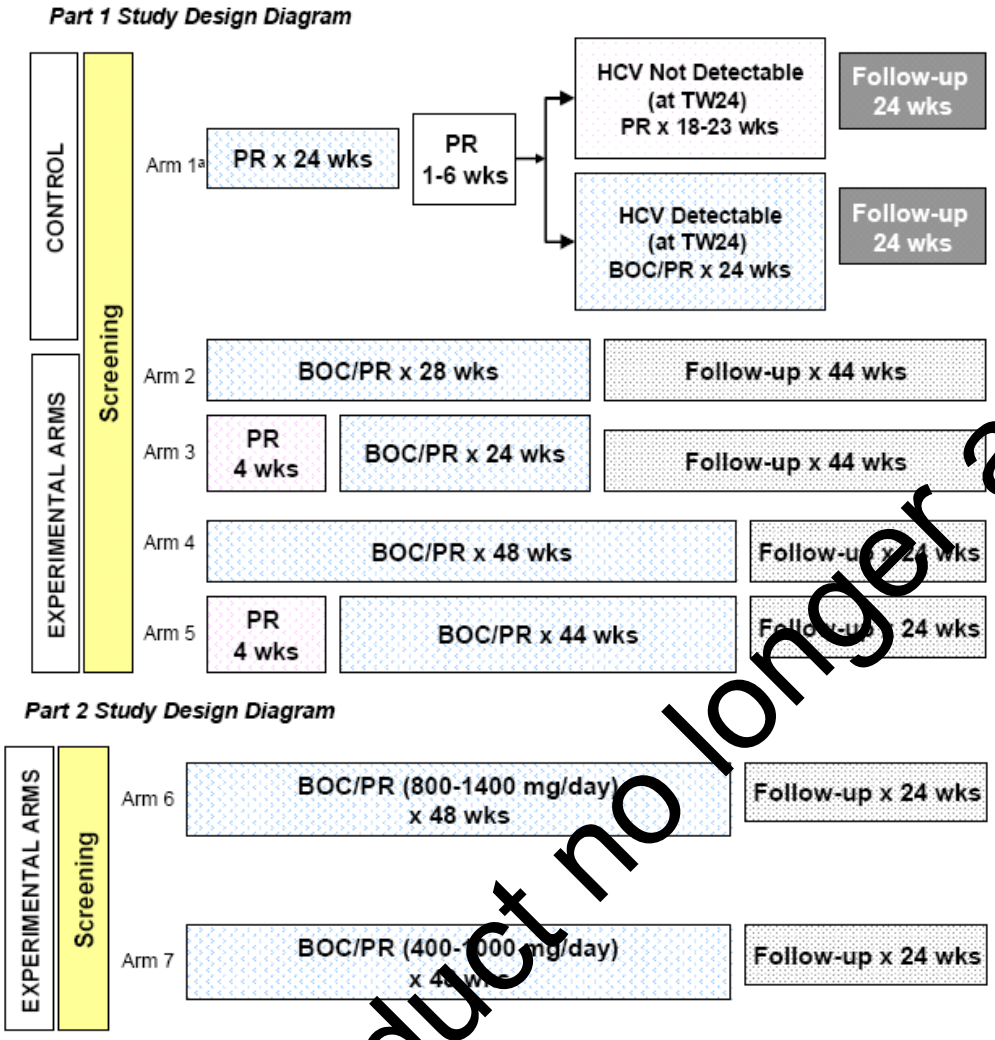
- determining the most effective dose and treatment duration of BOC (100 mg TID, 200 mg TID, 400 mg TOD or 800 mg TOD) in non responders patients,
- determining whether ribavirin is mandatory to enhance the efficacy of pegIFN and BOC, and
- evaluating the safety of BOC.

The multiple amendments of this study make its results hardly interpretable. Nevertheless lessons were learned which informed the design of the subsequent phase II study in treatment naïve patients:

- ribavirin is needed to prevent viral breakthrough with resistant variants
- The antiviral activity of boceprevir is dose-related 800 mg TID of boceprevir in combination with PegIntron resulted in the most rapid time to the first HCV-RNA negative samples. Furthermore, PK analysis suggested that increasing the dose further would not substantially increase trough concentrations.

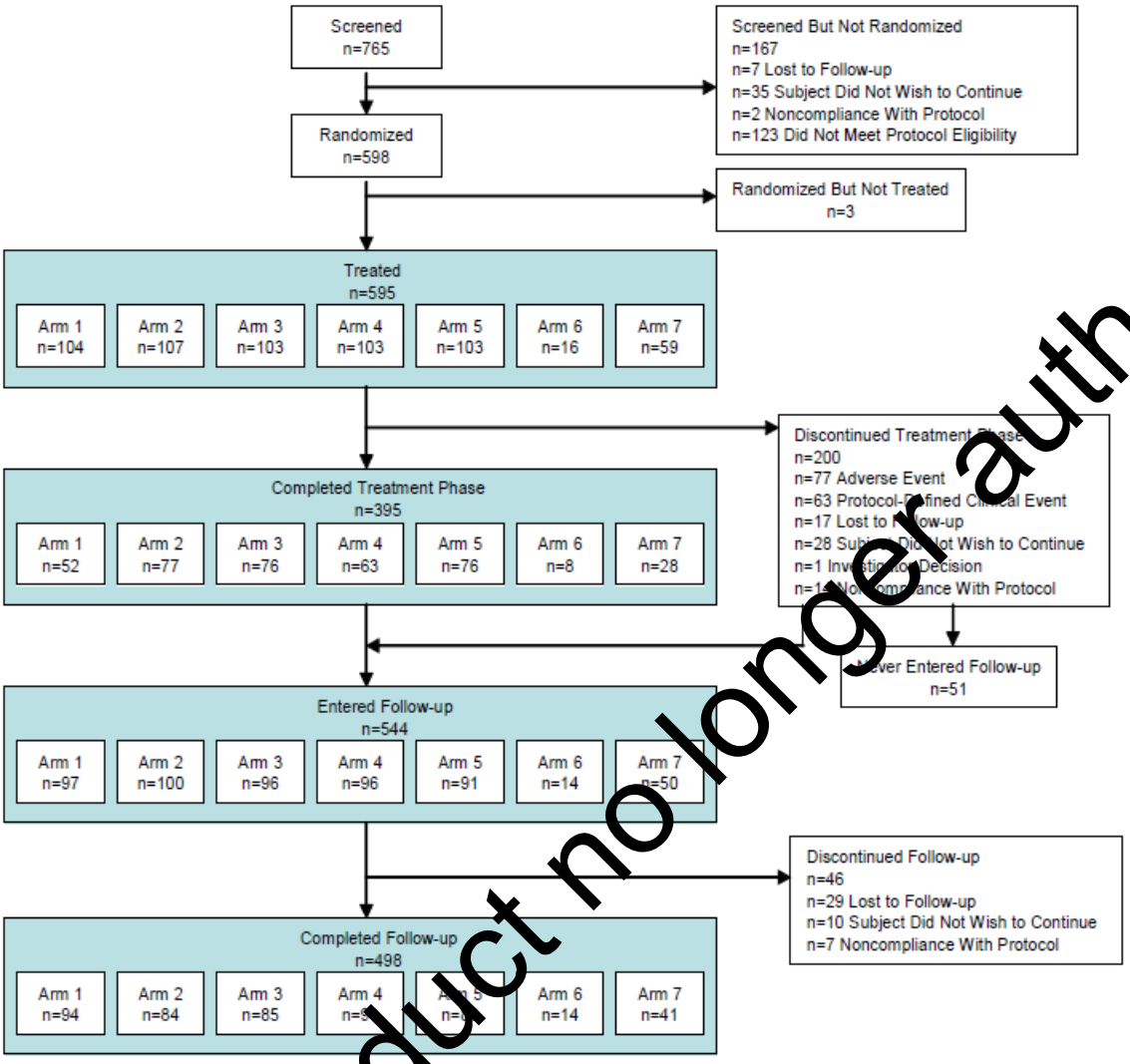
- SPRINT-1 was an open-label, randomized safety and efficacy trial in adult, treatment-naïve CHC subjects with genotype 1 infection. The study compared standard-of-care PEG2b (1.5 µg/kg) plus ribavirin (800 to 1400 mg/day) for 48 weeks to five treatment strategies containing boceprevir with only one dose tested (800 mg TID)

The study design was as follows:



The primary efficacy endpoint was SVR.

The study subject disposition is described in the figure below.



Baseline demographic and disease characteristics were similar across treatment arms; 60% (355/595) of subjects were males and 81% (481/595) were white, with a mean age of 47.5 ± 7.7 years and a mean weight of 81.8 ± 17.2 kg. Approximately 56% (334/595) had subtype 1a virus; 89% (531/595) had high viral load (>600,000 IU/mL) with a 6.54 mean log10 baseline viral load; 7% (41/595) of study subjects were cirrhotic based on local liver histopathology, and 16% (98/595) were black.

Results

The results are presented in the following table:

Table 2. Virologic Response (Undetectable HCV-RNA) and Relapse Rates

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

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

SVR rates were significantly higher in all arms in which standard of care (28 or 48 weeks, with or without lead-in) was combined with Boceprevir (54.2% to 74.8% vs 37.5%). Treatment for 48-weeks and a lead-in period resulted in the numerically highest SVR rate. Results from the low dose ribavirin arm did not support this strategy, which was therefore not used in the phase III studies

A secondary analysis was conducted according to which the pooled 48-week boceprevir arms with and without lead-in had significantly higher SVR rates compared to the pooled 28-week boceprevir arms with and without lead-in (P=0.0009). Furthermore, of interest, the difference in SVR in the pooled 28- and 48-week, lead-in arms vs the pooled 28- and 48-week, no lead-in arms was not statistically significant (P=0.2864); however, there was an overall numerical advantage of 5% for the lead-in arms. (See Table below)

Table 3. Pooled Treatment Comparisons and P-values for SVR

	Difference in SVR Rates (%)	Lower 95% CI (%)	Upper 95% CI (%)	P-Value[a]
Arms 2+3 (28 wk) vs Arm 1 (P/R)	17.7	6.3	29.2	0.0024
Arms 4+5 (48 wk) vs Arm 1 (P/R)	33.4	22.2	44.6	<.0001
Arms 4+5 (48 wk) vs Arms 2+3 (28 wk)	15.6	6.5	24.8	0.0009
Arms 3+5 (Lead-in) vs Arms 2+4 (No Lead-in)	5.1	-4.2	14.3	0.2864

Predictability of SVR Based on early response

SVR rates by Time to First Negative HCV-RNA is shown in the following table.

Table 4. SVR rates by Time to First Negative HCV-RNA

Time to First Negative HCV-RNA	SVR n/N (%)				
	Arm 1[a] P/R 48 wk n=104	Arm 2 P/R/B 28 wk n=107	Arm 3 P/R Lead-in P/R/B 28 wk n=103	Arm 4 P/R/B 48 wk n=103	Arm 5 P/R Lead-in P/R/B 48 wk n=103
≤4 wk[b]	8/8 (100)	32/43 (74.4)	54/66 (81.8)	32/38 (84.2)	62/66 (93.9)
>4 wk to 12 wk[b]	24/29 (82.8)	26/42 (61.9)	4/19 (21.1)	36/43 (83.7)	15/19 (78.9)
>12 wk[b]	7/23 (30.4)	0/3 (0.0)	0/1 (0.0)	1/6 (16.7)	0/1 (0.0)
Never	0/44 (0.0)	0/19 (0.0)	0/17 (0.0)	0/16 (0.0)	0/17 (0.0)
All Subjects	39/104 (37.5)	58/107 (54.2)	58/103 (56.3)	69/103 (67.0)	77/103 (74.8)

B = boceprevir; HCV-RNA = hepatitis C virus-ribonucleic acid; P = peginterferon alfa-2b 1.5 µg/kg QW; QW = once weekly; R = ribavirin 800 to 1400 mg/day; SVR = sustained virologic response.

b exposure to weeks of P/R for arm 1 and to weeks of boceprevir treatment for arms 2 through 5.

SVR rates were high regardless of total treatment duration in patients reaching a negative HCV-RNA at week 4 or earlier. However, in patients reaching there first negative HCV-RNA after week 4, SVR rates were clearly higher in patients receiving 48 weeks of total therapy, compared to 28 weeks. This informed the decision to use a response guided therapy algorithm in phase III. Furthermore, the fact that almost no patient that were treated with boceprevir and became negative after week 12 informed on the potential utility of a futility rule.

Rationale for 4-Week Lead-in with P/R on SVR

The theoretical rationale for the 4-week lead-in strategy is based on several factors. The 4-week lead-in allows PEG2b and ribavirin to reach steady-state concentrations and, potentially, for the host-dependent immune system to be primed by PEG2b. Also, the lower viral load at the time of initiation of boceprevir therapy might decrease the risk of selection of drug resistant variants and consequent viral breakthrough.

As stated above, SVR rates were numerically higher in arms using the lead in, Combining across treatment groups, the rate of viral breakthrough in the boceprevir lead-in groups was 4% (9/206) compared with 9% (19/210) in the boceprevir groups with no lead in (p=0· 057). Also, relapse rates were numerically lower in the arms using a lead in. These finding informed its use in the phase III program.

2.3.2. Main study(ies)

Two pivotal phase III studies, one in treatment naïve (P05216/SPRINT 2) and one in pretreated patients (P05101/RESPOND 2) have been carried out. These trials were conducted in the US, Canada, Western Europe and Argentina. First the study in treatment naïve subjects will be described, followed by the study in pretreated patients. Both studies started on 5 august 2008.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections). The studies are detailed and discussed hereafter.

Title: **A PHASE 3, SAFETY AND EFFICACY STUDY OF BOCEPREVIR IN PREVIOUSLY UNTREATED SUBJECTS WITH CHRONIC HEPATITIS C GENOTYPE 1**		
Study identifier	P05216	
Design	This was a Phase 3, randomized, multicenter study, double-blinded for boceprevir or placebo in combination with open-label PR, in previously untreated adult subjects with CHC (HCV genotype 1). The study compared standard-of-care PR (PEG2b 1.5 µg/kg QW plus RBV 600 to 1400 mg/day [WBD]) for 48 weeks to two treatment paradigms containing boceprevir 800 mg TID plus PR for a total duration of 28 or 48 weeks, including a 4-week lead-in with PR. A response-guided therapy (RGT) paradigm was used in Arm 2, whereby therapy was based on response at a specified time point on treatment. Thus, subjects randomized to Arm 2 received a 4-week PR lead-in followed by BOC/PR for 24 weeks; those with undetectable HCV-RNA at TW 8 through TW 24 completed therapy at TW 28 and entered follow-up, while those with detectable HCV-RNA at TW 8 or any subsequent assays and who did not discontinue for virologic futility at TW 24 received an additional 20 weeks of placebo plus PR, for a total treatment duration of 48 weeks. The switch from boceprevir to placebo occurred in a blinded fashion. Arm 3 consisted of a 4-week PR lead-in followed by 44 weeks of BOC/PR. A 24-week futility rule was followed for all arms, whereby therapy was discontinued for subjects with detectable HCV-RNA at TW 24.	
	Duration of main phase:	Approximately 22 months
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable
Hypothesis	Superiority	
Treatments groups	Arm 1 (PR Control)	PEG2b 1.5 µg/kg + RBV (WBD) for 4 weeks followed by placebo + PEG2b 1.5 µg/kg + RBV (WBD) for 44 weeks with 24 weeks post-treatment follow-up. A 24-week futility rule was followed for all arms, whereby therapy was discontinued for subjects with detectable HCV-RNA at TW 24 368 patients were randomized.
	Arm 2 (Response-guided therapy):	PEG2b 1.5 µg/kg + RBV (WBD) for 4 weeks followed by boceprevir + PEG2b 1.5 µg/kg + RBV (WBD) for 24 weeks. At the TW 28 visit, the interactive voice response system (IVRS) was to assign subjects to one of two groups based on their HCV-RNA results on and after TW 8. - At the TW 28 visit, subjects whose HCV-RNA was undetectable at TW 8 and at all subsequent assays through TW 24 were to be instructed that they had completed their assigned treatment and were to proceed to the 44-week follow-up. - At the TW 28 visit, subjects with detectable HCV-RNA at TW 8 or at any subsequent assays through TW 24 were to be assigned by IVRS to continue therapy with placebo + PR for an additional 20 weeks, to complete a total of 48 weeks on treatment with 24 weeks post-treatment follow-up. A 24-week futility rule was followed for all arms, whereby therapy was discontinued for subjects with detectable HCV-RNA at TW 24 368 subjects randomized;
	BOC/PR48 (Arm 3):	PEG2b 1.5 µg/kg + RBV (WBD) for 4 weeks followed by boceprevir + PEG2b 1.5 µg/kg + RBV (WBD) for 44 weeks with 24 weeks post-treatment follow-up. A 24-week futility rule was followed for all arms, whereby therapy was discontinued for subjects with detectable HCV-RNA at TW 24 366 subjects randomized;

Endpoints and definitions	Primary endpoint		The primary objective of this study was to compare the efficacy of two therapeutic regimens of boceprevir dosed 800 mg orally (PO) three times daily (TID) in combination with peginterferon alfa-2b (PEG2b) 1.5 □g/kg subcutaneously (SC) once weekly (QW) plus weight-based dosing (WBD) of ribavirin (600 mg/day to 1400 mg/day [RBV]) PO to therapy with PEG2b and RBV (PR) alone in previously untreated adult subjects with chronic hepatitis C (CHC) (hepatitis C virus [HCV] genotype 1). The primary endpoint is sustained virologic response (SVR), defined as undetectable hepatitis C virus-ribonucleic acid (HCV-RNA) at Follow-up Week (FW) 24. The study included two separate cohorts (Cohort 1 [white subjects] and Cohort 2 [black subjects]). The primary efficacy endpoint was analyzed in the Full Analysis Set (FAS), which included all randomized subjects who received at least one dose of any study medication (PEG2b, RBV, or boceprevir/placebo) in Cohort 1 plus Cohort 2. This combined analysis was based on Health Authority recommendations and was specified in the Data Analysis Plan. In addition, all efficacy analyses were performed by cohort.
	Key Secondary Endpoint		The key secondary objective of this study was to compare the efficacy of two therapeutic regimens of boceprevir when used in combination with PR (WBD) with the standard of care (PR [WBD] alone) in the modified Intent-to-Treat (mITT) data set, which included all randomized subjects who received at least one dose of experimental study drug (placebo for the control arm and boceprevir for the experimental arms).
	Other Secondary Efficacy Endpoints		In addition, the two boceprevir regimens (Response-Guided Therapy [RGT] and BOC/PR48) were to be compared as overall treatment regimens, and the early (undetectable HCV-RNA at Treatment Week [TW] 8 through TW 24) and late responders (detectable HCV-RNA at TW 8 or any subsequent visit by TW 24) in the RGT arm were to be compared with a matched group of early and late responders in the BOC/PR48 arm. These latter comparisons were meant to give additional insight into the questions of 1) whether 28 weeks of therapy is sufficient for early responders, and 2) whether two-drug therapy (PR) is sufficient for the last 20 weeks of therapy for late responders. Other secondary objectives of the study were as follows: • To evaluate the safety of boceprevir when used in combination with PR (WBD). • To define predictors of SVR, such as epidemiologic factors, disease characteristics, and on-treatment response. • To develop the relationship between steady-state pharmacokinetic parameters, obtained from a population-based pharmacokinetic model and responses in a subset of subjects.
Database lock	20 MAY 2010		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full analysis set		
Descriptive statistics and estimate variability	Since most of the subjects in Cohort 1 were white, this group of subjects is also referred to as “white subjects” in this report. Cohort 2 included only subjects whose self-reported race was black. In each cohort, there was a higher proportion of male subjects. In Cohort 2, median weight and BMI were greater and a higher proportion of subjects in each arm had HCV subtype 1a compared to subjects in Cohort 1. Most of the subjects in both cohorts had baseline Metavir fibrosis scores of F0, F1, or F2, and absence of to <5% steatosis. Overall, the proportion of subjects with cirrhosis and advanced fibrosis (F3/F4) was 9%. Only 19 of the 1097 treated subjects were on statin therapy at baseline.		

Effect estimate per comparison	Primary endpoint	**Sustained Virologic Response for Cohort 1, Cohort 2, and Cohort 1 Plus Cohort 2 (FAS)**

	FAS		
	Control	Experimental	
	Arm 1 PR48	Arm 2 RGT	Arm 3 BOC/PR48
Cohort 1	n=311	n=316	n=311
EOT(Undetectable HCV-RNA), n (%)	176 (56.6)	235 (74.4)	241 (77.5)
SVR n (%)	125 (40.2)	211 (66.8)	213 (68.5)
Δ SVR	--	26.6	28.3
95% CI for Δ	--	19.1, 34.1	20.8, 35.8
P value	--	<.0001	<.0001
Relapse n/N (%)	37/162 (22.8)	21/232 (9.1)	18/230 (7.8)
Cohort 2	n=52	n=62	n=55
EOT (Undetectable HCV-RNA) n (%)	15 (28.8)	26 (50.0)	36 (65.5)
SVR n (%)	12 (23.1)	22 (42.3)	29 (52.7)
Δ SVR	--	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)
Cohort 1 Plus Cohort 2	n=363	n=368	n=366
EOT (Undetectable HCV-RNA) n (%)	191 (52.6)	261 (70.9)	277 (75.7)
SVR n (%)	137 (37.7)	233 (63.3)	242 (66.1)
Δ SVR	--	25.6	28.4
95% CI for Δ	--	18.6, 32.6	21.4, 35.3
P value	--	<.0001	<.0001
Relapse n/N (%)	39/176 (22.2)	24/257 (9.3)	24/265 (9.1)

Analysis description	Key secondary analysis

Sustained Virologic Response for Cohort 1, Cohort 2, and Cohort 1 Plus Cohort 2 (mITT)

	mITT		
	Control	Experimental	
	Arm 1 PR48	Arm 2 RGT	Arm 3 BOC/PR48
Cohort 1	n=297	n=303	n=299
EOT (Undetectable HCV-RNA), n (%)	176 (59.3)	235 (77.6)	241 (80.6)
SVR n (%)	125 (42.1)	211 (69.6)	213 (71.2)
Δ SVR	--	27.5	29.1
95% CI for Δ	--	19.9 35.2	21.5, 36.8
P value	--	<.0001	<.0001
Relapse n/N (%)	37/162 (22.8)	21/232 (9.1)	18/230 (7.8)
Cohort 2	n=47	n=47	n=55
EOT (Undetectable HCV-RNA) n (%)	15 (31.9)	26 (55.3)	36 (65.5)
SVR n (%)	12 (25.5)	22 (46.8)	29 (52.7)
Δ SVR		21.3	27.2
95% CI for Δ		2.3, 40.2	9.0, 45.3
P value	--	0.0366	0.0107
Relapse n/N (%)	2/14 (14.3)	3/25 (12.0)	6/35 (17.1)
Cohort 1 Plus Cohort 2	n=344	n=350	n=354
EOT (Undetectable HCV-RNA) n (%)	191 (55.5)	261 (74.6)	277 (78.2)
SVR n (%)	137 (39.8)	233 (66.6)	242 (68.4)
Δ SVR	--	26.7	28.5
95% CI for	--	19.6, 33.9	21.4, 35.6
P value	--	<.0001	<.0001
Relapse n/N (%)	39/176 (22.2)	24/257 (9.3)	24/265 (9.1)

Title: **A PHASE 3 SAFETY AND EFFICACY STUDY OF BOCEPREVIR (SCH 503034) IN SUBJECTS WITH CHRONIC HEPATITIS C GENOTYPE 1 WHO FAILED PRIOR TREATMENT WITH PEGINTERFERON/RIBAVIRIN (Protocol No. P05101; RESPOND-2)**		
Study identifier	P05101	
Design	This was a randomized, parallel-group, multi-centre study, double-blinded for boceprevir or placebo in combination with open-label PR, in adult subjects with chronic HCV genotype 1 who demonstrated interferon responsiveness but failed to achieve SVR on prior treatment with peginterferon/ribavirin. Subjects were randomized to 1 of 3 treatment arms on Day 1, as described below. At the time of randomization, subjects were stratified based on response to their previous qualifying regimen (relapser vs nonresponder) and by HCV subtype (1a vs 1b). A 12-week futility rule was followed for all arms, whereby all subjects with detectable HCV-RNA at Treatment Week (TW) 12 discontinued therapy and entered follow-up. Treatment failures in the PR control arm (Arm 1) were offered the opportunity to receive treatment with boceprevir plus PR (BOC/PR) via an access study (P05514) or to proceed to the follow-up phase of this study. Subjects in the PGT arm (Arm 2) and the BOC/PR48 arm (Arm 3) proceeded directly to the follow-up phase of this study. Sites and subjects remained blinded as to whether subjects had been in Arm 2 or Arm 3	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Approximately 44 months not applicable not applicable
Hypothesis	Superiority	
Treatments groups	Arm 1 (PR Control)	PR for 4 weeks followed by placebo + PR for 44 weeks, with 24 weeks post-treatment follow-up. A 12-week futility rule was followed for all arms, whereby therapy was discontinued for subjects with detectable HCV-RNA at TW 12. 80 patients were randomized.

	Arm 2 (Response-guided therapy):		Subjects were assigned either a 36-week (a, below) or 48-week (b, below) course of therapy based on their HCV-RNA status at TW 8. PR for 4 weeks followed by BOC/PR for 32 weeks, then: a. 36-week regimen: subjects with undetectable HCV-RNA at TW 8 completed treatment and entered 36 weeks of post-treatment follow-up. b. 48-week regimen: subjects with detectable HCV-RNA at TW 8 were assigned an additional 12 weeks of placebo + PR (the switch from BOC to placebo occurred in a blinded fashion), followed by 24 weeks of post-treatment follow-up. A 12-week futility rule was followed for all arms, whereby therapy was discontinued for subjects with detectable HCV-RNA at TW 12. 162 subjects randomized;
	BOC/PR48 (Arm 3):		PR for 4 weeks followed by BOC/PR for 44 weeks, with 24 weeks post-treatment follow-up. A 12-week futility rule was followed for all arms, whereby therapy was discontinued for subjects with detectable HCV-RNA at TW 12. 161 subjects randomized;
Endpoints and definitions	Primary endpoint		The primary efficacy endpoint was the achievement of SVR, defined as undetectable plasma HCV-RNA at Follow-up Week (FW) 24 in subjects who received at least one dose of study medication (FAS). If a subject was missing data at FW 24 and after, and had undetectable HCV-RNA level at FW 12, the subject was considered an SVR.
	Key Secondary Endpoint		The key secondary efficacy endpoint was the achievement of SVR defined as undetectable HCV-RNA at 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; mITT).
	Other Secondary Efficacy Endpoints		3. The proportion of subjects with an early virologic response (eg, undetectable HCV-RNA at TW 2, 4, 8, or 12) in subjects who achieve SVR. 4. The proportion of subjects with undetectable HCV-RNA at FW 12. 5. The proportion of subjects with undetectable HCV-RNA at 72 weeks after randomization
Database lock	15 APR 2010		

Results and Analysis

Analysis description	**Primary Analysis**
Analysis population and time point description	Full analysis set
Descriptive statistics and estimate variability	In this study, 67% (269/404) of the randomized subjects were male, and 88% (355/404) were non-black. The mean age was 52.7 years (range, 26-74 years) and the mean weight was 85 kg. All subjects had genotype 1 (47% [189/403] subtype 1a, 44% [178/403] subtype 1b by TRUGENE™ assay), and 88% (353/403) had high viral load (>800,000 IU/mL), with a 6.63 mean log_{10} baseline viral load.
Effect estimate per comparison	Primary endpoint: Sustained Virologic Response, End of Treatment Response and Relapse Rates (FAS)

	FAS		
	Control	Experimental	
	Arm 1 PR48 n=80	Arm 2 RGT n=162	Arm 3 BOC/PR48 n=161
EOT (Undetectable HCV-RNA), n (%)	25 (31.3)	114 (70.4)	124 (77.0)
SVR, n (%)	17 (21.3)	95 (58.6)	107 (66.5)
ΔSVR′	--	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)

Analysis description	**Key secondary analysis**

Sustained Virologic Response, End of Treatment Response and Relapse Rates (mITT)

	mITT		
	Control	Experimental	
	Arm 1 PR48 n=78	Arm 2 RGT n=156	Arm 3 BOC/PR48 n=160
EOT (Undetectable HCV-RNA), n (%)	25 (32.1)	114 (73.1)	124 (77.5)
SVR, n (%)	17 (21.8)	95 (60.9)	107 (66.9)
ΔSVR	--	39.1	45.1
95% CI for Δ	--	(27.2, 51.0)	(33.4, 56.8)
P value	--	<0.0001	<0.0001
Relapse, n/N (%)	8/25 (32.0)	17/111 (15.3)	14/121 (11.6)

A Phase 3, Safety and Efficacy Study of Boceprevir in Previously Untreated Subjects With Chronic Hepatitis C Genotype 1 (Protocol No. P05216/SPRINT 2).

Studied Period: 05 August 2008 through 19 May 2010; Multicenter: 149 centres worldwide.

Methods

Study Participants

Main inclusion criteria
Adult subjects with CHC (HCV genotype 1) and with no previous treatment for CHC and HCV-RNA ≥10,000 IU/mL prior to treatment, and liver biopsy consistent with CHC were eligible for the study. *Of note*, the study included two separate cohorts (Cohort 1 comprised of white patients and Cohort 2 of black patients. Due to the poor responsiveness of black subjects to interferon and their underrepresentation in many trials, a second cohort (Cohort 2) of black subjects was enrolled so that a minimum number of black subjects (at least 150) could be evaluated separately. Cohort 2 data also were analyzed separately using similar data sets as for Cohort 1. In addition, a combined Cohort 1 plus Cohort 2 analysis was performed.

Main exclusion criteria
Subjects who were co-infected with human immunodeficiency virus (HIV) or hepatitis B virus (HbsAg positive), as well as patients with decompensated liver disease, were excluded from the study.

Treatments

Control
• **Arm 1 (PR48)**: PR= standard of care therapy consisting of Peginterferon alfa-2b PEG2b (1.5 µg/kg sc once weekly) plus ribavirin (RBV weight-based dose, 600 to 1400 mg PO daily) for 4 weeks followed by placebo (matched to boceprevir (BOC)) + PR for 44 weeks, with 24 weeks post-treatment follow-up.

Experimental therapy:
• **Arm 2** Response-Guided Therapy (RGT): Subjects were assigned either a 28-week or 48-week course of therapy based on their HCV-RNA status at TW 8 and thereafter.

PR for 4 weeks followed by BOC/PR for 24 weeks, then:

- At the TW 28 visit, subjects whose HCV-RNA was undetectable at TW 8 and at all subsequent assays completed their assigned treatment.
- At the TW 28 visit, subjects with detectable HCV-RNA at TW 8 or at any subsequent assays were to continue therapy with placebo + PEG2b 1.5 µg/kg + RBV (weight-based dose, 600 to 1400 mg PO daily) for an additional 20 weeks, to complete a total of 48 weeks on treatment . The switch from boceprevir to placebo was to occur in a blinded fashion.

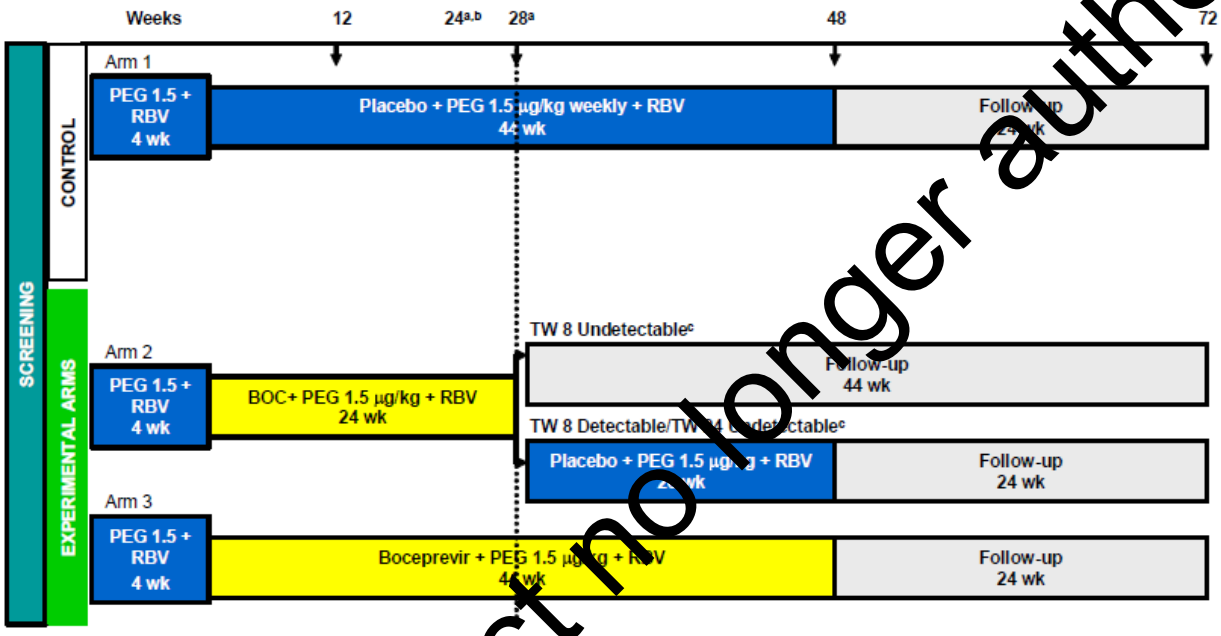
• **Arm 3** (BOC/PR48): PR for 4 weeks followed by boceprevir + PEG2b 1.5 µg/kg + RBV (weight-based dose, 600 to 1400 mg PO daily) for 44 weeks with 24 weeks posttreatment follow-up.

Boceprevir, supplied as 200-mg capsules, was administered at a dosage of 800 mg PO TID.

Weight-based RBV therapy was developed to deliver approximately 13 mg of RBV per kg of body weight. Recent evaluation of anaemia in PR therapy has shown that there is an increased anaemia risk in subjects weighing less than 50 kg, whose actual RBV dose at 800 mg is >16 mg/kg. For this reason, and based on results of a previous trial, the RBV dosing regimen in the current study was extended to include a lower dose (600 mg/day) for those weighing <50 kg.

A 24-week futility rule was followed for all arms, whereby therapy was discontinued for subjects with detectable HCV-RNA at TW 24.

The figure below outlines the structure of the trial:



Management of adverse events

This study permitted ribavirin dose reduction and/or erythropoietin use for subjects who developed anaemia. In the protocol guidelines for use of erythropoietin were provided.

Objectives and endpoints

The primary objective of this study was to compare the efficacy of two therapeutic regimens of boceprevir dosed 800 mg orally (PO) three times daily (TID) in combination with PEG2b 1.5 µg/kg subcutaneously (SC) once weekly (QW) plus weight-based dosing (WBD) of ribavirin (600 mg/day to 1400 mg/day) PO to therapy with PR alone in previously untreated adult subjects with CHC (HCV genotype 1) in Cohort 1 (the cohort of non-black/white subjects). The primary objective corresponds to providing treatment-specific estimates of SVR, defined as undetectable HCV-RNA at Follow-up Week (FW) 24.The primary efficacy endpoint was analyzed in the Full Analysis Set (FAS), which included all randomized subjects who received at least one dose of any study medication (PEG2b, RBV, or boceprevir/placebo).

The key secondary objective of this study, based on a protocol amendment as of December 2009, was to compare the efficacy of two therapeutic regimens of boceprevir when used in combination with PR (WBD) with the standard of care (PR [WBD] alone) in the Modified Intent-to-Treat (mITT) data set,

which included all randomized subjects who received at least one dose of experimental study drug (placebo for the control arm and boceprevir for the experimental arms).

In addition, the two boceprevir regimens (RGT and BOC/PR48) were to be compared as overall treatment regimens, and the early (undetectable HCV-RNA at TW 8) and late responders (detectable HCV-RNA at TW 8) in the RGT arm were to be compared with a matched group of early and late responders in the BOC/PR48 arm. These latter comparisons were meant to give additional insight into the questions of: 1) whether 28 weeks of therapy is sufficient for early responders, and 2) whether two-drug therapy (PR) is sufficient for the last 20 weeks of therapy for late responders.

Other secondary efficacy endpoints were:

• The proportion of subjects with early virologic response (eg, undetectable HCVRNA at TW 2, 4, 8, or 12) who achieved SVR.

HCV-RNA in plasma was measured with the Roche COBAS TaqMan assay, which has a limit of quantitation of 25 IU/ml and a limit of detection of 9.3 IU/ml.

Sample size

This study was projected to enrol 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 had 90% power to detect a combined 13% improvement in the SVR rate, assuming a control SVR rate of 45% (ie, 58% vs 45%).

Randomisation

Randomization occurred separately for Cohort 1 and Cohort 2 and was based on a computer generated random code provided by the sponsor's biostatistics department to the interactive voice response system (IVRS). Within Cohort 1 and Cohort 2, randomized treatment assignment was stratified by baseline viral load (high viral load >400,000 IU/mL) vs low viral load (≤ 400,000 IU/mL) and HCV genotype (1a vs 1b, based on the TRUGENE™ assay). Subjects with genotype 1 who could not be classified as 1a or 1b were to be randomly assigned to a treatment arm within their HCV-RNA strata.

Blinding (masking)

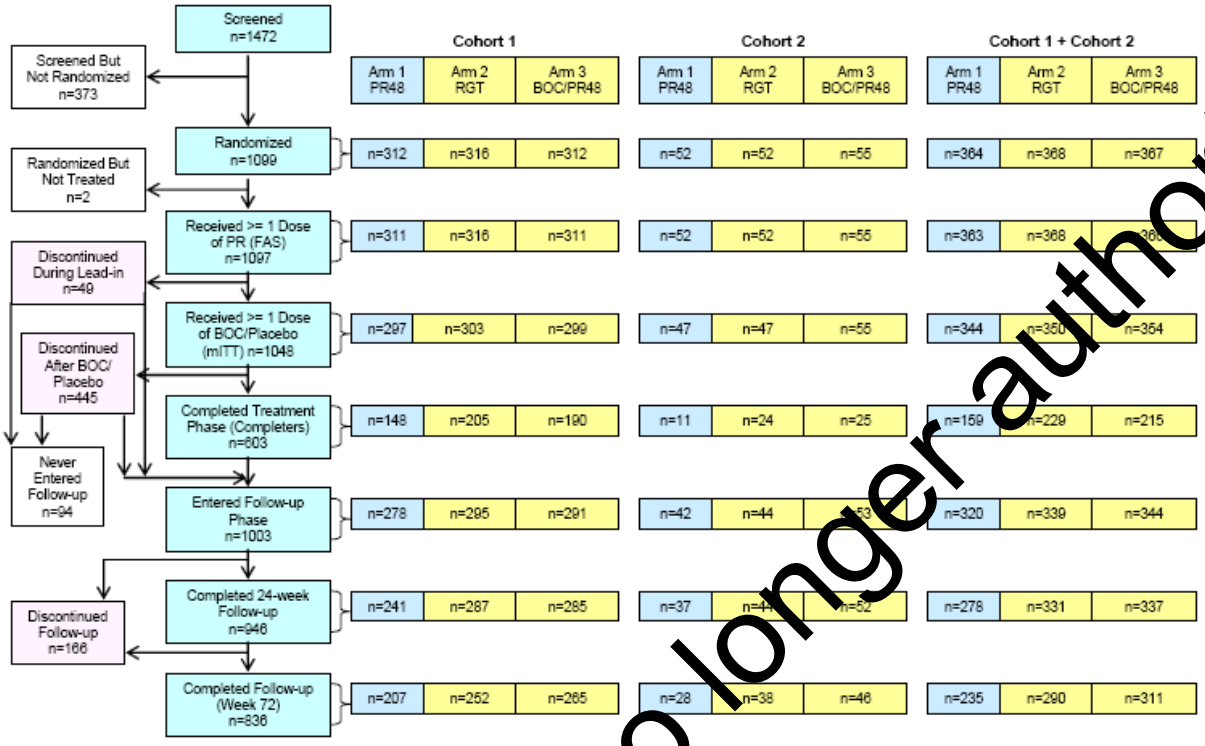
This was a double-blind study in which the sponsor, investigator, study personnel, and study participants were to be blinded with respect to boceprevir treatment. The randomization schedule for blinding of treatment was maintained by the sponsor, provided to the IVRS, and disclosed only after study completion and database closure.

Results

Participant flow

A total of 1472 subjects were screened of these a total of 1099 subjects were randomized; 1097 received at least one dose of PR (FAS), and 1048 received at least one dose of boceprevir or placebo (mITT). Forty-nine (4%) subjects discontinued treatment during the PR lead-in and never received boceprevir/placebo. The main reason for discontinuation during the lead-in included PR-related AEs such as fatigue, chills, and pyrexia. A total of 603 (55%) subjects completed treatment. The main reasons for treatment discontinuation after the lead-in were treatment failure and discontinuation due to AEs. Approximately the same proportion of subjects discontinued due to AEs across all arms (12%, 10% and 14%). The proportions of subjects who discontinued study drugs due to nonmedical reasons were similar across the three arms (8%, 9%, 12%).

Of the 373 subjects who failed screening, 277 (224 white/other and 53 black subjects) were not randomized because they did not meet protocol eligibility criteria. Additionally, 29 subjects failed screening because of administrative reasons, and 44 subjects withdrew consent.



Baseline data

Table 5. Demographics and baseline characteristics

	Screened Subjects			Screen Failures			Randomized Subjects		
	White n=1246	Black n=226	Total n=1472	White n=306	Black n=67	Total n=373	White n=940	Black n=159	Total n=1099
Sex, n (%)									
Female	496 (40)	89 (39)	585 (40)	116 (38)	27 (40)	143 (38)	380 (40)	62 (39)	442 (40)
Male	750 (60)	137 (61)	887 (60)	190 (62)	40 (60)	230 (62)	560 (60)	97 (61)	657 (60)
Race, n (%)									
White	1183 (95)	--	1183 (80)	286 (93)	--	286 (77)	897 (95)	--	897 (82)
American Indian or Alaskan Native	9 (1)	--	9 (1)	3 (1)	--	3 (1)	6 (1)	--	6 (1)
Asian	26 (2)	--	26 (2)	5 (2)	--	5 (1)	21 (2)	--	21 (2)
Black	--	226 (100)	226 (15)	--	67 (100)	67 (18)	--	159 (100)	159 (14)
Multiracial	25 (2)	--	25 (2)	11 (4)	--	11 (3)	14 (1)	--	14 (1)
Native Hawaiian or Other Pacific Islander	3 (<1)	--	3 (<1)	1 (<1)	--	1 (<1)	2 (<1)	--	2 (<1)
Age (y)									
Mean (SD)	48.6 (10.0)	51.9 (7.5)	49.1 (9.7)	48.1 (11.0)	53.5 (6.5)	49.1 (10.5)	48.7 (9.6)	51.8 (7.8)	49.1 (9.4)
Median	50.0	52.0	50.0	49.0	53.0	50.0	50.0	52.0	50.0
Range	18-76	22-73	18-76	18-73	40-69	18-73	18-76	22-73	18-76
Age, n (%)									
<40 y	207 (17)	13 (6)	220 (15)	62 (20)	0	62 (17)	145 (15)	13 (8)	158 (14)
≥40 to 64 y	992 (80)	207 (92)	1199 (81)	228 (75)	64 (96)	292 (78)	764 (81)	143 (90)	907 (83)
≥65 y	47 (4)	6 (3)	53 (4)	16 (5)	3 (4)	19 (5)	31 (3)	3 (2)	34 (3)
BMI									
Mean (SD)	27.6 (5.0)	29.9 (5.5)	27.9 (5.1)	28.4 (5.2)	29.5 (5.9)	28.6 (5.4)	27.3 (4.9)	29.9 (5.3)	27.7 (5.0)
Median	27.0	29.0	27.0	27.0	29.5	28.0	27.0	29.0	27.0
Range	17-50	17-52	17-52	18-47	17-44	17-47	17-50	20-52	17-52
Missing	15	1	16	5	1	16	0	0	0
BMI, n (%)									
<30	916 (74)	123 (54)	1039 (71)	200 (65)	34 (51)	234 (63)	716 (76)	89 (56)	805 (73)
≥30	315 (25)	102 (45)	417 (28)	91 (30)	32 (48)	123 (33)	224 (24)	70 (44)	294 (27)
Baseline Platelet Count (10^9/L), n (%)									
<150	145 (12)	18 (8)	163 (11)	56 (18)	9 (13)	65 (17)	89 (9)	9 (6)	98 (9)
>150	1078 (87)	202 (89)	1280 (87)	227 (74)	52 (78)	279 (75)	851 (91)	150 (94)	1001 (91)
Baseline ALT, n (%)									
Normal	267 (21)	66 (29)	333 (23)	60 (20)	18 (27)	78 (21)	207 (22)	48 (30)	255 (23)
Elevated	959 (77)	155 (69)	1119 (76)	231 (75)	44 (66)	275 (74)	733 (78)	111 (70)	844 (77)
Missing	15 (1)	5 (2)	20 (1)	15 (5)	5 (7)	20 (5)	0	0	0
Viral Load (IU/mL)									
≤400,000	125 (10)	10 (4)	135 (9)	47 (15)	5 (7)	52 (14)	78 (8)	5 (3)	83 (8)
>400,000	1103 (89)	211 (93)	1314 (89)	241 (79)	57 (85)	298 (80)	862 (92)	154 (97)	1016 (92)
Missing	18 (1)	5 (2)	23 (2)	18 (6)	5 (7)	23 (6)	0	0	0
Geometric Mean	2,750,601	4,004,999	2,912,828	1,588,420	3,308,410	1,808,892	3,254,530	4,314,800	3,390,059
Log_{10} of Geometric Mean[a]	6.44	6.60	6.46	6.20	6.52	6.26	6.51	6.63	6.53
HCV Subtype[b] (%)									
1	177 (14)	22 (10)	199 (14)	31 (10)	7 (10)	38 (10)	146 (16)	15 (9)	161 (15)
[illegible]	560 (45)	135 (60)	695 (47)	117 (38)	33 (49)	150 (40)	443 (47)	102 (64)	545 (50)
[illegible]b	459 (37)	63 (28)	522 (35)	108 (35)	21 (31)	129 (35)	351 (37)	42 (26)	393 (36)
Non-1[c]	18 (1)	--	18 (1)	18 (6)	--	18 (5)	0	--	0
Missing	32 (3)	6 (3)	38 (3)	32 (10)	6 (9)	38 (10)	0	0	0

a Baseline is geometric mean of all virology collections on or before the randomization date.
b HCV subtype as determined by TRUGENE HCV 5NC assay was used for subject stratification.
c HCV Subtype (TRUGENE assay): Non-1 includes 2a, 2b, 3a, 3d, 4a, 4c, Mixed Genotype.

Table 6. Demographic and Baseline Disease Characteristics for Cohort 1 Plus Cohort 2

	Number (%) of Subjects, FAS[a]					
	Control		Experimental			
	Arm 1 PR48[b] n=363		Arm 2 RGT[b] n=368		Arm 3 BOC/PR48[b] n=366	
Years Since HCV Exposure						
Mean (SD)	23.0	(12.1)	23.7	(12.0)	25.4	(11.7)
Median	25.3		25.3		28.3	
Range (min, max)	0.1 - 48.3		0.1 - 59.4		0.2	[illegible]
Missing	68		57		48	
METAVIR Fibrosis Score, n (%)						
F0	17	(5)	20	(5)	10	(3)
F1	246	(68)	238	(65)	246	(67)
F2	65	(18)	61	(17)	57	(16)
F3	11	(3)	18	(5)	18	(5)
F4	13	(4)	16	(4)	24	(7)
F0/1/2	328	(90)	319	(87)	313	(86)
F3/4	24	(7)	34	(9)	42	(11)
Missing	11	(3)	15	(4)	11	(3)
Baseline Steatosis, n (%)						
0 (0%)	128	(35)	107	(29)	108	(30)
1 (>0% and ≤5%)	172	(47)	187	(51)	190	(52)
2 (>5% and ≤32%)	50	(14)	53	(14)	54	(15)
3 (>32% and ≤66%)	4	(1)	6	(2)	3	(1)
Missing	11	(3)	15	(4)	11	(3)
Opioid Substitution Therapy						
Yes	1	(<1)	3	(1)	8	(2)
No	362	(100)	365	(99)	358	(98)

The study population mainly consisted of male (657/1099, 60%), white (940/1099, 82%) patients with mean age of 49 years old (range 18-76 years) and a mean BMI of 28. A large majority of patients had high viral load >400 000 UI/ml (92%) with a mean value of 6.53 log10 UI/ml; 50% were classified as G1a and 46% as G1b with TRUGENE method.

Overall, in the BOC arms only 40 patients had cirrhosis.

In each cohort, there was a higher proportion of male subjects Most of the subjects in both cohorts had baseline Metavir fibrosis scores of F0, F1, or F2, and absence of to <5% steatosis. Overall, the proportion of subjects with cirrhosis and advanced fibrosis (F3/F4) was 9%.

Outcomes and estimation

Efficacy

Table 7. The main efficacy results are shown in the table below

	COHORT 1 : White						COHORT 2: Black					
Groups	**PR48**		**RGT**		**BOC/PR48**		**PR48**		**RGT**		**BOC/PR48**	
FAS	N=311	*%*	N=316	*%*	N=311	*%*	N=52	*%*	N=52	*%*	N=53	*%*
SVR [a]	125	*40.2*	211	*66.8*	213	*68.5*	12	*23.1*	22	*42.3*	29	*54.7*
- Δ SVR			**26,6**		**28,3**				**19,2**		**31,7**	
- P value			**<0.0001**		**<0.0001**				**0.0440**		**0.0035**	
RR [c]	37	*22.8*	21	*9.1*	18	*7.8*	2	*14.3*	3	*13.0*	6	*17.1*
EOT [b]	176	*56.6*	235	*74.4*	241	*77.5*	15	*29*	26	*50*	36	*66*

	COHORT 1 + 2					
Groups	**PR48**		**RGT**		**BOC/PR48**	
FAS	N=363	*%*	N=368	*%*	N=366	*%*
SVR [a]	137	*37.7*	233	*63.3*	242	*66.1*
- Δ SVR			**25,6**		**28,4**	
- P value			**<0.0001**		**<0.0001**	
RR [c]	39	*22.2*	24	*9.3*	24	*9.1*
EOT [b]	191	*52.6*	261	*70.9*	277	*75.7*

a SVR: The last available value in the period at or after Follow-up (FW) 24. If there is no such value, the FW 12 value is carried forward. SVR24 rates (SVRwith "missing=failure" approach) were nearly identical. Subjects who were missing FW 24 results and had undetectable HCV-RNA at FW 12 included 3, 4, and 3 subjects in the PR48 control, RGT, and BOC/PR48 arms, respectively, in Cohort 1 and 1, 0, and 1 subject, respectively, in Cohort 2. Using the Cochran-Mantel Haenszel Chi-square test adjusted for baseline stratification factors: viral load (>400,000 vs. ≤400,000 IU/mL) and Genotype (1a vs 1b). In addition, cohort (race: Black vs. Non-Black) was also adjusted in the test for combined cohorts.
b Undetectable HCV-RNA at End of Treatment (EOT) regardless of treatment duration.
c Relapse rate was the proportion of subjects with undetectable HCVRNA at End of Treatment (EOT) and detectable HCV-RNA at End of Follow-up (EOF) among subjects who were undetectable at EOT and not missing EOF data.

For cohort 1 plus 2, the addition of boceprevir to PR therapy provided a significant 25-30% gain in SVR on top of the PR in naïve patients.

Relapse rates in Cohort 2 were similar in the boceprevir arms and control; however, the total number of subjects who relapsed was very small (2, 3, and 6 subjects respectively, per arm). The relapse rate (14%) in the control arm in cohort 2 was lower than the 26% observed in a previous large PR study (IDEAL) in black patients.

As regards the comparison between RGT and no RGT arms, efficacy results are close for the cohort 1 plus 2, regarding cohort 2 the fixed treatment duration is associated with an approx 10% increased SVR as compared to RGT.

There were no significant differences in outcomes between the FAS and the mITT population.

Sustained Virologic Response by Lead-in Response (Viral Load Reduction) by Cohort

SVR by lead-in response

The following table shows sustained virologic response in each arm by Lead in response (summary data for cohort 1+2)

Table 8. Sustained virologic response in each arm by Lead in response (summary data for cohort 1+2)

	SVR n/N (%),FAS[a]		
	Control	Experimental	
TW 4 HCV-RNA[b]	Arm 1 PR48[c] n=363	Arm 2 RGT[c] n=368	Arm 3 BOC/PR48[c] n=366
<1.0-Log_{10} Decline[d]	3/83 (3.6)	27/97 (27.8)	36/95 (37.9)
<0.5	0/25 (0.0)	13/47 (27.7)	11/37 (29.7)
0.5-<1	3/58 (5.2)	14/50 (28.0)	25/58 (43.1)
≥1.0-Log_{10} Decline[e]	133/260 (51.2)	203/252 (80.6)	200/254 (78.7)
1-<1.5	12/56 (21.4)	33/47 (70.2)	29/48 (60.4)
1.5-< 2	13/40 (32.5)	20/31 (64.5)	18/25 (72.0)
2-<3	25/56 (44.6)	44/55 (80.0)	42/57 (73.7)
3-<4	21/36 (58.3)	47/53 (88.7)	8/9 (88.9)
>=4	33/42 (78.6)	42/47 (89.4)	45/50 (90.0)
Undetectable	29/30 (96.7)	17/19 (89.5)	18/20 (90.0)
Missing	1/20 (5.0)	3/19 (15.8)	6/17 (35.3)

a Full Analysis Set (FAS)=all randomized subjects who received at least one dose of any study medication (PEG2b, RBV, or boceprevir).
b Reduction from Baseline after 4 weeks of PR for Arm 1 and after 4 weeks of PR lead-in prior to Boceprevir for Arms 2 and 3.
c Arm 1 (PR48) = PEG2b + RBV for 48 weeks. Arm 2 (RGT) = PR lead-in for 4 weeks, then BOC/PR for 24 weeks (subjects with undetectable HCV-RNA at Treatment Week [TW] 8 and all subsequent assays through TW 24) or BOC/PR for 24 weeks followed by placebo/PR for 20 weeks (subjects with detectable HCV-RNA at TW 8 or any subsequent assay up to TW 24). Arm 3 (BOC/PR48) = PR lead-in for 4 weeks, then BOC/PR for 44 weeks.
d <1.0-log10 decline in HCV-RNA at TW 4 from baseline.
e ≥1.0-log10 decline in HCV-RNA at TW 4 from baseline. Subjects with undetectable HCV-RNA at TW 4 are also included

Subjects with some interferon responsiveness (≥1.0-log10 decline in viral load at TW 4) attained higher SVR rates in both boceprevir-containing arms, as well as in the PR48 control arm, compared to those who had a <1.0-log10 decline in viral load at TW 4. Notably, addition of boceprevir to standard of care demonstrated improvement in SVR rates in subjects with poor interferon responsiveness (<1.0-log10 decline) when comparing to the RGT arms and the PR48 control arm (39% to 29% vs 5% in Cohort 1, and 31% to 25% vs 0% in Cohort 2).

Sustained Virologic Response Based on Demographic and Baseline Disease Characteristics

The following table represents SVR rates as per demographic and baseline characteristics

Table 9. SVR rates as per demographic and baseline characteristics

Cohort 1 Plus Cohort 2

Subgroup	Category	SVR, % (n/N) of Subjects, FAS[a]		
		Control	Experimental	
		Arm 1 PR48[b] n=363	Arm 2 RGT[b] n=368	Arm 3 BOC/PR48[b] n=366
All Subjects	All Subjects	37.7(137 /363)	63.3(233 /368)	66.1(242 /366)
Race Group	Non-Blacks (Cohort 1)	40.2(125 /311)	66.8(211 /316)	68.5(213 /311)
	Blacks (Cohort 2)	23.1(12 /52)	42.3(22 /52)	52.7(29 /55)
Ethnicity	Hispanic/Latino	24.0(6 /25)	69.0(20 /29)	66.7(26 /39)
	African American	17.8(8 /45)	43.5(20 /46)	56.5(26 /46)
	Others	42.0(123 /293)	65.9(193 /293)	67.6(190 /281)
Baseline Viral Load (IU/mL)	<=800,000	63.6(35 /55)	75.9(41 /54)	84.9(45 /53)
	>800,000	33.1(102 /308)	61.1(192 /314)	62.9(197 /313)
	<=400,000	80.8(21 /26)	78.1(25 /32)	88.0(22 /25)
	>400,000	34.4(116 /337)	61.9(208 /336)	64.5(220 /341)
Sex	Male	35.0(72 /206)	65.1(149 /229)	65.0(149 /229)
	Female	41.4(65 /157)	60.4(84 /139)	66.9(97 /145)
Age	<40 y	52.6(30 /57)	72.9(35 /48)	69.8(37 /53)
	40-64 y	35.4(103 /291)	62.7(193 /308)	65.7(201 /306)
	≥65 y	26.7(4 /15)	41.7(5 /12)	57.1(4 /7)
Baseline Weight	<75 kg	45.9(67 /146)	62.6(87 /139)	63.4(83 /131)
	>=75 kg	32.3(70 /217)	63.7(15 /235)	67.7(159 /235)
BMI	<=25	46.5(60 /129)	68.4(54 /79)	67.5(83 /123)
	25-30	33.1(49 /148)	64.6(129 /173)	65.2(90 /138)
	>30	32.6(28 /86)	47.9(45 /94)	65.7(69 /105)
Platelets	<=150,000 IU/mL	29.6(8 /27)	54.5(18 /33)	52.6(20 /38)
	>150,000 IU/mL	38.4(129 /336)	64.2(215 /335)	67.7(222 /328)
Fibrosis[c]	0	47.1(8 /17)	85.0(17 /20)	60.0(6 /10)
	1	39.8(96 /246)	66.8(159 /238)	67.5(166 /246)
	2	29.2(19 /65)	60.7(37 /61)	68.4(39 /57)
	3	27.3(3 /11)	50.0(9 /18)	66.7(12 /18)
	4	46.2(6 /13)	31.3(5 /16)	41.7(10 /24)
	Missing	45.5(5 /11)	40.0(6 /15)	81.8(9 /11)
Fibrosis[c]	0/1/2	37.5(123 /328)	66.8(213 /319)	67.4(211 /313)
	3/4	37.5(9 /24)	41.2(14 /34)	52.4(22 /42)
	Missing	45.5(5 /11)	40.0(6 /15)	81.8(9 /11)
Steatosis[c]	0	44.5(57 /128)	70.1(75 /107)	64.8(70 /108)
	1	34.7(59 /170)	65.8(123 /187)	65.8(125 /190)
	2	30.0(15 /50)	49.1(26 /53)	68.5(37 /54)
	3	25.0(1 /4)	50.0(3 /6)	33.3(1 /3)
	Missing	45.5(5 /11)	40.0(6 /15)	81.8(9 /11)
METAVIR Activity Score	0	50.0(3 /6)	83.3(5 /6)	75.0(3 /4)
	1	40.2(47 /117)	71.7(71 /99)	62.0(49 /79)
	2	34.2(39 /114)	64.1(75 /117)	62.6(82 /131)

	3	37.4(43 /115)	58.0(76 /131)	70.2(99 /141)
	Missing	45.5(5 /11)	40.0(6 /15)	81.8(9 /11)
Genotype[d] (TRUGENE)	1 (subtype unknown)	40.0(24 /60)	69.1(38 /55)	67.4(31 /46)
	1A	35.0(62 /177)	59.2(106 /179)	63.1(118 /187)
	1B	40.5(51 /126)	66.4(89 /134)	69.9(93 /133)
Genotype[e] (NS5B)	Other (Non 1)	100(2 /2)	100(1 /1)	100(1 /1)
	1A	34.4(78 /227)	59.4(139 /234)	62.0(147 /237)
	1B	39.7(48 /121)	71.0(88 /124)	72.6(85 /117)
	Missing	69.2(9 /13)	55.6(5 /9)	81.8(9 /11)
Opioid Substitution Therapy	YES	0.0(0 /1)	66.7(2 /3)	37.5(3 /8)
	NO	37.8(137 /362)	63.3(231 /365)	66.8(239 /358)
ALT	Elevated	35.9(93 /259)	63.3(179 /283)	68.3(190 /278)
	Normal	42.3(44 /104)	63.5(54 /85)	59.1(52 /88)
Statin Use	YES	100(3 /3)	66.7(6 /9)	85.7(6 /7)
	NO	37.2(134 /360)	63.2(227 /359)	65.7(236 /359)

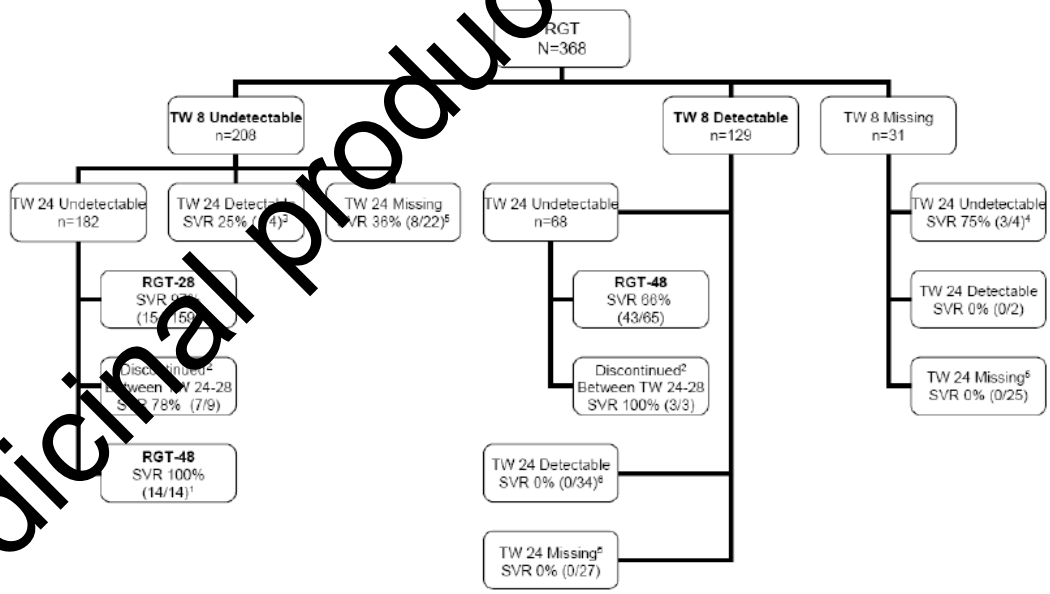
c Liver histology based on the central pathologist's reading.
d HCV subtype as determined by TRUGENE HCV 5NC assay was used for subject stratification.
e HCV subtype as determined by Virco assay based on sequencing of domain p329bp in the NS5B polymerase gene; all samples unavailable for retesting were classified as missing.

The analysis of SVR in the overall population by baseline characteristics shows no discernible association between SVR and sex. SVR rates were higher in subjects with a low baseline viral load and less fibrosis (F0-2 vs F3/4), as well as non-black race. HCV genotype 1b also resulted in higher SVR rates, particularly in the boceprevir arms. This is expected, as the genetic barrier to resistance is higher for subtype 1b compared to -1a.

Of note, as stated above, only 5% (53/1097) of the treated subjects were cirrhotic.

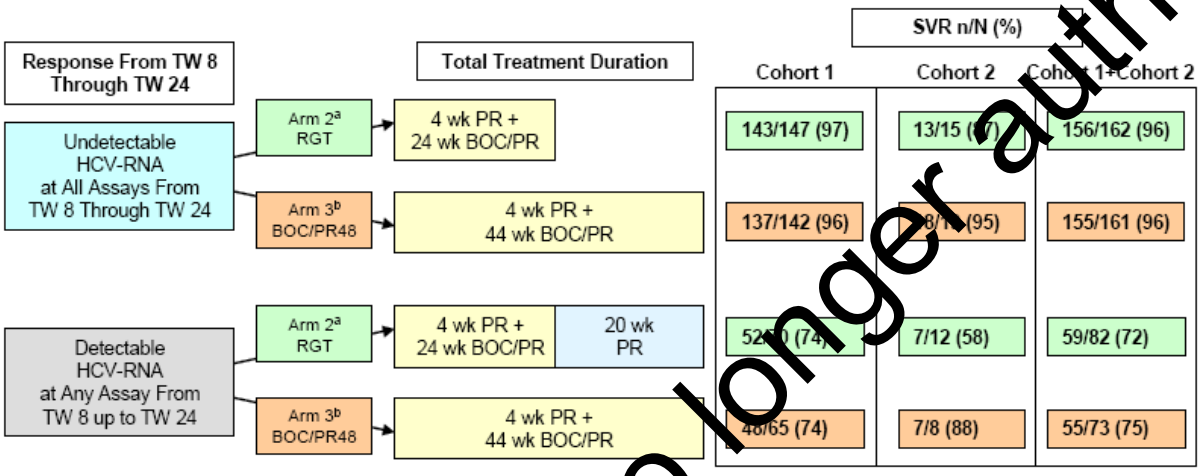
Comparison of outcomes in early and late responders in the RGT and BOC/PR48 arms

The following graph demonstrates the disposition of Subjects in the RGT Arm, Based on TW 8 and TW 24 Response (Cohort 1 Plus Cohort 2):



1 Fourteen subjects had a low positive HCV-RNA result(s) between TW 8 and TW 24 and per protocol were given 48 weeks of therapy. All of these subjects had two additional back–up samples from the same timepoint retested that showed undetectable HCV-RNA. Since HCV-RNA was not detected in 2 out of 3 samples, the positive result was considered to be a false positive. However, the retests were not completed prior to assignment of treatment duration, and the initial result with detectable HCV-RNA was used by the IVRS for treatment duration assignment.
2 Subjects discontinued therapy between TW 24 and TW 28 and were not assigned any treatment duration by the IVRS system.
3 Two subjects with viral breakthrough (0% SVR) discontinued treatment between TW 24 and TW 28, and two subjects with low positive results (<1000 IU/mL) were assigned to RGT-48 (subjects attained SVR) and RGT-28 (subjects relapsed) upon demonstrating undetectable HCV-RNA on retest.
4 Two subjects with undetectable HCV-RNA results beyond the defined visit window were assigned to RGT-28, and both of them attained SVR. One subject was assigned to RGT-48 and attained SVR, and one subject discontinued prior to TW 28.
5 Subjects discontinued prior to TW 24 and were not assigned any treatment duration.
6 One subject was assigned to RGT-48 and did not achieve SVR.

Below is represented outcomes in early and late responders in Arm 2 (RGT) and the Matched Subset in Arm 3 (BOC/PR48)



In the full analysis ITT dataset, both the RGT arm and the BOC/PR48 provided similar SVR rates. In the subgroup of early responders, there was no difference in outcome depending on whether patients were treated for a total of 28 or 48 weeks (see table below)

Table 10. Sustained Virologic Response in Early Responders (IVRS), P05216

	RGT	BOC/PR48	
All Subjects			
SVR, % (n/N)	**96.3** (156 /162)	**96.3** (155 /161)	0.6 [-3.8, 5.2]
EOT	100.0 (162/162)	98.8 (159/161)	-
Relaps	3.1 (5/161)	1.3 (2/157)	-

Further looking at subgroup analyses of patients with F3/F4 fibrosis and black patients that were early responders, numbers are too small for any formal conclusions of equivalence (see table 11)

Table 11

TREATMENT NAÏVE (P05216/SPRINT 2)		N=323
Response Guided Therapy (RGT)/Early responders	4W LI + 24W BPR = 28 W	n=161
FIXED TREATMENT DURATION WITH 44W TRITHERAPY	4 W LI+ 44W BPR = 48W	n=162

Looking into late responders in the respective treatment arms, the data presented above on outcomes as per treatment assignation has very similar point estimates for late responders in the RGT arm and

the BOC/PR48 arm – 72% (59/82) versus 75% (55/73). However, it is notable that 15 patients in the RGT arm with undetectable HCV-RNA levels at TW 8 had positive HCV-RNA results between TW 8 and TW 24 and per protocol were assigned to 48-weeks of therapy. One of these 15 patients had positive HCV-RNA levels at multiple time points; the other 14 patients had a single low positive HCV-RNA result and retesting of two additional back-up samples from the same time point (after the assignment of treatment duration) showed undetectable HCV-RNA results. Thus, 14 patients that were probably "real" early responders in the RGT arm were assigned to continue therapy with P/R for another 20 weeks. Importantly, among these 14 patients, who were misclassified and therefore should be discounted in the strict per protocol approach required when assessing what is essentially a non-inferiority claim (based on an underpowered study), 14/14 (100%) experienced SVR. Discounting these patients, outcomes among late responders in the respective treatment arms look as follows, with the point estimate favoring the BOC/PR arm by almost 10%. Of note, the only difference in received therapy between these arms is the duration of boceprevir therapy – 24 or 44 weeks.

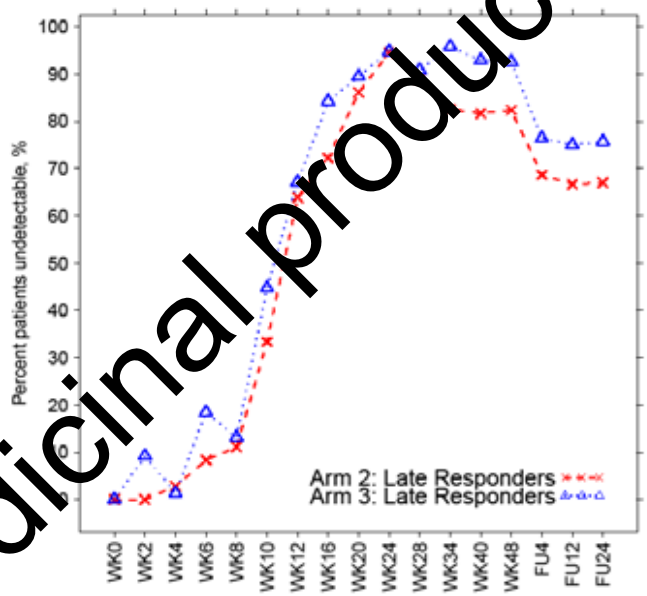
Table 12. Sustained Virologic Response in Late Responders (IVRS), P05216

	RGT	BOC/PR48	
All Subjects			
SVR, % (n/N)	*66% (45/68)	75.3 (55 /73)	8.2[-24.4, 6.3]
EOT	76% (52/68)_	90% (66/73)	
Relapse	13% (7/52)	14% (9/64)	

**14 patients with a "false positive" HCV RNA result between W8 and W24 are excluded from the analysis*

Furthermore, this difference appears to be largely due to virologic breakthrough when the patients on RGT were on PR alone (**Figure below**).

Table 13. Percentage of Treatment-naïve Patients with undetectable HCV RNA at Different Treatment Time Points for) or Late Responders ; SPRINT-2



This analysis suggests that treatment-naïve patients with detectable HCV RNA at TW8 but undetectable at TW24 (late responders) may benefit from receiving a longer duration of boceprevir plus PR.

A Phase 3 Safety and Efficacy Study of Boceprevir (SCH 503034) in Subjects With Chronic Hepatitis C Genotype 1 Who Failed Prior Treatment With Peginterferon/Ribavirin (Protocol No. P05101; RESPOND-2)

Methods

Study Participants

Main inclusion criteria
Adult subjects with CHC HCV genotype 1 who failed to achieve SVR after at least 12 weeks of previous treatment with PEG/RBV, who were partial responders (a ≥ 2 $\log_{10}$ reduction in HCV-RNA by Week 12 or who relapsed after an end-of treatment response) were eligible for the study.

Main exclusion criteria
Subjects who were co-infected with human immunodeficiency virus (HIV) or hepatitis B virus (HbsAg positive) were excluded from the study, as well as patients with decompensated liver disease. Other important exclusion criteria were subjects who had required discontinuation of previous interferon or Ribavirin regimen for an AE considered by the investigator to be possibly or probably related to ribavirin and/or interferon.

- **Treatments**

Subjects were randomized to 1 of the 3 treatment arms (1:1:2 ratio)

Control
Arm 1 (PR48): PR= standard of care therapy consisting of Peginterferon alfa-2b PEG2b (1.5 µg/kg sc once weekly) plus ribavirin (weight-based dose, 600 to 1400 mg) po daily) for 4 weeks followed by placebo (matched to boceprevir) + PR for 44 weeks with 24 weeks post-treatment follow-up.

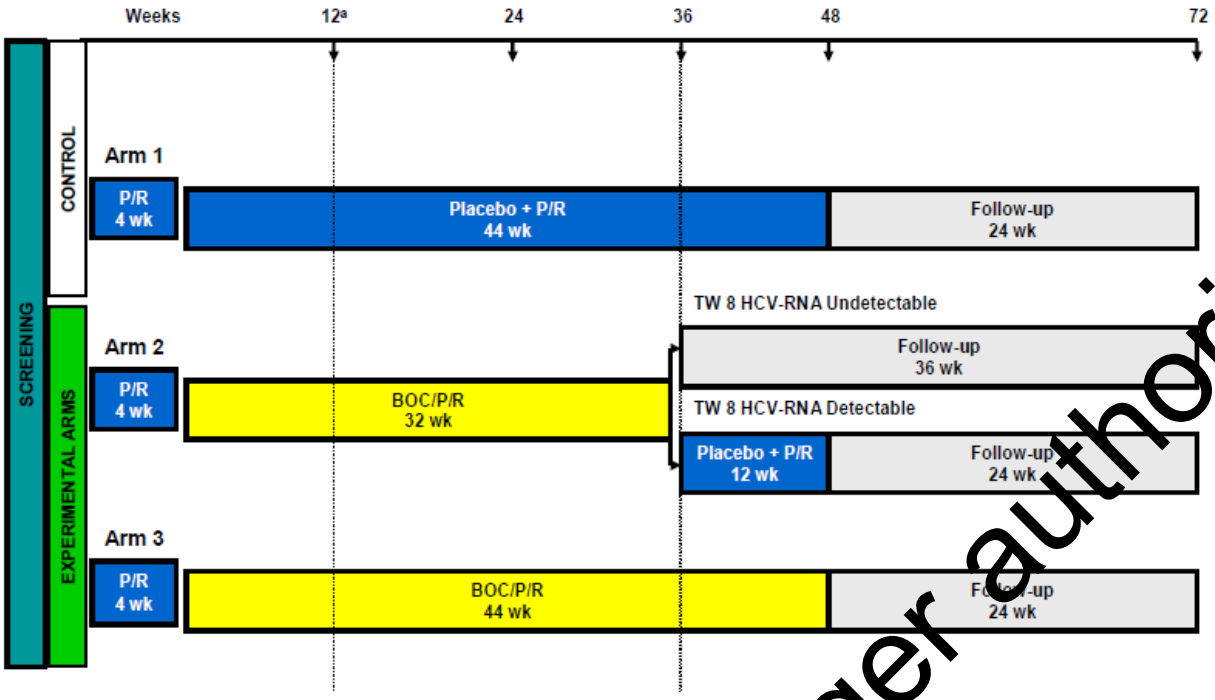
Experimental therapy:
Arm 2: Response-Guided Therapy (RGT): Subjects were assigned either a 36-week (a, below) or 48-week (b, below) course of therapy based on their HCV-RNA status at TW 8.

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

a. 36-week regimen: subjects with undetectable HCV-RNA at TW 8 completed treatment.

b. 48-week regimen: subjects with detectable HCV-RNA at TW 8 were assigned an additional 12 weeks of placebo + PR (the switch from BOC to placebo occurred in a blinded fashion), Arm 3 (BOC/PR48): PR for 4 weeks followed by boceprevir (BOC)/PR for 44 weeks, with 24 weeks post-treatment follow up.

Boceprevir, supplied as 200-mg capsules, was administered at a dosage of 800 mg PO TID.



There was a 12-week futility rule for all arms, wherein therapy was to be discontinued for all subjects with detectable HCV-RNA at TW 12.

Management of adverse events

This study permitted ribavirin dose reduction and/or erythropoietin use for subjects who developed anaemia. In the protocol guidelines for use of erythropoietin were provided.

Objectives and endpoints

The primary objective was to compare the efficacy of two therapeutic regimens (i.e. 32 weeks and 44 weeks) of boceprevir 800 mg dosed orally (PO) TID in combination with PEG2b 1.5 µg/kg subcutaneously (SC) once weekly (QW) plus weight-based dosing (WBD) of ribavirin (600 mg/day to 1400 mg/day) PO to therapy with PR alone in adult subjects with chronic hepatitis C HCV genotype 1 who failed previous treatment with a qualifying regimen of PEG/RBV. The primary efficacy endpoint was the achievement of SVR, defined as undetectable plasma HCV-RNA at Follow-up Week (FW) 24. The primary efficacy endpoint was analyzed using the Full Analysis Set (FAS), which included all subjects who received at least one dose of any study drug (PEG2b, RBV, or boceprevir/placebo).

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

HCV-RNA in plasma was measured with a Roche COBAS TaqMan assay with a limit of quantitation of 25 IU/ml and a limit of detection of 9.3 IU/ml.

Other secondary efficacy endpoints were:

The proportion of subjects with early virologic response (eg, undetectable HCVRNA at TW 2, 4, 8, or 12) who achieved SVR.

Sample size

This study was projected to enrol 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 has 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%). Of note, the sample size was not calculated to demonstrate the non-inferiority of a shortened treatment duration in patients designated as early responders, or of discontinuing boceprevir compared to its continuation in patients designated as late responders.

Randomisation

The study was randomised. Subject were stratified by prior response category (partial responders vs relapsers) and by viral genotype 1a versus -1b.

Blinding (masking)

This was a double-blind study in which the sponsor, investigator, study personnel, and study participants were to be blinded with respect to boceprevir treatment.

Statistical methods

The primary efficacy endpoint, the achievement of SVR, was summarized for each treatment arm using descriptive statistics (n, %). SVR rates were based on the last observation carried forward (LOCF) approach, in which the FW 12 HCV-RNA result was carried forward for subjects with missing HCV-RNA value at and after FW 24.

Results

Participants flow is presented in the figure below

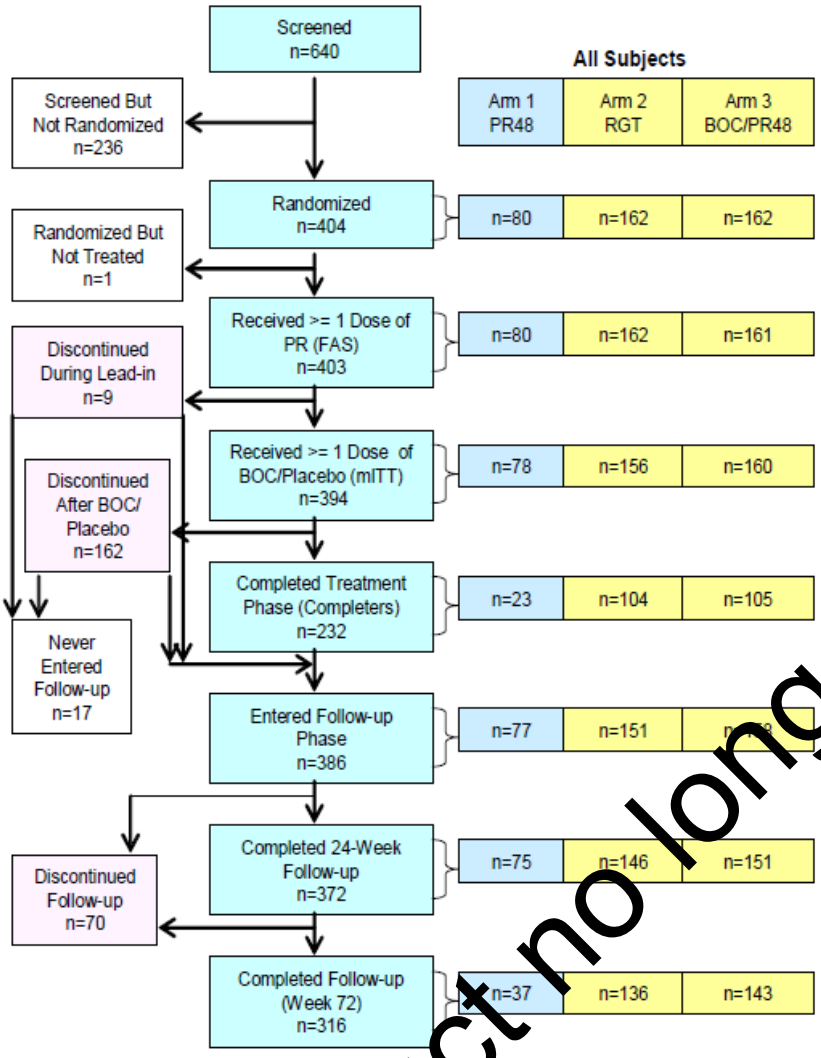


Table 14. Demographics and baseline characteristics

	Number (%) of Subjects, FAS[a]			
	Control	Experimental		
	Arm 1 PR48[b] n=80	Arm 2 RGT[b] n=162	Arm 3 BOC/PR48[b] n=161	Total n=403
Sex (n,%)				
Male	58 (73)	98 (60)	112 (70)	268 (67)
Female	22 (28)	64 (40)	49 (30)	135 (33)
Race (n,%)				
Non-Black	68 (85)	144 (89)	142 (88)	354 (88)
White	67 (84)	142 (88)	135 (84)	344 (85)
Asian	0	1 (1)	5 (3)	6 (1)
Multiracial	0	1 (1)	1 (1)	2 (<1)
Native Hawaiian or Other Pacific Islander	1 (1)	0	1 (1)	2 (<1)
Black	12 (15)	18 (11)	19 (12)	49 (12)
Age (y)				
Mean (SD)	52.9 (8.1)	52.9 (7.4)	52.3 (7.7)	52.7 (7.7)
Median	53.5	53.0	53.0	53.0
Range	29 - 70	29 - 74	26 - 74	26 - 74
Age (n,%)				
<40 y	4 (5)	5 (3)	7 (4)	16 (4)
40-<65 y	70 (88)	146 (90)	146 (91)	362 (90)
≥65	6 (8)	11 (7)	8 (5)	25 (6)
Weight (kg)				
Mean (SD)	85.6 (16.2)	85.2 (15.4)	84.2 (15.2)	84.9 (15.5)
Median	83.5	83.5	84.0	84.0
Range	48 - 124	51 - 125	51 - 123	48 – 125
Weight, n (%)				
<75 kg	17 (21)	42 (26)	44 (27)	103 (26)
≥75 kg	63 (79)	120 (74)	117 (73)	300 (74)
Height (cm)				
Mean (SD)	174.0 (10.5)	172.1 (10.1)	172.7 (9.2)	172.7 (9.8)
Median	175.0	173.0	175.0	174.0
Range	143 – 198	148 - 195	147 - 198	143 – 198
BMI				
Mean (SD)	28.2 (4.4)	28.8 (4.6)	28.3 (4.6)	28.4 (4.6)
Median	27.5	28.0	28.0	28.0
Range	22 - 43	19 – 44	17 - 42	17 – 44
Baseline Platelet Count (10^9/L), n (%)				
<150,000	10 (13)	21 (13)	19 (12)	50 (12)
≥150,000	70 (88)	141 (87)	142 (88)	353 (88)
Baseline ALT, n (%)				
Normal	25 (31)	53 (33)	46 (29)	124 (31)
Elevated	55 (69)	109 (67)	115 (71)	279 (69)
Viral Load (IU/mL)				
≤200,000	2 (3)	2 (1)	3 (2)	7 (2)

>200,000-400,000	4 (5)	5 (3)	4 (2)	13 (3)
>400,000-800,000	9 (11)	8 (5)	13 (8)	30 (7)
>800,000	65 (81)	147 (91)	141 (88)	353 (88)
Geometric Mean[c]	3,303,210	4,289,637	4,907,196	4,297,628
Log_{10} of Geometric Mean	6.52	6.63	6.69	6.63
Peginterferon-alfa Use in Qualifying Regimen				
PEG2a	42 (53)	79 (49)	68 (42)	189 (47)
PEG2b	38 (48)	83 (51)	93 (58)	214 (53)
Years Since Probable HCV Exposure				
Subjects with Known Years	65	136	132	333
Mean (SD)	29.0 (9.3)	27.7 (10.8)	27.4 (11.0)	27.8 (10.6)
Median	30.3	29.0	28.7	29.8
Range	4.1 – 48.3	1.3 – 48.3	2.1 – 54.3	1.3 – 54.3
Subjects Missing Years Since Exposure[d]	15	26	29	70
HCV Subtype (TRUGENE)[e] n (%)				
1 (subtype unknown)	6 (8)	13 (8)	17 (11)	36 (9)
1a	38 (48)	74 (46)	77 (48)	189 (47)
1b	36 (45)	75 (46)	67 (42)	178 (44)
HCV Subtype (NS5B)[f] n (%)				
1a	46 (58)	92 (58)	96 (60)	236 (59)
1b	34 (43)	66 (41)	61 (38)	161 (40)
non-1[g]	0	0	1 (1)	1 (<1)
Missing[h]	0	2 (1)	3 (2)	5 (1)
Response to Previous Qualifying Regimen				
Nonresponder	29 (36)	57 (35)	58 (36)	144 (36)
Relapser	51 (64)	105 (65)	103 (64)	259 (64)
Interferon Use in Previous Qualifying Regimen by Response to Previous Qualifying Regimen n/N (%)				
PEG2a Nonresponder	9/42 (21)	25/79 (49)	22/68 (32)	--
PEG2a Relapser	33/42 (79)	54/79 (68)	46/68 (68)	--
PEG2b Nonresponder	20/38 (53)	32/83 (39)	36/93 (39)	--
PEG2b Relapser	18/38 (47)	51/83 (61)	57/93 (61)	--
Statin Use				
Yes	4 (5)	8 (5)	2 (1)	14 (3)
No	76 (95)	154 (95)	159 (99)	389 (97)
Opioid Replacement Therapy				
Yes	0	1 (1)	4 (2)	5 (1)
No	80 (100)	161 (99)	157 (98)	398 (99)
Liver Histology[i]				
Cirrhosis	10 (13)	17 (10)	22 (14)	49 (12)
Non-Cirrhosis	66 (83)	132 (81)	128 (80)	326 (81)
Inadequate Portal Tracts	4 (5)	8 (5)	10 (6)	22 (5)
Missing	0	5 (3)	1 (1)	6 (1)

METAVIR Fibrosis Score, n (%)				
F0	5 (6)	8 (5)	5 (3)	18 (4)
F1	43 (54)	79 (49)	78 (48)	200 (50)
F2	13 (16)	30 (19)	36 (22)	79 (20)
F3	5 (6)	15 (9)	9 (6)	29 (7)
F4	10 (13)	17 (10)	22 (14)	49 (12)
Missing	4 (5)	13 (8)	11 (7)	28 (7)
Baseline Steatosis, n (%)				
0	23 (29)	36 (22)	45 (28)	104 (26)
1	39 (49)	81 (50)	74 (46)	194 (48)
2	12 (15)	25 (15)	30 (19)	67 (17)
3	1 (1)	7 (4)	1 (1)	9 (2)
4	1 (1)	0	0	1 (<1)
Missing	4 (5)	13 (8)	11 (7)	28 (7)

The study population mainly consisted of male (268/403, 67%), white (344/403, 85%) patients with mean age of 53 years old (range 26-74 years) and a mean BMI of 28. Twelve percent of the study population was of Black race and patients with cirrhosis accounted for 12% of the overall study population. The number of patients with cirrhosis is limited (n=49, 30 of whom being exposed to BOC). A large majority of patients had high viral load >800 000 UI/ml (88%) with a mean value of 6.63 log10 UI/ml; 47% were classified as G1a and 44% as G1b with TRUGENE method.

Baseline demographics and disease characteristics were well balanced among treatment arms (with the exception a slightly lower proportion of patients having HCV RNA > 800 000 IU/ml in the control arm as compared to BOC arms (81 vs 88-91%) and a higher rate of female patents in the RGT arm (40 vs 28-30% in other arms).

Numbers analysed

A total of 404 subjects were randomized and 403 received at least one dose of any study medicine (FAS) and were included in the efficacy analysis; of these 394 received at least one dose of boceprevir or placebo (mITT). The relation between lead in response and historical response to P/R was as follows (non-responder = partial responders with > 2 log10 decline at week 12 in the previous treatment attempt):

Table 15.

Lead-in Response[b] (Viral Load Reduction at TW 4)	Previous Treatment Response Number (%) of Subjects, FAS[a]	
	Nonresponder (n=144)	Relapser (n=259)
<1 log	56 (38.9)	46 (17.8)
1-<2 log	46 (31.9)	66 (25.5)
≥2 log or undetectable HCV-RNA	38 (26.4)	141 (54.4)
Missing	4 (2.8)	6 (2.3)

Notably, 18% of historical relapsers and 39% of historical partial responders had<1 log decline in viral load after 4 weeks of peginterferon alfa-2b and ribavirin.

Outcomes and estimations

Efficacy

The primary efficacy analysis in the FAS population was as follows:

Table 16.

Groups FAS	PR48 N=80	 %	RGT N=162	 %	BOC/PR48 N=161	 %
SVR [a]	17	*21.3*	95	*58.6*	107	*66.5*
- Δ SVR			37.4		45.2	
- P value			<0.0001		<0.0001	
- Previous partial-responder	2	*6.9*	23	*40.4*	30	*51.7*
- Previous Responder	15	*29.4*	72	*68.6*	77	*74.8*
EOT [b]	25	*31.3*	114	*70.4*	124	*77.0*
- Previous partial-responder	3	*10.3*	31	*54.4*	35	*60.3*
- Previous Responder	22	*43.1*	83	*79.0*	89	*86.4*
SVR by TW4 response						
-<1.0 log decline [f]	0	-	15	*32.6*	15	*34.1*
-≥1.0 log decline [g]	17	*25.4*	80	*72.7*	90	*78.9*
SVR by TW8 response						
- Undetectable RNA	7	*10.6*	64	*86.5*	74	*88.1*
- Detectable RNA	8	*12.3*	29	*40.3*	30	*42.9*
RR [c]	8	*32.0*	17	*15.3*	14	*11.6*
- Previous partial-responder	1	*33.3*	5	*17.9*	5	*14.3*
- Previous Responder	7	*31.8*	12	*14.5*	9	*10.5*
VB [d]	0	-	2	*1.2*	3	*1.9*
IVR [e]	1	*1.3*	7	*4.3*	4	*2.5*

a SVR: The last available value in the period at or after FW 24. If there is no such value, the FW 12 value was carried forward. P values were calculated using the two-sided Cochran-Mantel Haenszel (CMH) Chi-square test adjusted for the baseline stratification factors: previous treatment response (nonresponder vs relapser) and genotype (1a vs 1b).
b Undetectable HCV-RNA at End of Treatment (EOT) regardless of treatment duration.
c Relapse rate Relapse rate was the proportion of subjects with undetectable HCV-RNA at End of Treatment (EOT) and detectable HCV-RNA at End of follow-up (EOF) among subjects with undetectable HCV-RNA at EOT and not missing EOF data.
d Viral breakthrough (VB): Any subject who achieved undetectable HCV-RNA and subsequently had HCV-RNA >1,000 IU/mL.
e Incomplete Virologic Response (IVR): Any subject who had a ≥1.0 log10 increase in HCV-RNA from their lowest result (or a ≥2.0 log10 increase if the time interval from PEG2b injection to HCV-RNA sampling was different for the two samples) with an HCVRNA >1,000 IU/mL.
f Poorly interferon responsive: <1.0 log10 decline in HCV-RNA at TW 4 from baseline.
g Interferon responsive: ≥1.0 log10 decline in HCV-RNA at TW 4 from baseline. Subjects with undetectable HCV-RNA at TW 4 are also included.

Addition of BOC to SOC allow for a significant improvement of SVR in both the prior relapser patients (Δ=40-46%) and the prior partial responders patients (Δ=33-45%). Such results translate into a SVR reaching 75% in relapser patients and a SVR reaching 52% in prior partial responders.

Sustained Virologic Response Based on Demographic and Baseline Disease Characteristics

The following table shows SVR based on Demographic and Baseline Disease Characteristics. Previous treatment response, baseline viral load and cirrhosis were associated with response rates.

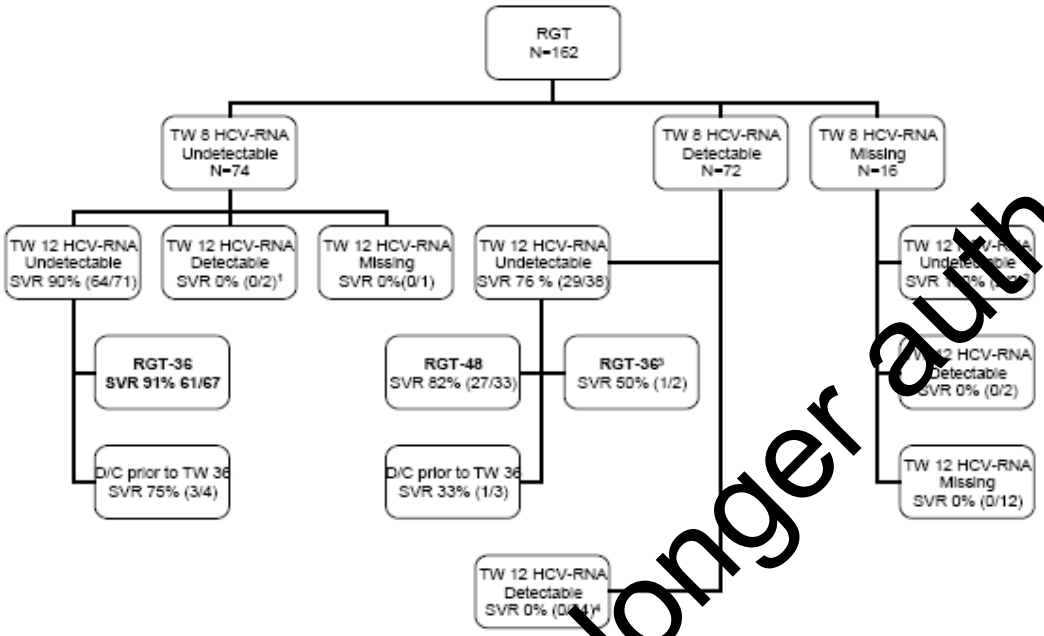
Table 17. Sustained Virologic Response by Baseline Characteristics

	SVR n/N (%), FAS[a]		
	Control	Experimental	
	Arm 1 PR48[b] n=80	Arm 2 RGT[b] n=162	Arm 3 BOC/PR48[b] n=161
Sex			
Male	13/58 (22.4)	59/98 (60.2)	75/112 (67.0)
Female	4/22 (18.2)	36/64 (56.3)	32/49 (65.3)
Race			
White	16/68 (23.5)	84/144 (58.3)	97/142 (68.3)
Black	1/12 (8.3)	11/18 (61.1)	10/19 (52.6)
Ethnicity			
Hispanic/Latino	1/2 (50.0)	2/5 (40.0)	6/9 (66.7)
African American	1/11 (9.1)	10/17 (58.8)	9/17 (52.9)
Other	15/67 (22.4)	83/140 (59.3)	92/135 (68.1)
Age			
<40 y	0/4 (0.0)	2/5 (40.0)	5/7 (71.4)
40 - 64 y	16/70 (22.9)	84/146 (57.5)	95/146 (65.1)
≥65 y	1/6 (16.7)	8/11 (72.7)	7/8 (87.5)
≤53 y (median age)	8/40 (20.0)	53/89 (59.6)	52/82 (63.4)
>53 y (median age)	9/40 (22.5)	42/73 (57.5)	55/79 (69.6)
Weight			
<75 kg	7/17 (23.5)	20/42 (47.6)	34/44 (77.3)
≥75 kg	10/63 (20.6)	75/120 (62.5)	73/117 (62.4)
BMI			
≤25	4/20 (20.0)	21/35 (60.0)	30/44 (68.2)
>25-30	11/42 (26.2)	41/68 (60.3)	44/66 (66.7)
>30	2/18 (11.1)	33/59 (55.9)	33/51 (64.7)
Baseline Platelet Count (10^9/L) n (%)			
<150,000/µL	2/10 (20.0)	8/21 (38.1)	13/19 (68.4)
≥150,000/µL	15/70 (21.4)	87/141 (61.7)	94/142 (66.2)
Baseline ALT			
Normal	8/25 (32.0)	37/53 (69.8)	30/46 (65.2)
Elevated	9/55 (16.4)	58/109 (53.2)	77/115 (67.0)
Status			
Yes	1/4 (25.0)	7/8 (87.5)	2/2 (100)
No	16/76 (21.1)	88/154 (57.1)	105/159 (66.0)
Baseline Viral Load (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)
≤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 Viral Load (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)
≤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)
Peginterferon-alfa Use in Qualifying Regimen			
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)
Response to Qualifying Regimen			
NR	2/29 (6.9)	23/57 (40.4)	30/58 (51.7)
Relapse	15/51 (29.4)	72/105 (68.6)	77/103 (74.8)
HCV Subtype (TRUGENE)[d]			
1 (subtype unknown)	0/6 (0.0)	9/13 (69.2)	11/17 (64.7)
1a	9/38 (23.7)	37/74 (50.0)	37/71 (52.0)
1b	8/36 (22.2)	49/75 (65.3)	49/67 (73.1)
HCV Subtype (NS5B)[e]			
1a	11/46 (23.9)	50/94 (53.2)	61/96 (63.5)
1b	6/34 (17.6)	44/63 (69.8)	43/61 (70.5)
Other (non-1a or 1b)	0	0	1/1 (100.0)
Missing	0	1/2 (50.0)	2/3 (66.7)
Erythropoietin Use			
Yes	6/17 (35.3)	53/66 (80.3)	51/74 (68.9)
No	11/63 (17.5)	42/96 (43.8)	56/87 (64.4)
Opioid Substitution Therapy			
Yes	0	1/1 (100)	4/4 (100)
No	17/80 (21.3)	94/161 (58.4)	103/157 (65.6)
Liver Histology[f]			
METAVIR Fibrosis Score			
F0	3/5 (60.0)	6/8 (75.0)	3/5 (60.0)
F1	9/43 (20.9)	52/79 (65.8)	55/78 (70.5)
F2	2/13 (15.4)	19/30 (63.3)	23/36 (63.9)
F3	2/5 (40.0)	8/15 (53.3)	4/9 (44.4)
F4	0/10 (0.0)	6/17 (35.3)	17/22 (77.3)
Missing	1/4 (25.0)	4/13 (30.8)	5/11 (45.5)
METAVIR Fibrosis Score			
0/1	14/61 (23.0)	77/117 (65.8)	81/119 (68.1)
2/4	2/15 (13.3)	14/32 (43.8)	21/31 (67.7)
Missing	1/4 (25.0)	4/13 (30.8)	5/11 (45.5)
Baseline Steatosis			
0 (0%)	5/23 (21.7)	24/36 (66.7)	31/45 (68.9)
1 (>0% and ≤5%)	10/39 (25.6)	48/81 (59.3)	54/74 (73.0)
2 (>5% and ≤32%)	1/12 (8.3)	17/25 (68.0)	16/30 (53.3)
3 (>32% and ≤66%)	0/1 (0.0)	2/7 (28.6)	1/1 (100)

A comparison of outcomes in the RGT and the BOC/PR48 arm, by early and late response

The subject disposition and SVR rates within the RGT arm is as follows:



1 Subjects did not meet criteria for viral breakthrough (HCV-RNA <1000 IU/mL at TW 12). One subject was assigned to RGT-36, based on undetectable HCVRNA upon retest, and 1 subject discontinued prior to treatment duration assignment at TW 36.
2 Two subjects had TW 8 HCV-RNA results outside the visit window, one was assigned to RGT-36 and one was assigned to RGT-48.
3 Two subjects had undetectable TW 8 HCV-RNA outside the visit window and were assigned to RGT-36 by IVRS. The detectable HCVRNA results that were included in the analysis for these 2 subjects represent an earlier nominal study visit.
4 Includes 1 subject with missing HCV-RNA at TW 12 and one subject who was assigned to RGT-48.

The table below represents the proportion of patients achieving SVR, EOT response and relapsing, by TW 8 response.

Table 18. Proportion of patients achieving SVR, EOT response and relapsing, by TW 8 response.

	Undetectable HCV-RNA at TW 8		Detectable HCV-RNA at TW 8	
	Arm 2 RGT[a]	Arm 3 BOC/PR48[a]	Arm 2 RGT[a]	Arm 3 BOC/PR48[a]
SVR[b], n/N (%)	64/74 (86.5)	74/84 (88.1)	29/72 (40.3)	30/70 (42.9)
EOT, n/N (%)	72/74 (97.3)	81/84 (96.4)	40/72 (55.6)	40/70 (57.1)
Relapse[c], n/N (%)	8/71 (11.3)	6/80 (7.5)	9/38 (23.7)	8/38 (21.1)

a Arm 4 (PR48) = PEG2b + RBV for 48 weeks.
Arm 2 (RGT) = PR lead-in for 4 weeks, then BOC/PR for 32 weeks (if undetectable HCV-RNA at TW 8) or BOC/PR for 32 weeks followed by placebo/PR for 12 weeks (if detectable HCV-RNA at TW 8).
Arm 3 (BOC/PR48) = PR lead-in for 4 weeks, then BOC/PR for 44 weeks.
b The last available value in the period at and after FW 24. If there was no such value, the FW 12 value was carried forward.
c Relapse rate was the proportion of subjects with undetectable HCV-RNA at End of Treatment (EOT) and detectable HCV-RNA at End of Follow-up (EOF) among subjects with undetectable HCV-RNA at EOT and not missing EOF data.

Viewing these outcomes, there is no apparent difference between 36 weeks of total therapy in the RGT arm and 48 weeks of total therapy in the BOC/PR48 arms, for early responders, nor is there any apparent advantage of of 44 weeks of boceprevir therapy in the BOC/PR48 arm, compared to a total of 32 weeks of boceprevir therapy against a background of 48 weeks of total therapy, in late responders in the RGT arm.

The table above represents all patients that reached treatment week 8. However, for all patients, treatment was similar up to week 36, regardless of treatment arm and early viral response. Thus, no events prior to week 36 could possibly be causally related to different treatment strategies within the respective arm. Therefore, the dataset comprising only patients reaching week 36 is considered more sensitive for detecting putative differences in terms of the effect of the different treatment strategies – discontinuing therapy at week 36 versus continuing for another 12 weeks in early responders, and discontinuing versus continuing boceprevir for another 12 weeks in late responders. Apart from being more sensitive to detect differences, this dataset is also representative of the probabilities needed to take into account for clinical decision-making at the time when a choice between strategies is necessary. The table below shows outcomes in the subset of patients that completed 36 weeks of therapy.

Table 19. Sustained Virologic Response, END of Treatment Response, and Relapse Rates in the Experimental Arms Based on Per Protocol IVRS Assignment

Protocol No. P05101

	Undetectable HCV-RNA at TW 8		Detectable HCV-RNA at TW 8	
	Arm 2 RGT[a]	Arm 3 BOC/PR48[a,b]	Arm 2 RGT[a]	Arm 3 BOC/PR48[a,b]
SVR[c], n/N (%)	63/71 (88.7)	71/73 (97.3)	28/35 (80.0)	29/40 (72.5)
EOT, n/N (%)	70/71 (98.6)	72/73 (98.6)	34/35 (97.1)	37/40 (92.5)
Relapse[d], n/N (%)	7/69 (10.1)	0/71 (0.0)	6/34 (17.6)	7/36 (19.4)

BOC = boceprevir 800 mg TID; CI = confidence interval; FW = Follow-up Week; HCV-RNA = hepatitis C virus-ribonucleic acid; IVRS = interactive voice response system; P = peginterferon alfa-2b 1.5 µg/kg QW; QW = once weekly; R = ribavirin 600 to 1400 mg/day; RGT = response-guided therapy; SVR = sustained virologic response; TID = three times daily; TW = Treatment Week.

[a] Arm 1 (PR48) = PEG2b + RBV for 48 weeks.
Arm 2 (RGT) = PR lead-in for 4 weeks, then BOC/PR for 32 weeks (if undetectable HCV-RNA at TW 8) or BOC/PR for 32 weeks followed by placebo/PR for 12 weeks (if detectable HCV-RNA at TW 8).
Arm 3 (BOC/PR48) = PR lead-in for 4 weeks, then BOC/PR for 44 weeks.

[b] Subjects who had >36 weeks of therapy.

[c] The last available value in the period at and after FW 24. If there was no such value, the FW 12 value was carried forward. SVR_{24} rates (SVR with "missing=failure" approach) are provided in ISE Section 6.2.6.12.

[d] Relapse rate was the proportion of subjects with undetectable HCV-RNA at End of Treatment (EOT) and detectable HCV-RNA at End of Follow-up (EOF) among subjects who were undetectable at EOT and not missing EOF data.

Among early responders, the point estimate favoured a longer treatment duration by a statistically significant 8.5% (95% CI 0.3-17%). This was, reciprocally, reflected in a significant 10.1% difference in relapse rates (95% CI 3-17%), indicating that discontinuing therapy at 36 weeks in treatment experienced early responders was associated with a higher risk of relapse, compared to continuing for another 12 weeks. On further analysis of patients categories as per prior response, race and degree of fibrosis, it is seen that, as expected, most early responders were prior relapsers rather than prior partial responders, and that there is no indication that the higher relapse rates seen with shorter therapy would be driven by prior partial responders. Furthermore, the majority of relapses were seen in non-black subjects with F1/F2 fibrosis, as seen in the table below, representing relapse rates *in early responders by previous response, race and fibrosis category.*

Table 20.

Subgroup	Category	Relapse, % (n/N)	
		RGT	BOC/PR48
All Subjects	All Subjects	10.1 (7/69)	0 (0/71)
Previous Response	Partial-Responder	6.7 (1 /15)	0 (0/20)
	Relapser	11.1 (6 /54)	0 (0/51)
Race	Blacks	0 (0/3)	0 (0/5)
	Non-Blacks	10.6 (7/66)	0 (0/66)
Fibrosis	F0/1/2	8.8 (5/57)	0 (0/58)
	F3/4	14.3 (1/7)	0 (0/13)
	Missing	20.0 (1/5))	0 (0/3)

In the subgroup of patients that were late responders and reached 36 weeks of therapy, the point estimate for SVR was higher in the RGT arm, where patients discontinued boceprevir at week 36, continuing with only P/R (80% versus 72.5% in the BOC/PR48 arm). While the dataset is very small (n=35 and 40 respectively), there was no indication of a higher rate of viral breakthrough or relapse in patients discontinuing boceprevir at week 36, and thus no positive signal of an advantage of a further 12 weeks of boceprevir therapy.

Analysis performed across trials (pooled analyses and meta-analysis)

Pharmacogenomic Analysis of IL28B in Phase III Studies of Boceprevir (SCH 503034)

Recently the association of a Interleukin (IL)-28B genetic polymorphism and sustained virologic response in HCV genotype 1 infected subjects was described[1] [2]. IL-28B can be genotyped as CC, CT, or TT at the polymorphic site rs12979860. Although the prevalence varies among racial groups, the CC genotype provided a stronger baseline predictor of SVR within each racial group than viral load, HCV genotype, cirrhosis or any other known predictor of responsiveness to interferon-based therapy.
The phase III studies evaluating BOC/PR versus PR were initiated prior to the identification of the association of IL28B with response to PR therapy. However, a retrospective analysis has been conducted with the object of determining the distribution of IL28B and its relationship to SVR. The analyses were performed using all randomized subjects who gave informed consent for pharmacogenomic (PGx) sampling and analysis, had non-missing PGx data, and received at least one dose of boceprevir (experimental arms) or placebo (control arm).

Results of testing for IL28B were available for 62% and 66% of subjects who received at least one dose of boceprevir or placebo in studies P05216 and P05101. The prevalence of the three genotypes in the subpopulation with IL28B samples was 28.4% CC, with 17.8% TT, and 53.8% CT. The CC genotype was slightly less common among previous treatment failures (24.3%, study P05101) compared with the population of previously untreated subjects (30.0%, P05216). See table 21 below.

[1] Ge D, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature. 2009;461:399-401.

[2] Thompson AJ et al. Interleukin-28B polymorphism improves viral kinetics and is the strongest pretreatment predictor of sustained virologic response in genotype 1 hepatitis C virus. Gastroenterology. 2010 Jul;139:120-9.

Table 21. Distribution of IL28B Genotypes in Pharmacogenomics Subpopulations

	Number (%) of Subjects		
	CC[a]	CT	TT
Pooled P05101 + P05216			
Arm 1: PR 48, n=269	77 (28.6)	145 (53.9)	47 (17.5)
Arm 2: RGT, n=323	105 (32.5)	165 (51.1)	53 (16.4)
Arm 3: BOC/PR 48, n=320	77 (24.1)	181 (56.6)	62 (19.4)
Combined Arms, n=912	259 (28.4)	491 (53.8)	162 (17.8)

In study P05216 the PR treatment arm (arm 1) had a significantly higher SVR in subjects with the CC genotype (78%) compared to those with the CT (28%) or TT (27%) genotypes. In both boceprevir treatment arms there was a smaller numeric advantage to treatment in the CC genotypes compared to CT or TT subjects. In the small P05101 study, it is difficult to interpret responses to placebo according to genotype because of the limited numbers of subjects. Furthermore, the interpretation of, e.g., a C/C genotype in a patient that has failed on interferon based therapy is not straightforward, as the phenotype (non-response) is not that which is characteristic of the genotype.

Table 22. SVR by IL28B type

	% (Number) of Subjects		
	CC[a]	CT	TT
Pooled P05101 + P05216			
Arm 1: PR 48	72.73 (56/77)	26.21 (38/145)	31.91 (15/47)
Arm 2: RGT	80.95 (85/105)	63.64 (105/165)	54.72 (29/53)
Arm 3: BOC/PR 48	79.22 (61/77)	71.82 (130/181)	62.90 (39/62)
P05216			
Arm 1: PR 48	78.13 (50/64)	28.45 (33/116)	27.03 (10/37)
Arm 2: RGT	81.82 (63/77)	65.05 (67/103)	54.76 (23/42)
Arm 3: BOC/PR 48	80.00 (44/55)	71.30 (82/115)	59.09 (26/44)
P05101			
Arm 1: PR 48	46.15 (6/13)	17.24 (5/29)	50.00 (5/10)
Arm 2: RGT	78.57 (22/28)	61.29 (38/62)	54.55 (6/11)
Arm 3: BOC/PR 48	77.27 (17/22)	72.73 (48/66)	72.22 (13/18)

BOC=boceprevir 800 mg TID; PR=pegylated interferon 1.5 µg/kg once weekly + ribavirin 600 to 1400 mg/day; RGT=response-guided therapy.

The results of this retrospective subgroup analysis should be viewed with caution because of potential differences of the sub-study population relative to the overall trial population. In fact, for all categories of patients, those participating in the pharmacogenetics substudy had higher SVR rates than the corresponding groups of non-participants. Thus the sensitivity of this analysis for detecting an added value of boceprevir in C/C patients may be compromised by participant selection.

Whether IL28B genotype could reliably identify patients who are unlikely to significantly benefit form the addition of boceprevir (higher SVR rates or short course treatment duration) to P/R bitherapy will be the subject of further investigations.

The SmPC warrants the attention of physicians on the current uncertainty on the degree of added value of Victrelis on top of the bitherapy in C/C patients.

Supportive studies

Title of Study: Long-Term Follow-Up of Subjects in a Phase 1, 2, or 3 Clinical Trial in Which Boceprevir or Narlaprevir was Administered for the Treatment of Chronic Hepatitis C (Protocol No. P05063)

Studied Period: 05 March 2007 to 04 March 2010 (Ongoing study); Multicenter: 49 sites in the USA and 24 international sites

This ongoing study is being conducted in two parts as described below:

Part 1 includes subjects who participated in a Phase 1, 2, or 3 clinical study in which boceprevir was administered.

Part 2 includes subjects who participated in a Phase 1, 2, or 3 clinical study in which narlaprevir (another experimental NS3/4A inhibitor) was administered.

Subjects are followed for 3.5 years after the End of Treatment (EOT) in the previous boceprevir or narlaprevir study. No medication is administered in this study.

The primary objectives are to:
- confirm the durability of the virologic response in subjects with SVR in previous study.
- characterize the long-term safety.
- characterize the natural history of HCV sequence variants in subjects who received at least one dose of study medication

Of the 979 subjects who received boceprevir in a previous phase I or phase II study 604 were enrolled is this follow-up study (290 sustained virologic responders and 314 treatment failures). Median follow up was 2 years. The majority were male (62%) and white (86%), with a median age of 52.0 years (range: 21-66 years).

SVR

None of the 290 sustained virologic responders had HCV-RNA virology results that met the criteria for a definite relapse (i.e. became serum HCV-RNA positive with no subsequent negative results during long-term follow-up.). One subject had reinfection confirmed by genotype subtype retesting. Three subjects who achieved SVR in the previous treatment study had isolated detectable HCV-RNA results during the long-term follow-up, and subsequently had undetectable HCV-RNA results on multiple occasions. These subjects were considered sustained virologic responders.

The majority of sustained virologic responders (93%) with normal ALT levels at FW 24 maintained normal ALT levels at their last available visit. Nineteen (7%) subjects with normal ALT at FW 24 in the previous treatment study had elevated ALT at the last available visit. Most abnormal ALT values were <1.5 x upper limit of normal (ULN).

HCV sequence analysis in patients with treatment failure.

Of the patients experiencing treatment failure, the putative return to wild type was explored in 183 subjects who had on-treatment resistance-associated amino acid variants (RAVs) compared to the baseline sample (wild type). At baseline 6% of all subjects had RAVs. In subjects without SVRpost-baseline RAVS were found in 79%.

Kaplan-Meier analysis shows that individual RAVs returned to wild type at different rates, T54A returned the fastest (median time 0.24 years), followed by V36M (median time 0.78 years); T54S and R155K returned at similar rates (median times 1.43 and 1.28 years, respectively). With regard to the treatment failures with RAVs, after 2 years after end of treatment approximately 60% of the RAVs returned to wild type. This means that resistant types are still present after two years this might have implications for future treatment of these patients.

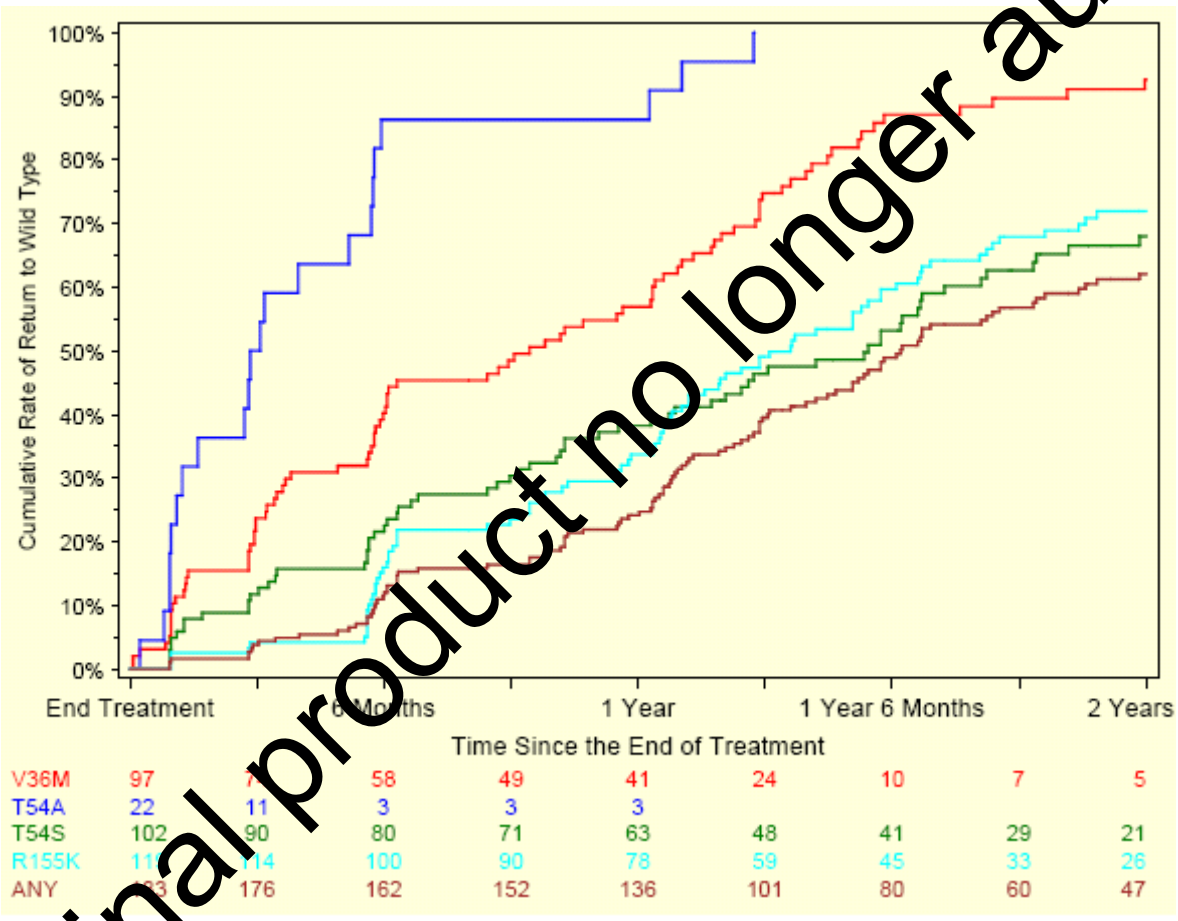


Figure: Kaplan-Meier for the Rate of Return to Wild Type

2.5.3. Discussion on clinical efficacy

Two pivotal phase III studies were performed, one naïve (P05216) and one in pretreated patients (P05101).

Design and conduct of clinical studies

Both phase III studies were double blind, multi-centers studies with centers from US, EU, Canada and South America. In both phase III studies (as well as in phase II studies) pegylated interferon alfa 2b was used.

The Lead in phase (4 weeks with the bitherapy Pegylated IFN+ribavirin before the addition of the boceprevir) brings the theoretical advantage of allowing the introduction of the antiviral agent once the steady state of ribavirin has been reached, i.e. under the optimal condition for the DAA (to best protect the DAA against functional monotherapy).

Whether or not the lead in phase increased the efficacy of this DAA, was specifically assessed in the phase II study in naïve patients (P03523), with comparative arms with or without lead in phase. This phase II study supported the lead in phase for the future development of this DAA in phase III.

The use of a lead in phase was associated with a trend for higher SVR, lower relapses as well as lower viral breakthrough. However, the difference was not statistically significant, and the virological merit of the lead-in phase has not been formally demonstrated.

A disputable non conservative 24 weeks futility rule was predefined in the phase III study in naïve patients whereas it was set at 12 weeks (as for the SOC) for treatment failure patients.

Regarding the target population the study population excluded subjects who were co-infected with HIV or HBV, subjects with decompensated liver disease, as well as null responders (as defined by a <2log decrease in HCV RNA at Week 12 during prior treatment with peg/rbv).

A study is on-going in the co-infected population (P05411). There is a particular medical need in this population is characterized by a more pejorative evolution (in terms of natural course and response to the SOC).

Concerning null responders it is noteworthy that this challenging population was excluded from the phase III study. However, the MAH considers patients with a < 1log decrease at the end of the 4-week lead in phase to be representative of those with a prior null response, and thus to have actually studied this population. On this basis, it is proposed to extend the indication to the null responder population

In clinical practice, however, categorization of patients relies on their historical response to the bitherapy at week 12.

Concerning Black patients, these are known as being poor responders to the SOC and as such represent a difficult to treat population. Of interest, the MAH specifically addressed the question of the added benefit of boceprevir to the SOC in this population through a specific cohort (cohort 2) in the Phase III study in naïve patients.

In both phase III studies the primary endpoint is the Sustained Virological Response (SVR) defined as undetectable HCV RNA 24 weeks after completion of therapy (SVR24). This primary efficacy criterion is in line with the EU guidelines. This SVR is correlated with cure.

In the studies, HCV RNA viral load were determined using the Roche COBAS TaqMan HCV/HPS Test, v2.0. The assay has a limit of quantitation of 25 IU/mL and of detection of 9.3 IU/mL. Thresholds of 95% sensitivity can vary for a given technology which evaluated the sensitivity thus, the threshold used in the trials are acceptable.

Both phase III studies were superiority studies, with the aim of detecting an approx 10% (in naïve, response rate in SOC estimated to approx 45%) to 20% (in treatment failure patients, response rate in SOC estimated to approx 20%)improvement in SVR rate over the SOC.

The statistical test and the approach (hierarchical order for testing null hypotheses of the 2 therapeutic regimens with BOC as compared to SOC) are in line with the CHMP guideline on multiplicity and is acceptable.

It was recently identified that a genetic polymorphism near the IL28B gene, encoding interferon-λ-3, was strongly associated with the likelihood of response to SOC. Recent US and EU guidelines recommend stratification according to IL28B genotype, but the phase III study was initiated before the release of these recommendations. More recently, a genetic variant leading to inosine triphosphatase (ITPA) deficiency has been associated with risk of ribavirin-related anaemia during PR therapy. A specific site amendment was made in the 2 phase III studies to perform IL28 genotype assay and ITPA. Results are provided for 60% of the whole population from both phase III.

Efficacy data and additional analyses

Regarding the Phase III trial SPRINT, overall (for cohort1+2), the addition of boceprevir to PR therapy provides a significant 25-30% gain in SVR on top of the PR in naïve patients.

The high level of statistical significance [P<0.0001, for each boceprevir arm vs control] confers robustness in the demonstration.

Addition of BOC to SOC confered a significant improvement of SVR in both the prior relapser patients (Δ=40-46%) and the prior partial responders patients (Δ=33-45%) as demonstrated in the RESPOND - 2 trial. Such results translate into a SVR reaching 75% in relapser patients and a SVR reaching 52% in prior partial responders. The high level of statistical significance (p<.0001) provides robustness in the efficacy demonstration.

Regarding IL28b, data from a retrospective analysis suggest that for naïve subjects with CC genotype the addition of boceprevir to PegIFN and ribavirin does not substantially improve response rates and as such the added value of boceprevir in patients with good prognostic factors of response to PR may be questioned. However it is important to highlight that more patients in the treatment arm benefited from a shorter treatment duration than patients treated with bitherapy alone. For naïve subjects with CT or TT genotype, the addition of boceprevir to PegIFN and ribavirin seems to improve response rates (below 30% versus 55% to 71%). For pretreated subjects addition of boceprevir seems to improve response rates for all genotypes. However, as the numbers of pretreated patients is small and the pharmacogenomic analysis was done in a subset of patients and baseline characteristics between the subset included in the pharmacogenomic analysis was not completely balanced with that of the not included subset, all these findings are uncertain. The MAH highlighted the limitations of the exploratory analysis and that the on treatment early viral response could be a stronger predictor of SVR. Furthermore it was highlighted that there are uncertainties on the clinical utility of IL28B genotyping in clinical practice.

It was agreed that only a prospective study will help to draw formal conclusion on the clinical utility of IL28B genotyping. The SmPC reflects the currently available level of information.

Appropriate treatment durations for different patient categories

Based on phase II data, the concept of a treatment duration tailored to the early kinetics of virologic response has emerged (i.e. the Response Guided Therapy/RGT). This concept was then formally tested in the two phase III studies.

Treatment naïve early responders received either 28 weeks of total therapy (4 weeks lead in + 24 weeks of triple therapy) or 48 weeks of total therapy (4 weeks lead in + 44 weeks of total therapy). Treatment naïve late responders received either (a) 4 weeks of lead in, followed by 24 weeks of triple therapy, and then another 20 weeks of P/R, or (b) 4 weeks of lead in followed by 44 weeks of triple therapy. Treatment experienced early responders received either 4 weeks of lead in followed by 32

weeks of triple therapy, or 4 weeks of lead in, followed by 44 weeks of triple therapy. Treatment experienced late responders received either (a) 4 weeks of lead in, followed by 32 weeks of triple therapy, and then another 12 weeks of P/R, or (b) 4 weeks of lead in, followed by 44 weeks of triple therapy.

SVR rates for treatment naïve early responders in P05216 that were treated for a total of 28 weeks, comprising about 45% of the studied treatment naïve populations, were very high, and similar to what was seen with 48 weeks of treatment. Relapse rates were low in both arms, with no indication of different relapse rates. On this basis, a relatively solid inference about the appropriateness of response guided therapy in treatment naïve patients can be drawn, with early responders receiving 4 weeks lead in + 24 weeks of triple therapy.

Concerning treatment naïve late responders, results from the P05216 study summarized above indicate that 24 weeks is too short in this subset, as discontinuing therapy at this time is associated by an apparent increase in viral breakthrough rates, as described above. However, data do not indicate what would be the optimal duration - that is, whether 20 weeks of further exposure to boceprevir is necessary, or if boceprevir treatment can be discontinued earlier, for instance at week 32. This has not been studied in treatment naïve patients, but it has been investigated in the treatment experienced population comprising of prior relapsers and prior partial responders. As stated above, approximately 45% of boceprevir treated patients qualified as early responders and were treated for 28 weeks. This roughly corresponds to the SVR rate in treatment naïve patients exposed to P/R. Thus, the late responder population would likely primarily consist of a mixture of would-be P/R relapsers, partial responders and null responders. This implies a rationale for looking at the outcomes of the P05101 study, were the virological efficacy of 32 weeks total boceprevir therapy (late responders, RGT arm) and 44 weeks total boceprevir therapy (late responders, BOC/PR48 arm) was directly compared. This small dataset failed to indicate any efficacy difference between 32 and 44 weeks of boceprevir exposure in prior relapsers and prior non-responders that are late responders to boceprevir based therapy. The point estimate in fact favors 32 weeks of boceprevir therapy, and the relapse rate is similar. What can further be inferred from the EOT response, which is higher in the RGT arm (32 weeks of boceprevir), is that, as opposed to the case with 24 weeks of boceprevir therapy in treatment naïve late responsers, there was no excess of viral breakthroughs when boceprevir was dosed for 32 weeks, in comparison to 44 weeks.

Now, it may be argued that this was demonstrated in a different population, but as stated above, the baseline interferon responsiveness in the subpopulation of treatment experienced late responders is likely to largely overlap with that of treatment naïve late responders. Therefore, a reasonable guess on available evidence is that 32 weeks would be sufficient for maximizing SVR rates in most interferon responder strata. In light of the safety profile of boceprevir, risk/benefit is considered to likely be more positive with 32 than with 48 weeks of therapy, though the uncertainties of this inference are acknowledged. On this basis it is proposed that the boceprevir regimen for treatment naïve late responders is 4 weeks of lead in + 32 weeks of triple therapy, followed by 12 weeks of P/R.

In treatment experienced early responders that were randomized to the RGT arm, and thus received 4 weeks of lead in followed by 32 weeks of triple therapy, SVR rates were lower than in corresponding patients randomized to 44 weeks of triple therapy. When looking at the dataset consisting of patients that actually received 36 weeks of similar therapy, a roughly 10% difference in SVR in favor of the longer duration is entirely explained by higher relapse rates in patients receiving a shorter duration of therapy. The 95% confidence limits of this difference are compatible with a 17% higher relapse rate in case of discontinuation of therapy at week 36.

It is recognized that this dataset is small, and that the difference is driven by less than 10 events. The uncertainty of the inference, due to the limited size of the dataset, is clear. Nonetheless, the likely

equivalence of a 36 and a 48 week total duration of therapy in treatment experienced patients is not considered sufficiently demonstrated in the light of these outcomes, with all recorded relapses taking place in the shorter treatment duration arm. Therefore, treatment experienced early responders should continue therapy after week 36. As already stated above, there is no indication that extending boceprevir therapy beyond 32 weeks is of any value in treatment experienced late responders. By inference, no benefit is expected in treatment experienced early responders either. Therefore, the difference seen in the early responder subset is attributed to the effect of continued P/R medication, and the recommended regimen for treatment experienced early responders is 4 weeks lead in, 32 weeks of triple therapy, followed by 12 weeks of P/R consolidation.

The recommended treatment regimen for treatment experienced late responders is 4 weeks lead in followed by 32 weeks of triple therapy, followed by 12 weeks of P/R. The rationale for a total of 32 rather than 44 weeks of therapy has been described above. There is no evidence for an added benefit of boceprevir use beyond week 36.

Cirrhotics represent a special case. Very few patients with the most advanced degree of liver histopathology were included in the boceprevir trials. No conclusion can be made on the optimal treatment duration in cirrhotics from these data. An important consideration in cirrhotics is that this subgroup contains the patients in whom achieving an SVR may be expected to have the most immediate clinical consequences. Thus, a particularly conservative approach to optimizing the likelihood of response can be motivated in this group. On the other hand, they may be the most sensitive to some boceprevir side effects, particularly thrombocytopenia and neutropenia. Therefore the primary recommendation 4 weeks lead in + 44 weeks of triple therapy. However, the SmPC should clearly state that adequate monitoring of side effects is tantamount, and that boceprevir should be discontinued if the side effect profile of the patients indicate that the risks may outweigh the benefits. Also for prior null responders, for whom the evidence of efficacy of boceprevir is altogether indirect, treatment durations of 4+44 weeks are primarily recommended.

Stopping rules

In the phase III studies the stopping rules were different for naïve and treatment experienced patients. A disputable non conservative 24 weeks futility rule was predefined in the phase III study in naïve patients whereas it was set at 12 weeks (as for the SOC) for treatment experienced patients. The MAH was asked to justify why conservative measures are not equally proposed for both naïve and treatment experienced patients.

The question is, should physician do something between week 12 and week 24, to avoid unduly keeping a treatment-naïve patient under unchanged treatment whereas no benefit can be anticipated (and only risk).

The following futility rule that would be applicable for both treatment naïve and prior treatment failure patients are proposed: discontinue all 3 drugs if HCV RNA is ≥100 IU/mL at Treatment Week 12; discontinue all 3 drugs if HCV RNA is detectable at Treatment Week 24.

These stopping rules simplifies the posology of Victrelis because the same futility rule is used for both treatment naïve and previous treatment failure patients, and because the Treatment Week (TW) 12 and 24 time points are already part of the standard of care for monitoring HCV RNA testing during therapy with peginterferon and ribavirin.

The futility rule is based on the observations in the Phase 3 program that patients with HCV RNA levels ≥100 IU/mL at TW 12 are unlikely to achieve SVR; and patients with low levels of detectable HCV RNA at TW12 still had a substantial possibility of achieving SVR.

The implementation of a stopping rule at TW12 (HCV RNA ≥100 IU/mL) means that only patients with very low (or undetectable) HCV RNA levels will remain on treatment after TW12, and therefore it is not considered necessary that additional HCV RNA testing occurs between TW12 and TW24.

Null responders

Prior null response to P/R therapy was an exclusion criteria from the pivotal study RESPOND 2/P05101 in treatment experienced. Despite this exclusion criteria, the MAH claimed that clinical experience was gained in "null responders" by using the lead in phase to re-qualify patients (<1 log copies/ml at week 4).

The MAH highlights that there is a close correlation between the historical week 12 response on prior treatment (<2 log copies/ml) and the week 4 on treatment (<1 log copies/ml). Furthermore when applying the week 4 definition of null responders, a significant benefit of the tritherapy is shown in RESPOND 2/P05101 over the PR in this challenging population (RGT 33%, no RGT 24%, PR 0%). While a lead in response of <1 log10 is not considered a sufficiently sensitive substitute for null response (defined as <2log10 decline at week 12, it is recognised that the findings in this category are supported by outcomes in the still more strictly defined subgroup of patients with <0.5 log10 decline during the lead in. Among such patients 0% reached SVR in the control arm, whereas 28-30% reached SVR in the boceprevir arms (pooled cohort 1 +2).

The total sample size underlying this point estimate is 84 patients (versus 25 patients in the P/R arm). Thus, there is hardly any doubt that boceprevir increases SVR rates in null responders, though an exact estimate of the magnitude of this effect is not available.

Overall, given the medical need in this population and waiting for further option, it is recognised that access to the drug should not be hampered by exclusion from the indication, however a statement is reflected in the boceprevir product information.

Assessment of paediatric data on clinical efficacy

No clinical studies in paediatric patients have been carried out.

2.3.4 Conclusions on the clinical efficacy

Boceprevir provides higher rates of SVR as compared to the current standard of care with Peginterferon alfa / Ribavirin (PR). The gain of SVR in the Phase III/SPRINT 2-P05216) in treatment naïve patients was of the magnitude of approximately 30%. In the Phase III/RESPOND 2-P05101 in treatment experienced the gain was approximately 40%. For both studies, superiority over placebo+ P/R was established with p<0.0001.

Regarding IL28b, data from a retrospective analysis question the added benefit of boceprevir in patients with good prognostic factors of response to PR. The limitations of the retrospective analysis are recognized and leave a level of uncertainty concerning the predictive value of IL28B that requires addressing by means of a prospective trial. A prospective study will be carried out to help draw formal conclusion on the clinical utility of IL28B genotyping.

Concerning the RGT, for treatment naive patients, a shorter treatment duration of 4 plus 24 weeks tritherapy is accepted for early responders. For treatment naive late responders and treatment experienced early and late responders the 4W PR+32W BPR+12 W PR appears an adequate balance between maximising SVR and the risks of prolonged exposure of tritherapy, notably anaemia.

Regarding patients with cirrhosis, the number of cirrhotic patients is overall very limited and mandates particular caution in terms of treatment recommendations. In these patients, a recommendation to maximise the tritherapy period until 48 weeks is given. However, taking into account that these patients are particularly challenging to manage in clinical practice due their hematological abnormalities, the feasibility of pursuing the tritherapy with the incremental risk of anaemia is uncertain. Therefore, this decision should be adapted according to the patients tolerance to treatment beyond 32 weeks. The same recommendation should apply for the challenging null responders patients.

Null responders where excluded for the Phase III trials, however given the medical need in this population and waiting for further options, it has been admitted that access to the drug should not be hampered by exclusion from the indication. Furthermore it can be acknowledged that the addition of boceprevir might increase the likelihood of achieving SVR in null responders waiting for optimal therapeutic management that might require in the future combination of antiviral agents.

2.4 Clinical safety

Patient exposure

During the course of clinical development of boceprevir, approximately 2827 subjects were exposed to any dose of boceprevir in 28 clinical trials, including 20 Phase I studies, three Phase II studies, and five Phase III studies as of the clinical database cut-off dates.

Phase I: 377 healthy volunteers, 18 subjects with hepatic impairment and 8 subjects with renal impairment and 176 subjects with chronic hepatitis C.

Phase II/III: 2098 subjects in study P03523, P05216, P05101, P03659, P05514 and P06086 (Note: study P06086 and P05514 were included because, though they are ongoing, they are open-label).

In these studies the total daily dose of boceprevir ranged from 300 mg up to 2400 mg. Most

(1900/2098, 91%) of the subjects received 2400 mg boceprevir daily as 800 mg TID, the dose being pursued for registration. The duration of boceprevir treatment in the Phase 2 and 3 studies ranged from 1 day up to 396 days. Sixty-six percent (66%) of subjects who received boceprevir 800 mg TID were treated for >24 weeks.

See table 23 below.

Table 23. Distribution of Treatment Duration By Dose of Boceprevir in the Phase 2 Through 3

Treatment Duration[b]	Number (%) Subjects Boceprevir Daily Dose[a] (mg) 300 mg n=44		600 mg n=39		1200 mg n=115		2400 mg as 800 mg TID n=1900	
Received Any Treatment	44	(100)	39	(100)	115	(100)	1900	(100)
≤24 Weeks	44	(100)	39	(100)	115	(100)	1900	(100)
>24 Weeks	24	(55)	20	(51)	69	(60)	1251	(66)
Statistics (Days)[c]								
Mean	153.7		147.1		151.9		184.7	
SD	39.9		52.5		37		98.6	
Median	162		155		159		169	
Minimum	74		3		20		[illegible]	
Maximum	206		215		207		[illegible]	

Key Studies Integrated for Safety Assessment (P03523, P05216, and P05101)

A total of 547 subjects in the PR arms and 1548 subjects in the BOC/PR arms of the key studies received at least one dose of any study medication.

Table 24. Distribution of Treatment Duration in the Key Studies.

Treatment Duration[b]	Treatment Naïve P03523/P05216 PR[a] n=467	BOC/PR n=1225	PEG/R Treatment Failure P05101 PR n=80	BOC/PR n=323	All Subjects PR[a] n=547	BOC/PR n=1548
Received Any Treatment	467 (100)	1225 (100)	80 (100)	323 (100)	547 (100)	1548 (100)
TW 4[c]	449 (96)	1189 (97)	79 (99)	318 (98)	528 (97)	1507 (97)
TW 24	399 ([illegible])	974 (80)	25 (31)	238 (74)	424 (78)	1212 (78)
TW 48	214 ([illegible])	467 (38)	23 (29)	140 (43)	237 (43)	607 (39)

The key studies for safety analysis are the two phase III studies: P05216 in naïve patients and P05101 in pretreated patients and the phase II study in naïve patients P03523. In these three studies 800 mg PO TID boceprevir was given, thus daily 2400 mg boceprevir i.e. the proposed dose. The phase II study in pretreated patients is appropriately not integrated because subjects were treated with different dosages of boceprevir.

In total 1548 subjects received boceprevir 800 mg TID of which 78% (1212) received boceprevir for at least 24 weeks; and 39% for 48 weeks.

Adverse events

Almost all patients experienced treatment related AEs (see table 25). With regard to dose modification due to AEs there is a substantially higher percentage in the experimental group compared to the control (39% versus 24%). Overall there is no difference in discontinuation due to AEs. However, for the pretreated study the percentage discontinuation due to AEs is substantially higher in the experimental arm 10% versus control 3%.

Table 25. Overview of Adverse Events, Deaths, and Study Drug Discontinuation and Dose Modifications Due to Adverse Events in the Key Studies

	Treatment-naive P03523/P05216		PEG/R Treatment Failure P05101		All Subjects	
	PR[a] n=467	BOC/PR n=1225	PR n=80	BOC/PR n=323	PR[a] n=547	BOC/PR n=1548
Median Treatment Duration (Days)	216	197	104	253	198	201
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Treatment-Emergent AE	460 (99)	1217 (99)	77 (96)	321 (99)	537 (98)	1538 (99)
Treatment-Related Treatment-Emergent AE	456 (98)	1212 (99)	77 (96)	320 (99)	533 (97)	1532 (99)
Serious AE	39 (8)	125 (10)	4 (5)	39 (12)	43 (8)	164 (11)
Death[b]	4 (1)	3 (<1)	0	1 (<1)	4 (1)	4 (<1)
Life-Threatening	7 (1)	13 (1)	0	9 (3)	7 (1)	22 (1)
Study Drug Discontinuation Due to AE	65 (14)	172 (14)	2 (3)	33 (10)	67 (12)	205 (13)
Dose Modification Due to AE[c]	121 (26)	505 (41)	11 (14)	100 (31)	132 (24)	605 (39)

AE=adverse event; BOC=boceprevir 800 mg PO TID; P=peginterferon alfa-2b; PEG=peginterferon alfa; PO=orally; PR=peginterferon alfa-2b+ribavirin; R=ribavirin; TID=three times daily.

Treatment-emergent AEs were similar across the treatment arms and were consistent with those reported with standard of care. Anaemia and dysgeusia are the only two events that were reported with a ≥10% difference in the BOC/PR arms compared with the pooled PR control arms of the key studies.

Anaemia, neutropenia, and thrombocytopenia occurred in 4% versus 1 % in the control arm. Nausea and vomiting, and depression were also more commonly reported in subjects receiving PR control or BOC/PR in the treatment-naive subjects (P03523/P05216) compared with previous treatment failures (P05101).

The profile of treatment-related AEs (considered possibly or probably related to study drug, by investigator) was similar to that of the treatment-emergent AEs. The most frequently reported treatment related AEs (considered possibly or probably related to study drug, by investigator) were: fatigue, anaemia, nausea, headache, and dysgeusia. No novel treatment related AEs were reported.

The most commonly reported treatment-related, treatment-emergent AEs (≥10% incidence) in the key studies are summarized in the table below.

Table 26. Treatment-Related, Treatment-Emergent Adverse Events in the Key Studies (Incidence Greater Than or Equal to 10%)

	Treatment-naive P03523/P05216		PEG/R Treatment Failure P05101		All Subjects	
	PR[a] n=467	BOC/PR n=1225	PR n=80	BOC/PR n=323	PR[a] n=547	BOC/PR n=1548
Median Treatment Duration (Days)	216	197	104	253	198	201
System Organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects Reporting Any Adverse Event	456 (98)	1212 (99)	77 (96)	320 (99)	533 (97)	1532 (99)
Blood and Lymphatic System Disorders						
Anaemia	142 (30)	611 (50)	16 (20)	144 (45)	158 (29)	755 (49)
Neutropenia	88 (19)	304 (25)	8 (10)	46 (14)	96 (18)	350 (23)
Gastrointestinal Disorders						
Diarrhoea	88 (19)	279 (23)	12 (15)	74 (23)	100 (18)	353 (23)
Dry Mouth	44 (9)	128 (10)	7 (9)	46 (14)	51 (9)	174 (11)
Dysgeusia	73 (16)	427 (35)	9 (11)	141 (44)	82 (15)	568 (37)
Nausea	187 (40)	556 (45)	30 (38)	134 (41)	217 (40)	690 (45)
Vomiting	54 (12)	228 (19)	6 (8)	43 (13)	60 (11)	271 (18)
General Disorders and Administration Site Conditions						
Asthenia	84 (18)	179 (15)	13 (16)	68 (21)	97 (18)	247 (16)
Chills	137 (29)	413 (33)	24 (30)	105 (33)	161 (29)	515 (33)
Fatigue	272 (58)	710 (58)	40 (50)	179 (55)	312 (57)	889 (57)
Influenza Like Illness	115 (25)	264 (22)	20 (25)	75 (23)	135 (25)	339 (22)
Injection Site Erythema	59 (13)	131 (11)	7 (9)	36 (11)	66 (12)	167 (11)
Injection Site Reaction	52 (11)	141 (12)	5 (6)	25 (8)	57 (10)	166 (11)
Irritability	108 (23)	266 (22)	10 (13)	67 (21)	118 (22)	333 (22)
Pain	39 (8)	124 (10)	3 (4)	24 (7)	42 (8)	148 (10)

Pyrexia	151 (32)	394 (32)	17 (21)	91 (28)	168 (31)	485 (31)
Investigations						
Weight Decreased	55 (12)	134 (11)	7 (9)	36 (11)	62 (11)	170 (11)
Metabolism and Nutrition Disorders						
Decreased Appetite	112 (24)	304 (25)	13 (16)	82 (25)	125 (23)	386 (25)
Musculoskeletal and Connective Tissue Disorders						
Arthralgia	79 (17)	216 (18)	11 (14)	66 (20)	90 (16)	282 (18)
Myalgia	110 (24)	275 (22)	19 (24)	79 (24)	129 (24)	354 (23)
Nervous System Disorders						
Dizziness	67 (14)	219 (18)	8 (10)	50 (15)	7[illegible] (14)	269 (17)
Headache	196 (42)	554 (45)	38 (48)	129 (40)	234 (43)	683 (44)
Psychiatric Disorders						
Anxiety	55 (12)	151 (12)	5 (6)	39 (12)	60 (11)	190 (12)
Depression	96 (21)	255 (21)	12 (15)	41 (13)	108 (20)	302 (20)
Insomnia	154 (33)	403 (33)	16 (20)	95 (29)	170 (31)	498 (32)
Respiratory, Thoracic and Mediastinal Disorders						
Cough	88 (19)	194 (16)	12 (15)	63 (20)	100 (18)	257 (17)
Dyspnoea	73 (16)	227 (19)	13 (16)	69 (21)	86 (16)	296 (19)
Dyspnoea Exertional	36 (8)	10[illegible] (8)	4 (5)	36 (11)	40 (7)	136 (9)
Skin and Subcutaneous Tissue Disorders						
Alopecia	126 (27)	333 (27)	13 (16)	71 (22)	139 (25)	404 (26)
Dry Skin	82 (18)	214 (17)	6 (8)	70 (22)	88 (16)	284 (18)
Pruritus	111 (24)	265 (22)	14 (18)	61 (19)	125 (23)	326 (21)
Rash	87 (19)	200 (16)	4 (5)	49 (15)	91 (17)	249 (16)

The treatment-related AEs reported after the PR lead-in (i.e., newly occurring or worsened in severity) included the well-known AEs associated with PR: Depression, irritability and weight loss are long-term effects of PEG therapy. Anaemia occurs with PEG/RBV therapy, and typically follows a pattern of decline for the first 12 weeks of treatment. Addition of boceprevir to PR therapy is associated with an additional decrement in Hgb and neutrophil count. Dizziness (13%) and dyspnea (14%) were reported more frequently in the BOC/PR arm after the lead-in compared to during lead-in (6% and 7%, respectively). Rash was reported more often in both the PR control arm (13%) and BOC/PR arm (16%) after lead-in than during lead-in (5%). Constitutional symptoms such as fever, chills, and myalgia were reported more often in the lead-in period compared with after lead-in in both the PR control and BOC/PR arms.

Adverse events during follow up.

The most common (≥10% incidence) treatment related AEs that were ongoing at the time of a subject's 30-day post-treatment follow-up visit and were still ongoing at the time of the subject's Follow-up Week 24 visit are listed in the table below

Table 27. Treatment-Related Adverse Events Ongoing After 6 Months of Follow-up (in Subjects Who Were Followed At Least 6 Months) in the Key Studies (Incidence Greater Than or Equal to 10%)

	Number (%) of Subjects					
	Treatment Naïve P03523/P05216		PEG/R Treatment Failure P05101		Total	
System Organ Class Preferred Term	PR[a] n=373	BOC/PR n=1095	PR n=75	BOC/PR n=297	PR[a] n=448	BOC/PR n=1392
Subjects Reporting Any Adverse Event	188 (50)	546 (50)	35 (47)	174 (59)	223 (50)	720 (52)
General Disorders and Administration Site Conditions	63 (17)	168 (15)	19 (25)	67 (23)	82 (18)	235 (17)
Fatigue	40 (11)	102 (9)	15 (20)	44 (15)	55 (12)	146 (10)
Psychiatric Disorders	64 (17)	188 (17)	10 (13)	59 (20)	74 (17)	247 (18)
Insomnia	32 (9)	98 (9)	3 (4)	34 (11)	35 (8)	132 (9)

Dose finding Study

Overall, a similar incidence of AEs was observed among all dosage groups, with at least 93% of subjects reporting AEs. For anaemia, see further laboratory findings).

Except for dysgeusia, events reported during the trial were well recognized as side effects associated with PR therapy. A dose-dependent increase in dysgeusia was reported when boceprevir was part of the therapy. At the lower doses of 100 mg and 200 mg, only 6% (3/48) and 4% (2/49) of subjects, respectively, experienced dysgeusia. The number increased in the group treated with 400 mg TID to 25% (36/146) of subjects. The highest incidence of dysgeusia was observed in the group treated with boceprevir at 800 mg TID, with 48% (31/65) reporting dysgeusia. Overall a percentage of 37% was found in the key safety analysis.

<u>Response guided therapy in the phase III Studies P05216 and P05101</u>

In order to capture the safety experience for all treated subjects, safety comparisons of RGT are presented first by a comparison of treatment in Arm 2 RGT (regardless of assignment) with the 48-week BOC/PR arms and the 48- week PR control arms in each of the two studies. If a safety advantage of Arm 2 RGT over BOC/PR48 was observed, then a secondary comparison of safety was made between the shorter RGT arm (in early virologic responders) and the longer RGT arm within Arm 2 of each study.

There were similar proportions of subjects with treatment-related AEs, and dose modifications due to AE in the RGT arms compared with the BOC/PR 48-week arms in both studies.

When the shorter RGT treatment arms are compared with the longer RGT arms, there are fewer SAEs and study drug discontinuations in the early virologic responders who qualified for shorter treatment in both the treatment-naïve and previous treatment failure study populations. There were similar

proportions of subjects with treatment-related AEs, and d, in ose modifications due to AE in the short and long RGT arms.

The safety differences between the shorter vs longer duration of therapy in Arm 2 are confounded by differences in the demographic characteristics of both groups. In Study P05216, subjects who qualified for shorter duration of treatment compared to long treatment were more likely to be white (88% vs 79%) and have a lower mean BMI (27.7 vs 28.5 kg/m^2). In Study P05101, subjects in the short RGT arm were more likely to be female (44% vs 20%), white (94% vs 80%), and younger (mean age 52.7 vs 54.0 years).

The pattern with respect to timing of onset of events appeared similar when comparing the PR and BOC/PR arms. Most (98-99%) subjects reported at least one AE early, within the first 28 weeks of treatment. After TW 28, however, 67% of PR-treated subjects and 70% of BOC/PR-treated subjects had the new onset of at least one AE. Hematologic events and fatigue were reported with new onset after TW 28 by ≥5% of subjects in both PR- and BOC/PRtreated subjects.

Serious adverse event/deaths/other significant events

Deaths
Eight subjects died in the key studies: one in study P03523, boceprevir arm (drug cocaine toxicity) unlikely related; six in study P05216: four in control arm: one cardio-respiratory arrest, unlikely related; one suicide, possible related; one death by accident, unlikely related; one death unknown cause, unlikely related. Two in boceprevir arms, one suicide possible related and one cardiac arrest, unlikely related. One death in study P05101: one suicide (SVR was attained, there were no significant AEs, the patient committed suicide during follow up phase), the death was unlikely related.

Other studies

There were no deaths in the phase I and dose-finding studies. In the ongoing study P05685 two subjects died: one multi organ failure/pneumonia staphylococcal, possibly related and one cardiac failure, unlikely related, treatment is still blinded. One subject in the screening phase for ongoing study P06086 died suddenly, considered unlikely related. And in the ongoing follow-up study P05053 where no medication is administered, three subjects died: one progression of hepatic cirrhosis, one hepatic neoplasm malignant and one pancreatic carcinoma all three were unlikely related. Thus in total an additional six subjects died.

In study P05685, there were more infections reported on boceprevir (22%) than control (12%). Of note in a cross study comparison of safety there was a marked increase in the risk of neutropenia (including grade 3/4) when boceprevir is combined to alfa 2a than when combined with alfa 2b. There is also an increased risk of grade 4 neutropenia. See table 28 below.

Table 28. Cross-Study Comparison of safety: P05685 and P05101 (Both Studies Evaluated Patients Who Previously Failed Therapy with PR).

	Study P05685		**Study P05101**	
	PegIFN alfa2a/RBV	**PegIFN alfa 2a/RBV/BOC**	**PegIFN alfa2b/RBV**	**PegIFN alfa2b/RBV/BOC**
	N=67	N=334	N= 80	N= 161
Treatment duration (mean)	105 days	**334 days**	104 days	**336 days**
AE	100%	100%	96%	100%
SAE	10%	13%	5%	14%
Death	0	2 (1%)	0	0
Drug discontinuation	4%	17%	3%	12%

Dose modification	22%	43%	14%	33%
Anaemia as AE	33%	50%	20%	47%
Hb<10g/dl	22%	37%	24%	35%
Hb<8.5g/dl	4%	13%	1%	14%
Use of EPO	30%	47%	21%	46%
Dysgueusia	25%	39%	11%	45%
Neutropenia as AE	18%	**31%**	10%	14%
Neutrophils<750/mm^3 Grade 3-4	18%	**28%**	9%	20%
Neutrophils<500/mm^3 Grade 4	3%	**14%**	4%	7%
Thrombocytopenia as AE	6%	7%	0%	6%
Platelets <50 x 10^9/L (Grade 3)	7%	10%	0	5%
Platelets <25 x 10^9/L (Grade 4)	0	1%	0	0

Other Serious Adverse Events

SAEs were reported in 8% of subjects in the PR control arm and 11% of subjects in the BOC/PR arms.

Most of the SAEs were reported by only one subject; SAEs reported by more than one subject were the types of events often associated with long-term PR therapy, and were reported with somewhat higher frequency in the boceprevir-containing arms (hematologic: 19/1548 [1%] vs 2/547 [<1%]; gastrointestinal: 29/1548 [2%] vs 6/547 [1%]; and psychiatric AEs: 24/1548 [2%] vs 5/547 [1%]).

See table below:

Table 29. Serious Adverse Events (Incidence Greater Than or Equal to 1%) in the Key Studies

	Number (%) of Subjects											
	Treatment-naive P03523/P05216				PEG/R Treatment Failure P05101				All Subjects			
	PR[a] n=467		BOC/PR n=1225		PR n=80		BOC/PR n=323		PR[a] n=547		BOC/PR n=1548	
Median Treatment Duration (Days)	216		197		104		253		198		201	
System Organ Class Preferred Term												
Subjects Reporting Any SAE	39	(8)	125	(10)	4	(5)	39	(12)	43	(8)	164	(11)
Blood and Lymphatic System Disorders	2	(<1)	14	(1)	0		5	(2)	2	(<1)	19	(1)
Anaemia	1	(<1)	9	(1)	0		5	(2)	1	(<1)	14	(1)
Neutropenia	0		7	(1)	0		0		0		7	(<1)
Gastrointestinal Disorders	6	(1)	20	(2)	0		9	(3)	6	(1)	29	(2)
Abdominal Pain	1	(<1)	3	(<1)	0		2	(1)	1	(<1)	5	(<1)
General Disorders and Administration Site Conditions	4	(1)	19	(2)	1	(1)	5	(2)	5	(1)	24	(2)
Chest Pain	0		6	(<1)	1	(1)	3	(1)	1	(<1)	9	(1)
Hepatobiliary Disorders	3	(1)	1	(<1)	1	(1)	1	(<1)	4	(1)	2	(<1)
Cholelithiasis	2	(<1)	0		1	(1)	0		3	(1)	0	
Infections and Infestations	8	(2)	30	(2)	1	(1)	6	(2)	9	(2)	36	(2)
Appendicitis	1	(<1)	0		0		3	(1)	1	(<1)	3	(<1)
Gastroenteritis	0		5	(<1)	1	(1)	0		1	(<1)	5	(<1)
Median Treatment Duration (Days)	216		197		104		253		198		201	
Musculoskeletal and Connective Tissue Disorders	1	(<1)	5	(<1)	0		3	(1)	1	(<1)	8	(1)
Intervertebral Disc Protrusion	0		2	(<1)	0		2	(1)	0		4	(<1)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	6	(1)	8	(1)	0		1	(<1)	6	(1)	9	(1)
Nervous System Disorders	3	(1)	13	(1)	1	(1)	3	(1)	4	(1)	16	(1)
Parkinsonism	0		0		1	(1)	0		1	(<1)	0	
Psychiatric Disorders	5	(1)	16	(1)	0		8	(2)	5	(1)	24	(2)
Depression	1	(<1)	4	(<1)	0		4	(1)	1	(<1)	8	(1)
Homicidal Ideation	0		2	(<1)	0		2	(1)	0		4	(<1)
Suicidal Ideation	2	(<1)	7	(1)	0		5	(2)	2	(<1)	12	(1)
Respiratory, Thoracic and Mediastinal Disorders	1	(<1)	8	(1)	0		3	(1)	1	(<1)	11	(1)
Dyspnea	0		2	(<1)	0		2	(1)	0		4	(<1)

The incidence of SAEs adjusted for exposure is presented the following table.

Table 30.

	PR N=547		BOC/PR N=1548	
	%	rate	%	rate
Anaemia	<1	0.2	1	0.7
Neutropenia	0	0.0	<1	0.4

Rate is the incidence rate per 100 person years.

When incidence is adjusted for exposure the incidence of severe anaemia appears somewhat higher in experiment arms rate 0.7 versus 0.2.The same is true for neutropenia. The lower exposure rate in the PR arms is due to the higher treatment failures (futility rule).

The cases of thyroid neoplasm were classified as mild.

Other studies

Overall, the types of SAEs reported in the ongoing studies were comparable to those reported in the key safety studies.

Laboratory findings

Anaemia

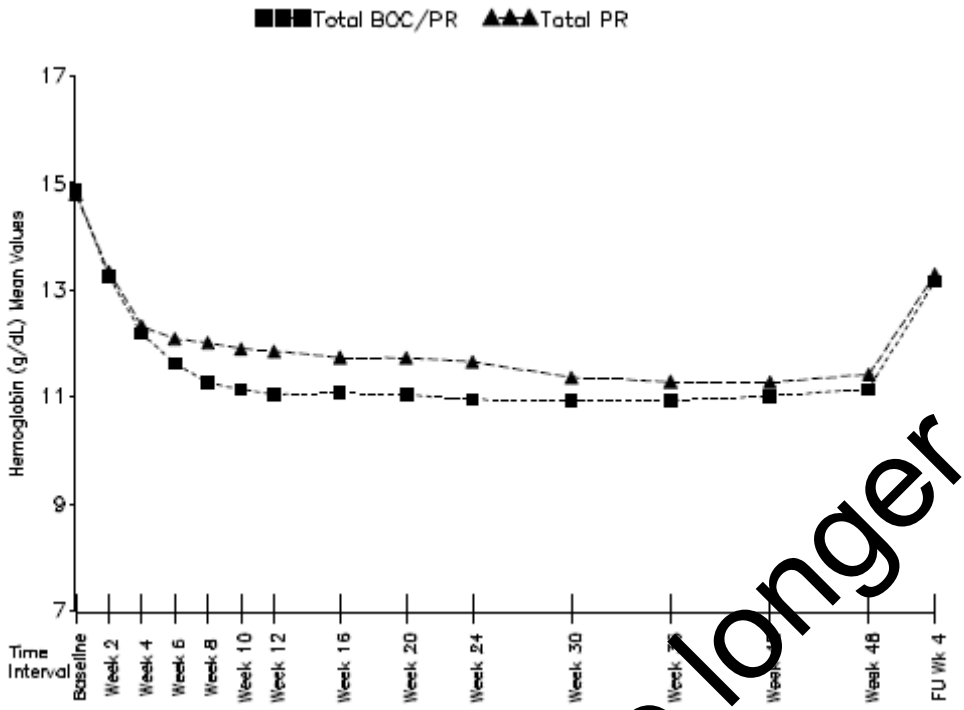
Subjects with Hgb values of <10 g/dl were considered anaemic whether or not the investigator assigned an AE of anaemia. The proportion of subjects reporting anaemia /hemolytic anaemia was higher in the boceprevir arms (49%) compared with the control arms (29%). Dose modifications due to anaemia/hemolytic anaemia occurred twice as often in the BOC/PR arms (26%) compared with PR control arms (13%).

Table 31. Hemoglobin distribution

		Number (%) of Subjects					
		Treatment-naive P03523/P05216		PEG/R Treatment Failure P05101		All Subjects	
	WHO Grade	PR[a] n=467	BOC/PR n=1225	PR n=80	BOC/PR n=323	PR[a] n=547	BOC/PR n=1548
Number of Subjects Included[b]		n=461	n=1215	n=80	n=322	n=541	n=1537
Hemoglobin (g/dL)							
8.5 to <10[c]	NA	119 (26)	522 (43)	19 (24)	127 (39)	138 (26)	649 (42)
<8.5[d]	NA	15 (3)	69 (6)	1 (1)	31 (10)	16 (3)	100 (7)

With PR, the typical pattern is one of an early fall in Hgb concentration by TW 4, followed by stabilization and a plateau maintained to the end of treatment, with a return to baseline levels after discontinuation of therapy. With the addition of boceprevir at TW 4 (most study arms in the key studies had 4-week PR lead-in), Hgb concentrations continued to decline up to TW 6 to TW 8. In these studies, the change in Hgb over time beyond TW 8 was confounded by the use of EPO in approximately

43% of subjects in the BOC/PR arms (compared to 24% in the PR control arms)). The pattern of mean Hgb concentration over time was similar in the BOC/PR arms and the PR control arms (Figure below). An additional ~1 g/dl decrement in Hgb concentrations was observed in the boceprevir-containing arms.



Mean Hemoglobin Concentration Over Time by Treatment Arm in the Key Studies

Multivariate logistic regression analysis was performed to identify baseline and disease characteristics associated with anaemia. In the treatment-naïve populations of studies P03523 and P05216 and using the full model, treatment with boceprevir, low baseline Hgb, female sex and age >40 were significant factors for developing anaemia (treatment [BOC/PR vs Control, OR 2.9, p<0.0001], baseline Hgb [OR 0.6, p<0.0001], sex [female vs male, OR 1.9, p<0.003], and age [≤40 vs >40 years, OR 0.4, p<0.0001]).

Multivariate logistic regression analysis was also performed to identify baseline and disease characteristics associated with anaemia in the previous treatment–failure population in Study P05101. Similar risk factors for anaemia were seen compared to the treatment-naïve population, with the addition of race (non-black being associated with an increased risk.

AE terms potentially representing clinical symptoms of anaemia were selected. AEs that are characteristic of anaemia were reported with similar frequency in the PR (76%) and BOC/PR arms (80%). The most common (≥10%) events in each arm were fatigue (57% PR, 57% BOC/PR), asthenia (18% PR, 16% BOC/PR), dyspnea (16% PR, 19% BOC/PR), and dizziness (14% PR, 17% BOC/PR).

Table 32.

	All Subjects			
	PR[a] n=547		BOC/PR n=1548	
	Hgb <10 g/dL n=154	Hgb ≥10 g/dL n=387	Hgb <10 g/dL n=749	Hgb ≥10 g/dL n=788
Subjects Reporting Any Adverse Event	132 (86)	286 (74)	639 (85)	589 (75)
General Disorders and Administration Site Conditions	128 (83)	264 (68)	565 (75)	534 (68)
Asthenia	31 (20)	66 (17)	107 (14)	139 (18)
Chest Pain	8 (5)	6 (2)	11 (1)	13 (2)
Fatigue	101 (66)	211 (55)	476 (64)	412 (52)
Dizziness	30 (19)	45 (12)	154 (20)	118 (15)
Respiratory, Thoracic, and Mediastinal Disorders	52 (34)	70 (18)	243 (32)	177 (22)
Dyspnoea	37 (24)	49 (13)	165 (22)	130 (16)

The overall the incidence of AEs characteristic of anaemia (fatigue, dizziness and dyspnoea) were reported in similar frequencies. When the AEs are described for subjects with Hgb < 10g/dl compared to ≥ 10 g/dl, subjects with Hgb < 10g/dl experienced more fatigue, dizziness and dyspnoea, regardless of the treatment group.

Management of anaemia

The use of EPO and/or RBV dose reduction was recommended if the Hgb concentration decreased to <10 g/dl; it was recommended that RBV be interrupted or discontinued if the Hgb concentration decreased to <8.5 g/dl.

The anaemia was managed by RBV dose reduction alone in 10% and 7% of PR-treated and BOC/PR-treated subjects, respectively; with erythropoietin use alone in 37% and 33% of subjects, respectively,

and with both RBV dose reduction and erythropoietin use in 32% and 46% of subjects, respectively. in 21% of PR-treated subjects and 14% of BOC/PR-treated subjects with hemoglobin <10 g/dl, neither of these methods were retorted to.

In total EPO was used in 131/547 (24%) patients in PR arms and 667/1548 (43%) in BOC/PR arms.

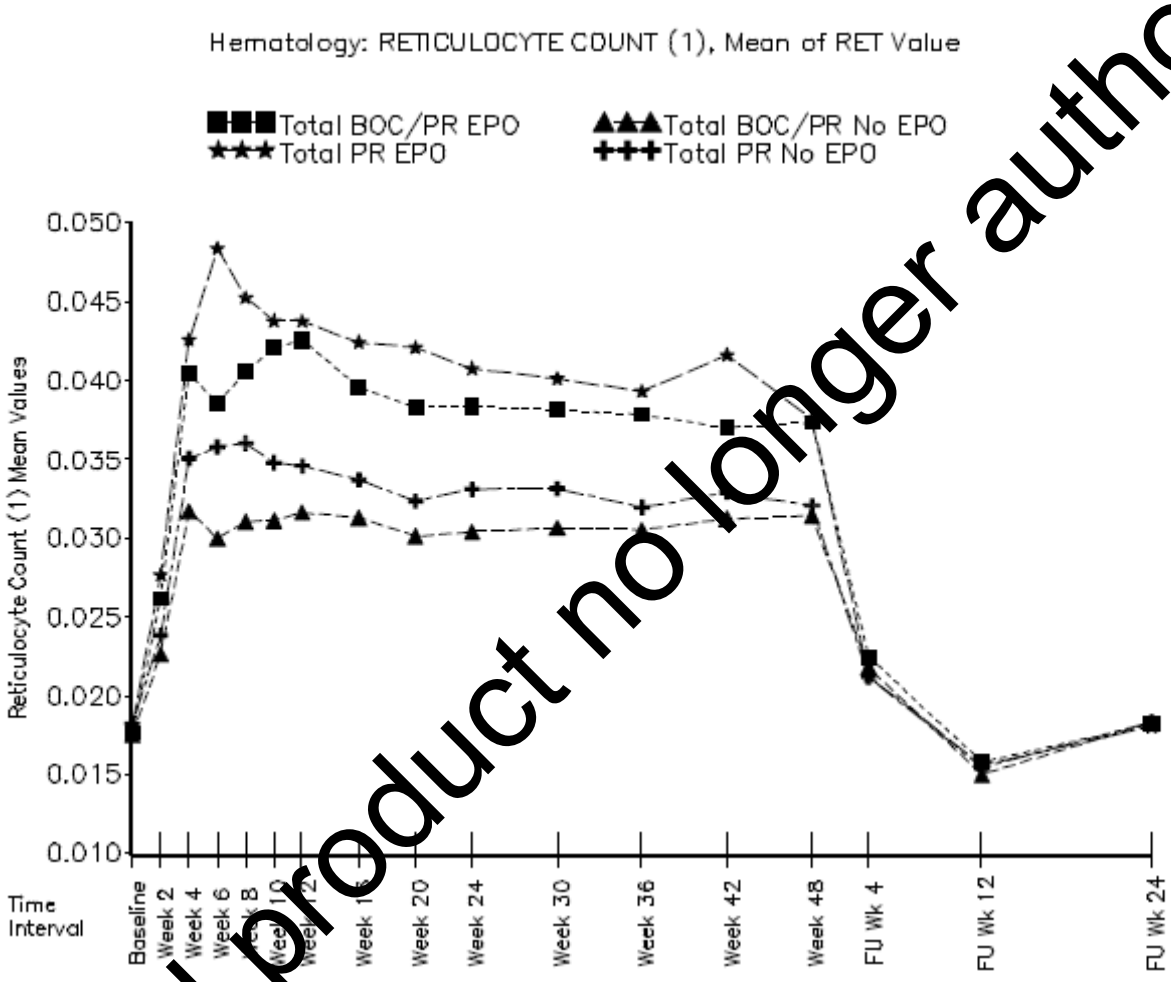
Medically important AEs potentially attributable to the use of erythropoietin, such as cardiovascular events, thrombotic or thromboembolic events were evaluated. These events occurred with similar frequency in subjects who received EPO and those who did not (4% and 6%, respectively).

One case of arterial thrombosis resulting in below-the-knee amputation in a 56-year old black female with stable hypertension was observed in study P05216 arm 3 (BOC/PR48). The investigator assessed the event as possibly related to EPO.

There was one case diagnosed as Pure Red blood Cell Aplasia (PRCA) reported in the follow-up period of Study P05216 in a 56-year old white female with no significant past medical history and normal baseline Hgb, randomized to BOC/PR48. While on long acting EPO in follow up phase her Hgb decreased to 6.6 g/dl. Bone marrow biopsy revealed PRCA considered probably related to EPO use. Also the presence of anti-EPO antibodies was found.

Overall in the 798 patients who used EPO, 1 case of PRCA was observed.

The mean reticulocyte counts for subjects by EPO use (with or without EPO initiation) are shown graphically for the key studies in the figure below.



The total reticulocyte count is lower in BOC arms compared to PR arms regardless of the use of EPO.

Transfusions

Of the 2095 treated subjects in the key studies, 41 (2%) received a transfusion for the management of anaemia; two (<1%) subjects in the pooled PR control arms and 39 (3%) subjects in the BOC/PR arms.

Neutropenia

Neutropenia is a side effect of PEG and was reported by 18% of all subjects PR arm and 23% of subjects in the BOC/PR arms of the key studies. After PR treatment initiation in the key studies, there was a rapid decline and then a plateau in the mean neutrophil counts after 8 weeks to 12 weeks that was maintained to the end of treatment, with counts returning to baseline levels at the end of Follow-up. This is the typical pattern seen with interferon-based therapies. The change from baseline to lowest

postbaseline value was slightly greater in the BOC/PR arms than in the PR control arms; but did not lead to an increase in the overall incidence of infections. Three subjects (all in BOC/PR arms) experienced severe infections that occurred within the 2 weeks surrounding the occurrence of Grades 3 and 4 neutropenia. In addition, two cases of life-threatening neutropenia/decreased neutrophil count were reported, both in subjects treated with BOC/PR.

The use of G-CSF in the BOC/PR arms vs the PR arms was also somewhat higher (9% vs 6%, respectively). G-CSF use was somewhat more common in BOC/PR-treated vs PR-treated treatment-naïve subjects (10% vs 6%) than BOC/PR-treated treatment-failure subjects (7% vs 6% of PR control subjects). The proportion of subjects that met the dose reduction criterion (Grade 3 neutropenia) was higher in the BOC/PR arms than in the PR control arms (22% and 13%); the proportion of subjects that met the discontinuation criterion (Grade 4 neutropenia) was also greater in the BOC/PR arms than in the PR arms (7% vs 4%) see table 33 below.

Table 33.

	Number (%) of Subjects					
	Treatment Naïve P03523/P05216		PEG/R Treatment Failure P05101		All Subjects	
	PR[a] n=467	BOC/PR n=1225	PR n=80	BOC/PR n=323	PR[a] n=547	BOC/PR n=1548
Number of Subjects Included[b]	n=461	n=1215	n=80	n=322	n=541	n=1537
Neutrophil Count (10^9/L)						
0.5 to <0.75[c]	65 (14)	279 (23)	7 (9)	62 (19)	72 (13)	341 (22)
<0.5[d]	19 (4)	94 (8)	3 (4)	21 (7)	22 (4)	115 (7)

Co-administration with alfa 2a vs alfa 2b (historical comparison P05685 vs P05101)

It has to be underlined, that the risk of neutropenia (including grade 4) is markedly increased when boceprevir is combined to alfa 2a. This was associated with a higher risk of infection.

Table 34.

	Study P05685		**Study P05101**	
	PegIFN alfa2a/RBV	**PegIFN alfa 2a/RBV/BOC**	**PegIFN alfa2b/RBV**	**PegIFN alfa2b/RBV/BOC**
	N=67	N=334	N= 80	N= 161
Treatment duration (mean)	105 days	**334 days**	104 days	**336 days**
AE	100%	100%	96%	100%
SAE	10%	13%	5%	14%
Death	0	2 (1%)	0	0
Drug discontinuation	4%	17%	3%	12%
Dose modification	22%	43%	14%	33%
Anaemia as AE	33%	50%	20%	47%
Hb<10g/dl	22%	37%	24%	35%
Hb<8.5g/dl	4%	13%	1%	14%
Use of EPO	30%	47%	21%	46%
Dysgueusia	25%	39%	11%	45%
Neutropenia as AE	18%	**31%**	10%	14%
Neutrophils<750/mm^3	18%	**28%**	9%	20%

Grade 3-4				
Neutrophils<500/mm^3 Grade 4	3%	**14%**	4%	7%
Thrombocytopenia as AE	6%	7%	0%	6%
Platelets <50 x 10^9/L (Grade 3)	7%	10%	0	5%
Platelets <25 x 10^9/L (Grade 4)	0	1%	0	0

Platelet counts

Decreases in platelet counts are known to occur with interferon treatment. Mean platelet counts decreased from baseline during treatment, reaching a plateau from TW 12 to TW 48 and returning to near baseline levels by FW 24. More subjects in the BOC/PR arms (3%) met the platelet count dose-reduction criterion (Grade 3 thrombocytopenia) than did subjects in the PR control arms (1%); three

treatment-naïve subjects in the BOC/PR arms (3/1536 [<1%]) met the discontinuation criterion, compared with 0% of subjects in the PR control arms (see table below). Subjects with lower baseline platelet counts were more likely to meet the criteria for dose modification or study drug discontinuation.

Table 35. Distribution of Platelet Counts During the Treatment Phase,

	Number (%) of Subjects					
	Treatment-naive P03523/P05216		PEG/R Treatment Failure P05101		All Subjects	
	PR[a] n=467	BOC/PR n=1229	PR n=80	BOC/PR n=323	PR[a] n=547	BOC/PR n=1548
Number of Subjects Included[b]	n=458	n=1214	n=80	n=322	n=538	n=1536
Platelet Count (10^9/L)						
25 to <50[c]	5 (1)	35 (3)	0	12 (4)	5 (1)	47 (3)
<25[d]	0	3 (<1)	0	0	0	3 (<1)

Safety in special populations

Fertility, pregnancy and lactation

There were no pregnant women exposed to boceprevir during clinical trial.

Inhibin B was tested as a surrogate for Sertoli cell function in the testes and was evaluated in 571 male subjects. In addition, semen analysis was conducted in 19 males. These results showed no evidence of altered testicular function.

Boceprevir showed no antagonistic activity on the human estrogen receptor α or on the human androgen receptor.

Safety in subjects with advanced fibrosis and cirrhosis

A total of 143 subjects with cirrhosis participated in the key safety studies (112 in the BOC/PR treatment rams and 31 in the PR control arm). The median treatment duration in cirrhotic subjects was 175 days in the PR control arms and 239 days in the BOC/PR arms of the key studies, compared to 198 days and 201 days, respectively, in the overall study population.

The main results are presented in the table 36 below:

Table 36. Overview of Adverse Events, Deaths, and Study Drug Discontinuations and Dose Modifications Due to EAs in the Key Studies, by Presence of Cirrhosis

Protocol Nos. P03523, P05216, and P05101

	Number (%) of Subjects					
	Treatment Naïve P03523/P05216		PEG/R Treatment Failure P05101		All Subjects	
	PR[a]	BOC/PR	PR	BOC/PR	PR[a]	BOC/PR
Median Treatment Duration (Days)	216	197	104	253	198	201
Cirrhosis	**n=21**	**n=73**	**n=10**	**n=39**	**n=31**	**n=112**
Treatment-Emergent AE	21 (100)	73 (100)	10 (100)	39 (100)	31 (100)	112 (100)
Treatment-Related, Treatment-Emergent AE	21 (100)	73 (100)	10 (100)	38 (97)	31 (100)	111 (99)
Serious AE	3 (14)	11 (15)	0	7 (18)	3 (10)	18 (16)
Death	0	0	0	0	0	0
Life-Threatening Treatment-Related AE	1 (5)	0	0	2 (5)	1 (3)	2 (2)
Study Drug Discontinuation Due to AE	2 (10)	10 (14)	1 (10)	6 (15)	3 (10)	16 (14)
Dose Modification Due to AE[b]	10 (48)	31 (42)	3 (30)	13 (33)	13 (42)	44 (39)
No Cirrhosis	**n=435**	**n=1126**	**n=66**	**n=260**	**n=501**	**n=1386**
Treatment-Emergent AE	429 (99)	1118 (99)	63 (95)	258 (99)	492 (98)	1376 (99)
Treatment-Related, Treatment-Emergent AE	426 (98)	1113 (99)	63 (95)	258 (99)	489 (98)	1371 (99)
Serious AE	36 (8)	110 (10)	4 (6)	30 (12)	40 (8)	140 (10)
Death[c]	4 (1)	3 (<1)	0	1 (<1)	4 (1)	4 (<1)
Life-Threatening Treatment-Related AE	6 (1)	13 (1)	0	5 (2)	6 (1)	18 (1)
Study Drug Discontinuation Due to AE	62 (14)	159 (14)	1 (2)	25 (10)	63 (13)	184 (13)
Dose Modification Due to AE[b]	107 (25)	461 (41)	6 (9)	83 (32)	113 (23)	544 (39)

AEs=adverse events; BOC=boceprevir 800 mg PO TID; P=peginterferon alfa-2b; PEG=peginterferon alfa; PO=orally; PR=peginterferon alfa-2b+ribavirin; R=ribavirin; TID=three times daily.

a: Excludes events for 36 subjects in Study P03523 after they crossed over from Arm 1 (PR) to BOC/PR (see the P03523 CSR for events in these subjects).

b: Excludes subjects who discontinued due to adverse events.

c: Deaths are included in serious AE count.

In the key studies, the safety profile of boceprevir has been evaluated in only 73 naïve patients and 39 pre-treated patients. No death has been reported in cirrhotic subjects. In boceprevir-containing arms, more patients with cirrhosis experienced serious adverse reactions and AE leading to treatment discontinuation. The safety profile of boceprevir appears to be globally similar in these patients compared with patients without cirrhosis. Similar results are retrieved for patients with advanced liver fibrosis (score F3/F4). The number of patients with cirrhosis and advanced liver fibrosis is limited.

Safety in HCV/HIV co-infected subjects

The safety of boceprevir is currently being investigated in a Phase 2 study. Study P05411 is a double-blind, placebo-controlled aimed at evaluating the efficacy and the safety of boceprevir in combination with standard of care in treatment-naïve co-infected patients with HIV and HCV genotype 1. Patients received Boceprevir or placebo + pegylated interferon alfa2b and ribavirin 600 to 1400 mg/day during 48 weeks.

The study is currently ongoing. A three month safety update is available from this study with the cut off date of 01 December 2010. Data remain blinded at the time this summary.

The cumulative data from this study up to 01 December 2010 are summarized below:

As of 1 December 2010, 93 subjects had been enrolled and had received at least one dose of PR and 88 subjects had reached TW 4 and received at least one dose of boceprevir or placebo. Median treatment duration was 141 days.

As of the safety update report, the treatment phase was ongoing for 75 (81%) of the 93 treated subjects and the follow-up phase was ongoing for 13 of the 16 subjects who had entered follow-up 18 (19% had discontinued treatment and 8 (9%) discontinued treatment due to AEs.

No deaths were reported during this study as the cut off date of 01 December 2010. 10 subjects (11%) experienced SAEs including two subjects who had a SAE of anaemia.

The other SAEs concerned gastrointestinal disorders, fatigue and influenza like illness, 1 neurotoxicity and 1 agitation. There was also a SAE of ventricular fibrillation.

Regarding anaemia, the protocol provided guideline for the use of EPO. However, the decision whether to use EPO or reduce the ribavirin dose was made at the discretion of the investigator.

As of 01 December 2010, 23% (21/93) of the subjects had initiated erythropoietin use and 4 of the 93 treated subjects (4%) required a transfusion.

Hematologic laboratory values during the treatment phase are summarized in the table 37 below:

Table 37. Lowest Hematologic Laboratory Values during the Treatment Pase, by Modified WHO Category.

Protocol No. P05411

	WHO Grade	Number (%) of Subjects			
		SUR Period[a] n=93		Cumulative Period n=93	
Hemoglobin (g/dL)					
Number of Subjects[b]		92		92	
9.5 - <11.0	1	28	(30)	29	(32)
8.0 - <9.5	2	14	(15)	15	(16)
6.5 - <8.0	3	2	(2)	2	(2)
8.5 - <10[c]	N/A	23	(25)	23	(25)
<8.5[d]	N/A	4	(4)	5	(5)
Neutrophils (10^9/L)					
Number of Subjects[b]		92		92	
1.0 - 1.5	1	26	(28)	28	(30)
0.75 - <1.0	2	24	(26)	28	(30)
0.5 - <0.75[c]	3	10	(11)	10	(11)
<0.5[d]	4	3	(3)	3	(3)
Platelets (10^9/L)					
Number of Subjects[b]		92		92	
70 - 100	1	16	(17)	17	(18)
50 - <70	2	2	(2)	2	(2)
25 - <50	3	4	(4)	4	(4)
WBC (10^9/L)					
Number of Subjects[b]		92		92	
2.0 - 2.9	1	37	(40)	39	(42)
1.5 - <2.0	2	16	(17)	17	(18)
1.0 - <1.5[c]	3	3	(3)	3	(3)
<1.0[d]	4	2	(2)	2	(2)

Note: The table summarizes the worst category observed within the period per subject per laboratory test (ie, the lowest value for the hematologic parameters). Values represent central laboratory results.

SUR=safety update report; WBC=white blood cells; WHO=World Health Organization.

[a] SUR column includes subjects with worsening grade when compared to Original Application cutoff data and includes new subjects.

[b] Only subjects with at least one treatment value for a given laboratory test are included.

[c] Criterion for dose reduction.

[d] Criterion for discontinuation or interruption of treatment.

Overall, as of the cut off date of 01 December 2010, 30% of patients experienced decrease Hb < 10g/dl including 5% who experienced Grade 4 decreased Hb< 8.5g/dl (that correspond with criteria for discontinuation or interruption of treatment). There were also 14% of patients who experienced decrease neutrophils < 750/mm^3 including 3% who had Grade 4 decreased neutrophils < 500/mm^3.

There were no grade 4 decreased platelets during the study. However, 4% of patients experienced decreased platelets < 50 x 10^9/L.

Safety in patients in hepatically and renally impaired subjects (studies P03747 and P05579)

The safety of boceprevir was evaluated in 18 hepatic-impaired subjects matched to healthy control subjects. Subjects received a single 400mg dose of boceprevir. In this study (P03747), on (4%) subject, in the severe impairment group, reported one AE of vomiting during the study which was mild in intensity and possibly related to treatment. There were no death, no SAE and no subject who discontinued because of an AE.

The safety of boceprevir was also evaluated in renally-impaired subjects (6 healthy subjects and 8 subjects with end stage renal disease (ESRD). In this study, healthy subjects received one 800mg single dose of boceprevir. Renally impaired subjects received a second 800mg single dose to determine the effect of dialysis.

A total of 2 subjects (14%) (both in the ESRD group) reported 3 AEs (ventricular extrasystoles and flatulence in one subject and catether thrombosis in another subject) of moderate severity and which were considered unlikely related to treatment. There were no death, no SAE and no subject who discontinued because of an AE.

Safety related to drug-drug interactions and other interactions

A total of five clinical drug-interactions studies in healthy subjects were conducted in the boceprevir clinical pharmacology program. Boceprevir interactions with the AKR inhibitors ibuprofen and diflunisal; the CYP 3A4/5 inhibitors clarithromycin, ketoconazole, and ritonavir; the CYP3A4/5 inducer efavirenz, the CYP3A4/5 substrate midazolam, the nucleotide reverse transcriptase inhibitor tenofovir and an oral contraceptive have been studied.

Overall, no important safety concern was raised from these drug-drug interactions studies.

In the key studies, the following CYP3A4/5 substrates, inhibitors and inducers were also examined as concomitant medications:

- Substrates: HMG- CoA reductase inhibitors, phosphodiesterase-5 inhibitors, benzodiazepines, calcium channel blockers, methadone, oral contraceptives
- Substrate/Inhibitor: macrolides antibiotics
- Inhibitor: azole antifungals
- Inducer: St John's Wort
- Substrate/Inducer; Pioglitazone, Steroïd

- Other: Antidepressants

In general, subjects using these drugs (statins, calcium channel blockers, macrolides antibiotics, oral contraceptives and methadone) in the BOC/PR or in the PR-treatment arms had a similar safety profile than those that did not use them. There were no clinically relevant adverse events reported with significant different frequency in both treatment groups. However, the number of subjects using these drugs concomitantly was limited.

Discontinuation due to adverse events

Discontinuation due to AEs

Overall, there was no difference between the PR control (12%) and BOC/PR (13%) arms in percentage of subjects that experienced AEs that resulted in study discontinuation. In the study in pretreated patients (P05101), there were fewer discontinuations due to AEs in the PR control arm (3%) compared to the BOC/PR arms (10%); while in the studies in naive patients this was comparable 14% for control as well as experimental arms. Events resulting in discontinuation were anaemia, asthenia, fatigue, nausea, depression, and suicidal ideation.

Although overall discontinuation is comparable between control and experimental treatment, when incidence is corrected for exposure the incidence of anaemia and neutropenia leading to discontinuation appear to be higher in the experimental arms compared to control. The lower exposure rate in the PR arms is due to the higher treatment failures (futility rule).

The incidence of discontinuation due to AEs adjusted for exposure is presented the following table.

Table 38.

	PR N=547		BOC/PR N=1548	
	%	rate	%	rate
Anaemia	1	1.2	1	2.4
Neutropenia	0	0.0	<1	1.1

Rate is the incidence rate per 100 person years.

Dose modification

AEs led to dose modifications in 39% of subjects in the BOC/PR arms and in 24% of subjects in the PR control arms of the key studies. Dose modification of only boceprevir or placebo (not for PEG2b and RBV) occurred in 1% of subjects.

The proportion of subjects with PEG2b dose modifications was similar in the PR arms and BOC/PR arms; however, the boceprevir-containing arms had a greater proportion of subjects with RBV dose reduction (29%) than did the PR control arm (16%). In subjects with anaemia (Hgb <10 g/dl), the anaemia was managed by RBV dose reduction alone in 10% and 7% of PR-treated and BOC/PR-treated subjects, respectively; with EPO use alone in 37% and 33% of subjects, respectively, and with both RBV dose reduction and EPO use in 32% and 46% of subjects, respectively. None of these methods was used for the management of Hgb <10 g/dl in 21% of PR-treated subjects and 14% of BOC/PR-treated subjects.

Main AEs leading to dose modification were anaemia (24% versus 12% for experimental versus control), neutropenia (12% versus 7% for experimental versus control).

The incidence of dose modification due to AEs adjusted for exposure is presented the following table.

Table 39.

	PR N=547		BOC/PR N=1548	
	%	rate	%	rate
Anaemia	12	18.6	24	37.7
Neutropenia	7	11.9	12	19.0

Rate is the incidence rate per 100 person years.

The other studies did not reveal other additional information.

Post marketing experience

No post-marketing data are available.

2.4.1 Discussion on clinical safety

Globally, the addition of boceprevir to standard of care/peginterferon plus RBV led to an increase in the rate of serious adverse events and the rate of adverse events leading to study drug discontinuation or dose modification compared with the control arm. The difference was more marked in pre-treated patients than in naïve patients.

The most frequently reported adverse reactions in boceprevir treatment arms were comparable to those reported in the control arm: flu-like syndrome (fatigue, chills, headache), hematologic disorders and (anaemia) and gastrointestinal disorders. However, compared with the control arm, the addition of boceprevir increased significantly the risk of developing anaemia, neutropenia and gastrointestinal disorders such as diarrhoea, nausea but also in a higher extent dysgueusia.

There was by contrast no apparent increase of the risk of having other IFN –related adverse reactions, such as psychiatric disorders, cardiovascular disorders or endocrine disorders.

The most significant aspect of the safety profile of the drug is the high rate of anaemia and dysgueusia that occurred in 49% and 37% of boceprevir-treated subjects respectively.

Regarding dysgueusia, this event generally did not lead to study drug discontinuation (only in 2 patients in the clinical development program) and few events were judged serious by the investigator.

More problematic is the occurrence of anaemia since decrease in Hb < 10 g/dl was reported twice as often in boceprevir-treated subject compared with placebo-treated subjects (49% versus 29% respectively). In summary, the addition of boceprevir to SOC was reflected by an additional decrease of Hb of approximately 1 g/dl versus -2.5 to 3.5 g/dl with peginterferon and ribavirin only. Consequently, the proportion of subjects who required dose reduction of antiviral therapy and/or the use of erythropoietin was much higher in boceprevir treatment arms, whatever the studied population (naïve or pre-treated). More boceprevir-treated patients also required transfusion.

The mechanism of boceprevir-induced anaemia, has not been elucidated.

The benefit /risk ratio of EPO in the management of HCV therapy-induced anaemia requires further substantiation even though a scientific rational is admitted to support its use in this context. Globally, as part of the assessment of the MAA of boceprevir, it is important to ensure that the need of using EPO due to anaemia in more of 40% of boceprevir-treated subjects does not induce additional safety concerns.

Regarding this issue, the MAH has explored the safety data in patients who received EPO in the clinical development program. In terms of safety, there was no apparent increased risk of developing adverse events commonly associated with erythropoietin in EPO users versus non EPO users in the Boceprevir development program. A slight increase of thrombo-embolic events is however observed in boceprevir –treated subjects who receive EPO (1.2%) versus those who did not receive EPO (0.7%). This slight increase is mainly driven by a slight higher percentage of deep vein thrombosis (0.6% vs 0.2%) and pulmonary embolism (0.3% vs 0.1%). Globally, these differences were not unexpected due to the known safety profile of EPO.

More problematic is the occurrence of one serious of Pure Red Cell Anaemia (PRCA) with anti-EPO antibodies in the boceprevir clinical development program (with an incidence of 1.5 per 1000 patients). Reassuringly, the patient fully recovered and was no longer transfusion dependant. The occurrence of PRCA cannot be attributed to boceprevir only, rather to tritherapy and use of EPO. It is likely that the immunomodulatory effect of IFN and the impact of the underlying disease itself may increase the risk of developing PRCA in patients co-receiving EPO.

Overall, it is difficult to ascertain based on the available data whether anaemia can be adequately managed with only RBV dose reduction without impacting on the efficacy results of the tritherapy. In some situations where the anaemia is not very pronounced it may be easily manageable with low ribavirin dose reduction. However, if high dose reduction of RBV is required for severe Hb level decrease, one can not exclude an impact on efficacy and other measures may be considered in practice in order to maintain RBV concentrations and achieve better response rates.

The addition of boceprevir to standard of care was also associated to an increased risk of developing neutropenia and Grade 3/4 neutropenia and, in a lesser extent, to an increased risk of developing thrombocytopenia.

Due to the potential increased risk of Grade 3/4 neutropenia-related infections, it is important that physicians are alerted on this concern and the need of monitoring this potential adverse reaction by a warning in section 4.4 of Victrelis SmPC. The risk of neutropenia was identified as being further increased when boceprevir was combined with pegylated interferon alfa 2a as compared to alfa 2b.

Four cases of thyroid neoplasm were reported in the key studies, all of which represented thyroid nodules based on the literal terms provided by the investigators. Two cases occurred in BOC/PR-treated patients. Taking together the pre-clinical findings which cannot exclude an effect on the thyroid hormone levels and the thyroid gland, the 2 cases in clinical studies where the contribution of boceprevir could not be excluded and was assessed as 'probable' thyroid neoplasm is included in the boceprevir SmPC as are the reported AEs goitre, hypo- and hyperthyroidisms.

Safety with Response Guided Therapy in the key studies P05216 and P05101

Two of the key safety studies included a response –guided therapy (RGT) arm in which subjects were assigned to either a 28- or a 48-week treatment duration (study P05216 in treatment-naïve subjects) or a 36- or 48-week treatment duration (study P05101 in previous PEG/R treatment failures) based upon their on-treatment virologic response at week 8.

This offers the opportunity to shorten the treatment duration for a proportion of patients achieving undetectable HCV-RNA at week 8 (early virologic responders).

The benefit of the RGT in terms of reduction of adverse events is not striking although it may offer the advantage to reduce the occurrence of such late-occurring events in patient who had undetectable HCV RNA at week 8.

In terms of laboratory findings, excluding hematology disorders, the MAH has presented an analysis of liver function tests across studies that did not reveal safety concern. An analysis of other blood chemistry values revealed that the addition of boceprevir to peginterferon/ribavirin is associated with higher incidences of increase in uric acid, triglycerides and cholesterol total. A slight higher rate of gout was observed in boceprevir-treated subjects. Although the clinical impact of these findings was probably low due to the limited treatment duration. The boceprevir SmPC reflects these findings.

Regarding the impact on QT/QTc prolongation, the assessment of the thorough QT/QTc study performed according to ICH E14 guideline was overall reassuring with negative results, however there was some dose dependent trend toward a prolongation of the QT interval. In addition, there was some concerns raised in relation to the preclinical studies regarding this issue. As such a thorough review for any signal of potential proarrhythmic effect of boceprevir has been made. No patient in either treatment group experienced torsades de pointes, QT prolongation, a ventricular arrhythmia, or sudden death. Overall although it can be concurred with the MAH that the clinical data are reassuring so far, it remains that boceprevir has a proarrhytmic potential based on electrophysiological findings and the trend observed toward a prolongation of the QT interval in the dedicated ICHE14 study.

The cardiac safety profile will continue to be assessed when boceprevir will be prescribed in normal condition of use.

2.4.2 Conclusions on the clinical safety

Globally, the addition of boceprevir to peginterferon plus RBV/standard of care led to a slight increase in the rate of serious adverse events and the rate of adverse events leading to study drug discontinuation or dose modification compared with the control arm. The difference was more marked in pre-treated patients than in naïve patients.

However the main safety concern associated with the use of boceprevir is the marked increase of anaemia as compared to the already significant rate of anaemia with the SOC. Although the available data provide some degree of reassurance, the clinical dossier so far does not allow to fully appreciate to what extent the management of the substantial incremental anaemia induced by boceprevir on top of PR could per se negatively affect the benefit-risk balance of boceprevir, having in mind that on the one hand ribavirin dose reduction could potentially alter the benefit and on the other hand the EPO use, through its safety profile (associated with risk of PRCA and thrombosis events), could alter the risk. Additional investigations are being undertaken in this context.

2.5. Risk management plan

The safety specifications, pharmacovigilance plans, and risk minimisation activities of combination therapy of boceprevir, when used in the context of approved tritherapy with pegintron and ribavirin, have been addressed within the current Risk Management Plan for boceprevir and there are no new safety concerns within the context of this extension of indication of Pegintron/Rebetol to reflect the tritherapy. The MAH will fully reflect the tritherapy indication in the RMPs of PegIntron/ViraferonPeg and Rebetol at the time of the next regular PSUR submission.

User testing

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable. The CHMP noted that recommendations from the recent readability testing conducted by MAH and approved by the CHMP for both PegIntron/ViraferonPeg and Rebetol (PegIntron/ViraferonPeg, submitted within EMEA/H/C/280-329/II/95-94, CHMP opinion adopted 23 SEP 2010; and Rebetol PRC/FUM059, CHMP conclusions adopted 08 NOV 2010) have been applied to Patient Information Leaflets wording, therefore preserving the current approved level of readability.

2.6 Benefit-Risk Balance

Benefits

- Beneficial effects

The results of both phase III studies show a significant improvement of SVR over standard of care (PEG/RBV), of around 30% in treatment naïve patients (P05216/SPRINT 2) and 40% in treatment experienced patients (P05101/RESPOND 2).

In addition, treatment naïve early responders could benefit from a significant reduction of the total treatment duration (28 weeks as compared to 48 weeks with the current bitherapy). When considering the burden of treatment, this benefit is worthy of being taken into consideration.

Given that SVR is correlated with cure, the addition of boceprevir to the current SOC will significantly increase the individual likelihood of being cured, avoiding progression to cirrhosis and hepatocellular carcinoma.

- Uncertainty in the knowledge about the beneficial effects.

Recently the importance of patient genotype IL28B as a strong predictor of SVR in HCV genotype 1 infected patients became known. This was after the start of the phase III studies. Thus patients were not stratified for this baseline characteristic. This information was only available for approximately 60% of treatment naïve and pretreated patients (patients who gave their informed consent).

Although overall addition of SOC to PR resulted in significant higher SVR rates, pharmacogenomic analysis in which SVR rates were evaluated according to patients IL28B genotype, indicate that treatment naïve patients with genotype IL28B CC might not substantially benefit from additional boceprevir to PR, contrary to patients with IL28B genotype CT or TT.

Taking into account the particular burden of anaemia, measures have been put in place within the boceprevir marketing authorisation to address the CHMP concerns (See Victrelis EPAR).

As a shortened duration of therapy might not be considered appropriate if this results in a net loss of efficacy, shortened treatment duration has not been found approvable for treatment experienced early responders.

The treatment experienced population in the phase III study, excluded the challenging population of Null Responders qualified as such based on their prior response to pegylated IFN and interferon at week 12. Based on a retrospective analysis performed with requalifying on the basis of their on treatment virologic response at treatment week 4 (using the peginterferon alfa/ribavirin lead in period) as compared to baseline, it was admitted that null responders might gain some benefit in adding Victrelis to the bitherapy. However, this cannot be reliably quantified from the retrospective analysis.

Moreover, the optimal management of null responders remains to be established and might in the future require antiviral combination.

The proportion of patients with cirrhosis is limited, with only 100/1097 (9%) in the phase III in naïve patients and 49/403 (12%) in the phase III in treatment experienced patients.

Risks

- Unfavourable effects

The main safety concern with boceprevir is the increase in the risk of anaemia as compared to bitherapy Forty-nine percent of boceprevir-treated patients experienced anaemia < 10 g/dl during treatment versus 29% in placebo-treated subjects.

- Uncertainty in the benefits of the product

One of the main areas of uncertainty is to what extent anaemia associated with the use of boceprevir in combination with standard or care can be managed without EPO, taking into account the need for sufficient ribavirin exposure, and also taking into account that the use of EPO raises safety concerns (risk of PRCA notably) and could impact the benefit risk balance.

Overall even though the data at the time of opinion provide sufficient reassurance, the clinical dossier so far does not allow to fully appreciate to what extent the management of the substantial incremental anaemia induced by boceprevir on top of PR could per se negatively affect the benefit-risk balance of boceprevir, taking into account that ribavirin dose reduction could potentially alter the benefit and on the other hand the EPO could alter the risk.

As such measures have been put in place for the MAH of boceprevir to address these concerns.

The clinical consequence of resistance to boceprevir (in terms of response to boceprevir and impact to subsequent lines of therapies) is unknown.

Electrophysiological data carries some concerns as regards the cardiotoxicity of the drug in real life (co-administration, electrophysiological disturbances). Attention of physicians is warranted by a specific statement in the SmPC and this issue will be monitored in pharmacovigilance.

Benefit-risk balance

- Benefit-risk balance

Boceprevir has been shown to significantly increase the percentage of treatment naïve and treatment experienced patients chronically infected by HCV genotype 1 achieving Sustained Virologic Response (correlated with cure) and will reduce the treatment duration for some patients.

Considering the limited response rate achieved so far with the Peg-IFN+ ribavirin in patients chronically infected with HCV genotype 1 and given the burden of such a treatment, this represents a significant therapeutic advance.

This benefit is regarded as overweighing the safety issues associated with this drug, even though the incremental anaemia and perhaps also neutropenia is anticipated as being a particular burden in clinical practice.

For patients with the favourable CC genotype further substantiation of the added benefit of boceprevir to peginterferon alfa and ribavirin is warranted, it is however noted that a higher proportion of patients treated with tritherapy will benefit form a shorter treatment duration as compared to treatment with bitherapy alone

2.7 Changes to the Product Information

The following sections of the SmPC for PegIntron/ViraferonPeg and Rebetol cross reference the boceprevir SmPC, as it is expected that physicians will use the boceprevir SmPC for the use of tritherapy:

- **4.1 Therapeutic indications**
- **4.2 Posology and method of administration**
- **4.3 Contraindications**
- **4.8 Undesirable effects**
- **5.1 Pharmacodynamic properties**

3. Overall conclusion and impact on the benefit/risk balance

The CHMP considers that the benefit-risk balance of the present extension of indication, to add the tritherapy in combination with boceprevir for adult patients with hepatitis C virus genotype 1 infection for PegIntron/ViraferonPeg and Rebetol is positive. Of note data in support of this indication has already been assessed and concluded upon by the CHMP at the time of approval of boceprevir. The CHMP agrees with the changes to the product information proposed by the MAH.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication to reflect the triple combination use of peginterferon alfa 2b, ribavirin and boceprevir in the treatment of Hepatitis C. In the labelling of Rebetol the use of "Lot" and "Exp" has been aligned in all languages.

The requested worksharing procedure proposed amendments to the update of Summary of Product Characteristics, Labelling and Package Leaflet.