EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Assessment report

Victrelis

boceprevir

Procedure No.: EMEA/H/C/002332/

Note

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

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SCIENCE MEDICINES HEALTH

26 May 2011
EMA/CHMP/314280/2011

Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

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International Nonproprietary Name: boceprevir

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Product information

Name of the medicinal product:	Victrelis
Applicant:	Merck Sharp & Dohme Ltd Hertford Road, Hoddesdon Hertfordshire EN11 9BU United Kingdom
Active substance:	boceprevir
International Nonproprietary Name/Common Name:	boceprevir
Pharmaco-therapeutic group (ATC Code):	Protease inhibitors (J05AE)
Therapeutic indication(s):	Victrelis is indicated for the treatment of chronic hepatitis C (HCV) genotype 1 infection, in combination with peginterferon alpha and ribavirin, in adult patients with compensated liver disease who are previously untreated or who have failed previous therapy
Pharmaceutical form(s):	Capsule, hard
Strength(s):	200 mg
Route(s) of administration:	Oral use
Packaging:	blister (PVC/alu)
Package size(s):	336 (4 packs of 84)

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List of abbreviations

AE	adverse event
ALT	alanine transaminase
ANC	absolute neutrophil count
aPTT	Activated Partial Thromboplastin Time
AUC	area under the concentration-time curve
BMI	body mass index
BND	benzphetamine N-demethylase
CHC	chronic hepatitis C
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL/F	apparent clearance
C_{max}	maximum drug concentration
CSR	clinical study report
CV	coefficient of variation
CYP	cytochrome P450
DMC	data monitoring committee
DNA	deoxyribonucleic acid
ECOD	7-ethoxycoumarin O-deethylase
ELISA	enzyme linked immunosorbent assay
EROD	7-ethoxyresorufin O-deethylase
ESRD	end-stage renal disease
ETR	end of treatment response
EU	European Union
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IFN	interferon
IFNα	interferon alfa
ITT	intention-to-treat
IU	international units
IV	intravenous(ly)
LOD	limit of detection
MedDRA	Medical Dictionary for Regulatory Activities
PCR	polymerase chain reaction
PD	Pharmacodynamics
PEG-IFN	pegylated interferon
PEG-IFNα2a	peginterferon alfa-2a
PEG-IFNα2b	peginterferon alfa-2b
PK	pharmacokinetics
PT	Prothrombin Time
PROD	7-pentoxyresorufin O-dealkylase
RBV	ribavirin
RNA	ribonucleic acid
SAE	serious adverse event
SC	subcutaneous(ly)
SOC	Peg+Ribavirin = Bitherapy
SVR	sustained virologic response
$t_{1/2,a}$	absorption half-life
$t_{1/2,z}$	elimination half-life
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States of America

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Merck Sharp & Dohme Ltd. submitted on 23 November 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Victrelis, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 27 April 2010.

The applicant applied for the following indication treatment of chronic hepatitis C (HCV).

The legal basis for this application refers to:

A - Centralised / Article 8(3) / New active substance.

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/88/2011 for the following condition:

- *Treatment of chronic hepatitis C*

on the agreement of a paediatric investigation plan (PIP)

At the time of the submission of the application the PIP was not yet completed as some measures were deferred.

Scientific Advice:

The applicant received Scientific Advice from the CHMP on 20 May 2010. The Scientific Advice pertained to insert non-clinical and clinical aspects of the dossier.

Licensing status

Boceprevir is approved in the United States.
The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Philippe Lechat** Co-Rapporteur: **Barbara van Zwieten-Boot**

- The application was received by the EMA on 23 November 2010.
- Accelerated Assessment procedure was agreed-upon by CHMP on 18 November 2010.
- The procedure started on 15 December 2010.

- The Rapporteur's first Assessment Report was circulated to all CHMP members on 9 March 2011. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 7 March 2011. In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on 14 April 2011 the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 15 April 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 April 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 5 May 2011.
- During the meeting on 16-19 May 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Victrelis on 19 May 2011. The applicant provided the letter of undertaking on the specific obligations and follow-up measures to be fulfilled post-authorisation on 19 May 2011.

2. Scientific discussion

2.1. Introduction

2.2. Quality aspects

2.2.1. Introduction

Victrelis is presented in the form of hard capsule for immediate release, and contains 200 mg of boceprevir as active substance.

Other ingredients are:

Capsule content: sodium lauryl sulfate, microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, pre-gelatinized starch, magnesium stearate

Capsule shell : gelatin, titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172)

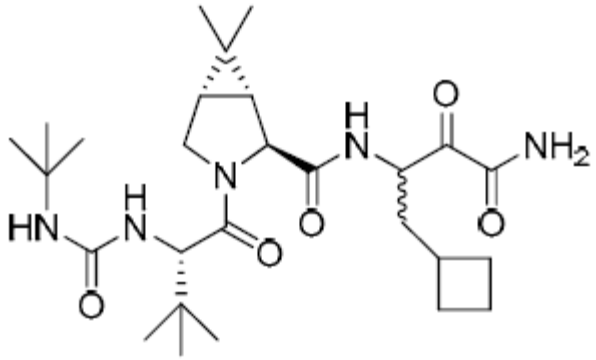
Red printing ink containing: shellac, red iron oxide (E172)

The capsules are packaged into unit dose blister cells thermoformed from clear Aclar/PVC film and sealed with a peelable paper faced foil lidding.

2.2.2. Active Substance

Boceprevir is a white to off-white, poorly wettable powder, which is hygroscopic, poorly soluble in water and a non ionisable therefore its solubility is not pH dependant. In addition, Boceprevir is obtained as an amorphous substance.

The structure of Boceprevir is presented hereafter:



Boceprevir contains 5 chiral centres, four of them have a fixed stereochemical configuration controlled during the synthesis and the last one is obtained as a mixture of 2 configurations R and S. Thus, Boceprevir is manufactured as an equal mixture of two diastereoisomers in an approximate amount of 1:1.

Manufacture

The commercial process is carried out using a three-step synthesis starting from three key starting materials.

Adequate In-Process Controls are applied during the manufacture of the active substance. The specifications and control methods for intermediate products, starting materials and reagents, have been presented and are satisfactory.

Specification

The active substance specification at release includes test for description, identification (HPLC, IR), XRD, specific surface area (Ph. Eur.), sulphated ash, heavy metals (Ph. Eur.), moisture content, assay (HPLC), diastereomer content (HPLC), related compounds (HPLC), residuals solvents (GC) and acetic acid (GC).

The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance.

Batch analysis data for a large number of batches of active substance (n=44) are provided. The results are within the specifications and demonstarte the consistency of production.

Stability

Stability studies were performed on the 3 primary batches manufactured under the intended commercial process for up to 18 months refrigerated condition (5°C ± 3°C) and up to 6 months at 25°C/ 60% RH. One supportive phase III stability batch data was completed up to 18 months at 5°C ± 3°C, 12 months at 25°C/ 60% RH, 6 months at 30°C/ 75% RH and over 3 months at 40°C/75% RH. The parameters followed during the stability testing were description, assay, diastereoisomer content, related compounds, dimers content, moisture content, XRD, specific surface area and hydrate (diol) content.

Forced conditions stability studies (heat, humidity, acid, base and oxidative conditions) were performed to study degradation pathways of the active substance) along with photostability testing. The stability data provided support a 24-month retest period and the storage conditions: "store at refrigeration (2°C to 8°C), protect from light and moisture".

2.2.3. Finished Medicinal Product

Pharmaceutical Development

A wet granulation capsule formulation in a size 0 capsule shell was developed to meet drug loading requirements. During the development the relevant physicochemical and biological properties of the drug substance that could influence the performance of the drug product and its manufacturability was studied.

The formulation and manufacturing process development followed a systematic and risk-based approach in order to establish linkages between inputs (raw materials, process parameters), intermediate attributes, and critical quality attributes (CQAs). Principles of Quality by Design have been applied to some extent and science-based risk management processes have been used to facilitate risk reduction. Extensive development studies have been carried out in order to acquire better understanding of the manufacturing process and to define appropriate control strategy to produce a consistent quality product.

The Phase II/Phase III clinical formulation and the intended commercial formulation have identical capsule fill blends and differ only in the colour of the capsule shell. A comparison between dissolution profile and stability of the Phase III capsules and the intended commercial capsules was performed. The excipients used are lactose monohydrate, microcrystalline cellulose, sodium laury sulphate, purified water, pregelatinised starch and magnesium stearate. They are all of Ph. Eur. quality and controlled according to their respective monographs.

The components of capsule shell and the ink, though not developed in this section, are of Ph. Eur. quality or in compliance with relevant EU Directives.

Victrelis is packaged into unit dose blister cells thermoformed from clear Aclar/PVC film and sealed with a peelable paper faced foil lidding. A peelable blister format was selected to avoid capsule breakage that occurs with push through blisters. Efficiency of the packing has been demonstrated in stability studies. The capsules have been shown stable when blisters have been exposed to an ICH photostability without secondary packaging.

Adventitious agents

Magnesium stearate is of vegetable origin.

Gelatin of hard gelatin capsules is of bovine origin and covered by TSE CEPs: R1-CEP 2004-247-Rev 00. The capsules do not contain any gelatine of porcine origin.

Declarations for lactose are provided by the suppliers attesting that bovine materials (milk) used in the manufacture of lactose are sourced from healthy animals and collected in the same conditions as milk for human consumption.

Manufacture of the product

The manufacturing process includes standard unit operations and equipment for capsule production via high-shear wet granulation.

The manufacturing process includes granulating solution preparation, high-shear, wet granulation, particle size reduction (wet), fluid-bed drying, particle size reduction (dry), extragranular blending, lubrication blending, unit dosing (capsule filling) and primary packaging.

The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process. Data were provided on a large number of batches (n=18). The manufacturing process has adequately been characterised and the process validation protocol is satisfactory. The in process controls are adequate for this pharmaceutical form.

The batch analysis data show that the hard capsules can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation.

Product specification

The specifications includes acceptance criteria and tests using validated methods (when appropriate) for description, identification (IR, HPLC), assay (HPLC, degradation products (HPLC), Dimers (HPLC), total degradation products (HPLC), moisture, dissolution (HPLC), uniformity of dosage units (Ph Eur), diastereoisomers content and microbial contamination.

The specifications proposed for the finished product are appropriate to control the quality of this medicinal product for the intended purpose.

Batch data are provided for pilot and production batches and indicate satisfactory uniformity as well as compliance with the specification.

Stability of the product

Stability studies were performed at 5°C± 3°C up to 18 months for three primary batches, up to 24 months for a supportive batch used in phase III clinical trials and up to 6 months for the three commercial batches. In accelerated conditions, stability data are available up to 6 months at 25°C/60% RH and 3 months at 40°C/ 75% RH for the 3 primary batches, up to 6 months at 25°C/ 60% RH for the supportive batch and 6 months for the 3 commercial batches at 30°C/ 75% RH. The batches were tested for description, assay, degradations products, moisture content, dissolution, diastereoisomer content, enol content, diol content and microbial contamination were followed.

A simulated in-use stability program was performed to support short term patient in-use storage which includes four batches packaged in the proposed commercial package. The batches were stored at the long term storage condition of 5°C over different length of time (6, 18, 23 and 36 months) prior to the initiation of simulated in-use stability studies. Parameters studied were description, assay, degradation products, moisture content, dissolution, diastereoisomer and enol content.

Photostability studies were performed on one batch packaged in the intended commercial pack under ICH light conditions. The batch was tested for description, assay, dimers, moisture content, and dissolution; results compared to their respective control samples.

In accordance with EU GMP guidelines, any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

Based on available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve these as Follow Up Measures after the opinion, within an agreed timeframe

2.3. Non-clinical aspects

2.3.1. Introduction

The activity of boceprevir was investigated *in vitro* in a replicon system using three different constructs and in a biochemical enzyme assay with recombinant NS3-NS4A. The emergence of resistant mutants was investigated in a replicon system and in samples from patients (genotype 1 non-responders). The activity of mutant proteases was investigated in enzyme assays and in replicon assays. The activity of boceprevir was not investigated in animal studies.

Cross selectivity was tested in an extensive panel of proteases, other enzymes and receptors.

Safety pharmacology studies were performed to examine the potential effects of boceprevir on cardiovascular, respiratory, central nervous, renal and gastrointestinal systems.

Pivotal safety pharmacology and toxicology studies were performed in compliance with GLP.

One of the pre-clinical study as requested in the PIP was submitted in this application. The study was a one-month thyroid hormone evaluation study of boceprevir in juvenile rats.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Mechanism of action and effects on cells in culture

The mechanism of inhibition involves boceprevir covalently, yet reversibly, binding to the NS3 protease active site serine (Ser139) through a ketoamide functional group. Upon binding the NS3 protease active site serine, boceprevir prevents the HCV protease from cleaving the intermediate viral polyprotein into functional units, thereby effectively inhibiting HCV replication.

The effects of boceprevir on viability of human cell lines and primary cell cultures were evaluated by standard MTS methods (Promega). Minimal cytotoxicity was observed in several human cell lines (CC50 was 80 - >100 µM).

In vitro antiviral potency/activity of boceprevir

Antiviral activity of boceprevir was evaluated in a biochemical assay for slow binding inhibitors of NS3 protease and in the HCV replicon system. The inhibitory constant, Ki, for boceprevir was 14 ± 1 nM for genotype 1a and 1b. Ki for genotypes 2a and 3a was 39 nM and 25 nM respectively. In the bicistronic subgenomic replicon system (genotype 1b), the inhibitory concentration (IC50 and IC90) values for boceprevir were approximately 200 nM (n=25) and 400 nM (n=25), respectively, in a 72-hour assay. IC90 values of monocistronic and genome-length replicons were 700 nM (n=2) and 1000 nM (n=1) respectively.

In another study, *in vitro* antiviral activity of boceprevir was investigated in 3-day assays in a replicon system based on genotypes 1a and 1b. IC50 was 300 – 900 nM and IC90 500 – 1400 nM. In the presence of 50% human serum, the replicon IC50 value for boceprevir was 500 nM.

The effect of prolonged exposure to boceprevir was investigated in an HCV bicistronic subgenomic replicon. With exposure to boceprevir for 2 weeks, at concentrations of ≥2.5 µM, replicon RNA was almost eradicated by day 15 (estimated 1 copy per 10 cells left).

Resistance

In replicon assays, boceprevir induced an up to 6-12 fold increase in IC90 after 8-10 passages and an up to 8-48 fold increase after approximately 30 passages. Resistance-associated variants (RAVs) in replicon cells were observed at positions V36, Q41, M43, T54, Q86, S122, A150, R155, A156, V170, E176. A second mutation generally increased fold change above that induced by a single mutation. A156T conferred the highest level of resistance (increase in IC90 80-fold), but also significantly reduced replicon fitness. In a replicon assay, the combination of boceprevir at 6xIC90 (2.5 µM) and interferon alpha at 1xIC90 (1 IU/ml) reduced resistance from 0.14% to 0.005% of the cell population.

HCV samples from patients from a Phase II clinical study were sequenced (codons 1-181 of the NS3 region) and analysed by a selection pressure based method (Ka/Ks) to predict drug resistance mutations. Patients were genotype 1 non-responders to boceprevir treatment (n=252. Mutations identified by this analysis were V36M, T54A/S, R155K, A156S, V170A, V55A/I, V158I, V163L. V158I and V163L were novel mutations in this study. V158I conferred low level resistance to boceprevir (fold change Ki 2.5 and EC50 in replicon assay 3.3). V163L did not affect boceprevir activity
The NS3 protease domain of viral RNA from HCV genotype 1-infected patients (n=22; subtype 1a: n=8, subtype 1b: n=14) in a Phase 1b trial was sequenced before treatment, after 14-day treatment and after a 14-day follow-up period. The A156T mutation, conferring high resistance (>120-fold increase in IC50 in a replicon assay) but exhibiting low fitness, was not found in these patients.

Pharmacokinetic/pharmacodynamic (PK/PD) relationship

Among patients from Phase 3 clinical trials, the most detected RAVs were V36M, R155K and T54S for genotype 1a and T54A, T54S, V170A, A156S and V55A for genotype 1b. Overall, post-baseline RAVs were detected in 15% of the subjects. The overall percentage was similar among treatment failure subjects and treatment naïve subjects and for shorter treatment (response-guided therapy) and standard treatment. 53% of patients who did not achieve sustained virologic response (SVR) had

RAVs. More subjects with poor interferon response had RAVs (41%) compared to interferon responsive subjects (6%).

It is assumed that suppression of HCV replication *in vivo* will depend on maintaining plasma trough concentrations (Cmin) at levels ≥ IC90 as determined in the replicon assays. The estimate of the required Cmin is 200 ng/ml (400 nM).

Data show that Cmin correlates better with maximal HCV-RNA drop than Cmax or AUC.
Follow-up data from Phase 1 and 2 patients showed that among treatment failures with RAVs, after 2 years after end of treatment approximately 60% of the RAVs return to wild type. Final data with subjects from phase III studies are awaited.

Secondary pharmacodynamic studies

Boceprevir contains an electrophilic moiety. Activated nucleophiles, which are present in many proteases and esterases, have the potential to react with the electrophilic moiety. The applicant performed two studies in which the selectivity of boceprevir was investigated.

In study D-46277, cross reactivity of boceprevir with human cathepsins G, H and L was investigated using spectrophotometric assays. In a study described in reports D-55146 and D-46276, an extensive panel of cellular proteases, other enzymes and receptors was tested for inhibition by boceprevir. Only cathepsin L was inhibited by boceprevir to a substantial extent.

Safety pharmacology programme

Safety pharmacology in vitro

Cardiovascular system

In mouse L-929 cells expressing the hERG potassium channel, 1 μM boceprevir had no effect on hERG-mediated potassium currents.

In isolated canine Purkinje fibers, 0.1 and 0.3 μM boceprevir did not significantly affect action potential parameters, i.e. amplitude, resting potential, maximal rate of depolarization and action potential duration (APD60 and APD90) under either normal (1Hz) or low (0.5Hz) stimulation rates. Exposure to 1 μM (measured concentration =0.813 μM) boceprevir did not affect amplitude, resting potential or maximal rate of depolarization but produced an increase in ADP60 and ADP90 that was inverse frequency-dependent. The reference substance dl-Sotalol HCl (50 μM) caused a pronounced prolongation of ADP that was inverse frequency-dependent.

Safety pharmacology in vivo

Cardiovascular system

Single oral administration of 75 or 200 mg/kg boceprevir to conscious cynomolgus monkeys did not induce treatment-related changes in blood pressure up to 5 hours after administration. Following exposure to 200 mg/kg boceprevir, heart rates were significantly elevated during hours 4 and 5 post-dosing as compared to vehicle. The maximum increase in heart rate was nominally 28 bpm. The corrected QT interval (QTc) revealed no significant difference between the test article dosed groups

and the vehicle at any of the time intervals. Significant RR interval shortening was found for the high-dose group compared to vehicle from 3.5 through 5 hours post-dose. QT intervals were also significantly shortened, as compared to vehicle, at 0.5, 1, 2.5, 4 and 4.5 hours for the high dose group.

Respiratory system

Single oral administration of 10, 30 or 100 mg/kg boceprevir to rats did not induce treatment-related changes in arterial pH or blood gases (paO2, paCO2 or bicarbonate) up to 4 hours after dosing. Single oral administration of 25, 75 or 200 mg/kg boceprevir to conscious rats did not induce treatment-related changes in respiratory rate, tidal volume or minute volume up to 5 hours after administration.

Central nervous system

Single oral administration of 10, 30 or 100 mg/kg boceprevir to conscious rats had no effect on behavioural, neurological and autonomic function (measured in a modified Irwin test) up to 4 hours after dosing.

In an additional study utilizing a functional observational battery and locomotor activity assessments, single oral administration of 25, 75 or 200 mg/kg boceprevir had also no effect on overall behaviour, locomotor activity, spinal reflexes and autonomic function up to 1 h after dosing [01400].

Gastrointestinal system

Single oral administration of 10, 30 or 100 mg/kg boceprevir to rats did not demonstrate any drug-related effect on gastric emptying or intestinal transit time, whereas the reference compound atropine produced a significant inhibition of gastric emptying and intestinal transit time.

Renal system

Single oral administration of 10, 30 or 100 mg/kg boceprevir to rats did not significantly affect urine volume, electrolyte excretion or creatinine clearance.

Pharmacodynamic drug interactions

<u>*In vitro* potency/activity of boceprevir in combination with interferon alfa-2b</u>
To investigate the effect of boceprevir on interferon alfa-2b activity, in a replicon system, escalating doses of boceprevir (10 nM to 5 mM) were added to a standard titration of interferon alfa-2b (0.1 to 40 IU/ml) to generate a 10 x 10 matrix of concentrations varying from below the IC50 to above the IC90 for both drugs. At 72 hours, replicon RNA levels were estimated using the standard, single-tube multiplex assay. Evaluation of varying combinations of boceprevir and interferon alfa-2b that produced 50% suppression of replicon RNA showed additivity of effect; no evidence of synergy or antagonism was detected (Malcolm et al, 2006).

<u>Interaction with HIV protease inhibitors</u>
The activity of boceprevir in the presence of various concentrations of HIV protease inhibitors atazanavir (1-10 µM), lopinavir (5-20 µM) and ritonavir (0.3-10 µM) was measured in replicon cells using Taqman analysis. Boceprevir inhibited replicon RNA in a dose-dependent manner with EC90 =

300 nM. The HIV protease inhibitors had minimal effect (2-3 fold) on boceprevir EC50 and EC90. No cell toxicity (CC50 > 5 µM) was observed in replicon cells as a result of exposure to these combinations. The influence of boceprevir on the activity of the HIV protease inhibitors was investigated in a cell-based HIV infection assay (astroglioma cells). Boceprevir up to 5 µM had minimal effect (< 3-fold) on antiviral activity of atazanavir and ritonavir. There was a slight decrease (10-fold) in EC50 values of lopinavir in the presence of higher concentrations (above clinical exposure) of boceprevir. No cell toxicity was observed.

2.3.3. Pharmacokinetics

Victrelis (boceprevir) is a racemic mixture of two diastereomers (SCH 534128 and SCH 534129). Only the diastereomer SCH 534128 is pharmacologically active.

Both non-validated and validated LC-MS/MS methods have been used for the detection of boceprevir, its individual diastereomers, and its major human metabolite SCH 629144 (collective designation for SCH 783007, SCH 783005, SCH 783006, and SCH 783004) in plasma. The LC-MS/MS methods are considered sufficiently accurate and precise by the CHMP.

Absorption was generally rapid in all species. After oral administration, the bioavailability of boceprevir was moderate in male mice, rats, and dogs (34%, 26%, and 30%, respectively) but was low in fasted male monkeys (4%). Subsequent studies in rats and male monkeys showed that the bioavailability of both SCH 534128 and SCH 534129 was similar. In monkeys, the bioavailability increased under fed conditions (10-13%). The half-life of boceprevir is short, ranging from 1 to 5 h in the pre-clinical species and humans. In addition, the half life of the active diastereomer SCH 534128 ranged from 1 to 4 h in rat and monkey and ~2 h in humans. No information was provided on the half-life in other pre-clinical species.

From TK data obtained after a single dose, gender-related differences in systemic exposure were evident in rodents with females more exposed than males given the same boceprevir dose (up to 3-fold in mice and rats). In addition, there was some inter-study variability regarding the exposure levels measured for a given dose and in a given sex, particularly at high dose levels. A time-related effect on the kinetics of boceprevir was observed in mice only, with a decrease in exposure levels probably related to the induction of cytochrome P450 enzymes.

Animals were treated once daily in the pre-clinical repeated dose studies and humans were treated two or three times a day (every 8 to 12 hours) in the clinical studies. In addition, the ratio of the two diastereomers is species dependent. In mice, the steady state SCH 534128:SCH 534129 ratio was 1.2:1 and the ratio in male mice was greater than the ratio in female mice. The steady state SCH 534128:SCH 534129 ratio was 1:1 in rat plasma. In monkey, the SCH 534128:SCH 534129 ratio was approximately 1:5.9 in plasma at steady state. The ratio of diastereomer concentrations in humans at steady-state was 2.2:1 (SCH 534128:SCH 534129).Therefore, the comparison of the kinetic parameters is hampered.

Exposure values in juvenile rats were higher than exposure values in adult rats on a restricted diet; but lower than exposure values in adult rats fed ad libitum. However, based on the comparison of exposure data obtained in adult and juvenile male rats under fed conditions, it cannot be excluded that the pharmacokinetics in juveniles are different than that in adults and may be caused by not fully expressed liver metabolic enzymes in the juvenile.

Boceprevir is moderately bound to plasma proteins in all species, and was shown to cross the placenta in pregnant rats. In rats administered radiolabeled boceprevir, the highest radioactivity levels were measured in the liver, bladder, kidneys, prostate gland, other endocrine tissues (adrenal, harderian, and salivary glands), and bone marrow. The results did not indicate a specific binding of drug-related radioactivity to melanin-containing tissues, and there was no gender-related difference in the tissular distribution profile. Only bladder, liver, kidney, bone marrow, endocrine glands and reproductive organs contained quantifiable levels of radioactivity at 8 h post-dose. All tissues, except bone marrow, were below quantifiable limits after 24 h. Based on the provided distribution data, the fact that patients are treated every 8 h hours and similar half-lives in rat and humans, accumulation in humans can be expected in bone marrow and endocrine glands. Effects on bone marrow were not specifically investigated in the pre-clinical toxicity studies. However, no toxicity was observed in bone marrow and blood after 6 months repeated dosing in rat.

Boceprevir undergoes extensive metabolism in all tested species. *In vitro*, human liver microsomes converted approximately 99% of boceprevir to metabolites, and at least 31 metabolites were produced. *In vivo*, the percentage of drug excreted unchanged was weak and the number of produced metabolites was of the same order. The metabolism of boceprevir involves mainly oxidation and/or reduction, and hydrolysis reactions. Two main pathways can be described. The first involves the reduction of boceprevir to SCH 629144 (4 stereoisomers SCH783005, SCH783007, SCH783006, SCH783004) and is catalysed by the cytosolic aldo-keto reductase (AKR) family of enzymes, more precisely AKR1C2 and 1C3 isoforms. AKR1C3 preferentially metabolised SCH 534128 to SCH 783007 and AKR1C2 preferentially metabolised SCH 534129 to SCH 783004. Metabolising data indicate that the formation of the different SCH 629144 diastereomers is different between the different species with more SCH 783006 in rat compared to the other pre-clinical species and humans. Exposure to SCH 629144 increased as the dose of boceprevir was increased. AKR1C2 and 1C3 are expressed in the liver and in hormone-associated tissues (prostate, uterus, mammary gland, testes). Therefore, this metabolic pathway would take place in both hepatic and extra-hepatic tissues. Data showing that boceprevir has no potential for auto-inhibition of this pathway were provided.

The second pathway involves the CYP3A4 and CYP3A5 isoenzymes, mainly responsible for the formation of oxidized metabolites. Another metabolite, SCH 503034-K (M0BA), is a hydrolytic cleavage product and also a low-level impurity in the drug substance whose formation depends on the presence of SLS (sodium lauryl sulphate) in the formulation. In humans dosed with boceprevir as capsule, the circulating levels of SCH 503034-K relative to parent drug were lower than levels that may raise a safety concern. Therefore, this metabolite was clinically not relevant.

In all species, the main route of excretion was via the faeces, as a combination of biliary excretion of metabolites and excretion of unabsorbed drug. In rats, a limited fraction of an oral dose (3%) underwent enterohepatic circulation. In lactating rats, boceprevir-related radioactivity was rapidly excreted into maternal milk. No information was provided concerning the precise composition of radioactivity as found in rat milk samples. Consequently, the SmPC mentions that a risk to the newborn/infant cannot be excluded and that breast-feeding must be discontinued prior to initiation of therapy in patients who will be administered boceprevir

Boceprevir is an inducer of CYP2B and 3A in mice, but not in other species including humans. A study on human liver microsomes showed that it is rather a competitive inhibitor of CYP3A4/5 at concentrations in the range of that reached in patients.
Boceprevir was shown to be both a P-glycoprotein and a weak BCRP substrate. These findings and a warning about a likely interaction with inhibitors of these transporters are reported in the SmPC.

Regarding the inhibitory potential for transporters, it can be concluded that boceprevir is not expected to significantly inhibit MRP2 and BCRP at therapeutic concentrations. Nevertheless, it was shown to be a P-glycoprotein and an OATP1B1 inhibitor in vitro.

In an enzyme induction study with three batches of human hepatocytes, boceprevir did not cause significant induction of CYP1A2, CYP3A4 and CYP2B6. As these enzymes are sensitive indicators for activation of the AhR, PXR and CAR receptors, and activation of these receptors can also result in the induction of some of the UGT enzymes, the potential that boceprevir will cause significant induction of UGT enzymes is low.

2.3.4. Toxicology

Toxicology

Single dose toxicity

Single-dose toxicity studies were conducted in rats, dogs and monkeys by the oral route which is used in patients. An additional study was performed in rats by the intraperitoneal route. The observed maximum non-lethal oral acute doses in rat, dog and monkey were respectively 2000, 300 and 1000 mg/kg.

Repeat dose toxicity

Repeat-dose toxicity studies were conducted in mice for up to 3 months, rats for up to 6 months, and monkeys for up to 12 months. In repeat-dose studies in mice, no **overt** toxicological effects were seen up to 900 mg/kg (ca 23 x human dose, ca 3.6 x human AUC of active isomer SCH 534128). Target organs for mild effects were liver, kidney and spleen.

In rats, target organs/tissues identified were testes, epididymides, prostate, adrenal glands, thymus and liver in males. Effects on testes and epididymides were sertoli cell vacuolation, spermatid degeneration, atrophy of seminiferous tubules, and luminal cellular debris in the epididymides. A decrement of prostate weight with no histopathologic correlate was seen in study 01290, but not in other studies. Effects on urine chemistry in male and female rats and on testes in males appeared at 75 mg/kg (ca 2 x human dose, ca 1.3 x human AUC of boceprevir). Established NOAEL is 15 mg/kg, thus much lower than the intended human exposure.

In monkeys, minor effects were seen in some studies on P450 enzymes, liver weight, serum cholesterol, but not in the 12 month study. Most important were increases in activated partial thromboplastin time (APTT) seen in monkeys without associated clinical observations, changes in other clinical pathology parameters suggestive of haemorrhage, or gross pathology evidence of haemorrhage that would indicate a defect in haemostasis (NOAEL of 25 mg/kg which represents a monkey to human exposure multiple of 0.15 based on AUC of boceprevir (SCH 503034).. The APTT has been monitored in clinical studies, and no clinically meaningful effects have been identified. It is agreed that the effect on APTT of boceprevir seen in monkeys is probably not an important risk factor for humans.

Genotoxicity

The genotoxicity of boceprevir was evaluated *in vitro* in an Ames test, and in human peripheral blood lymphocyte and mouse micronucleus assays. Boceprevir was not genotoxic in this ICH-compliant battery of tests.

Carcinogenicity

The carcinogenic potential of boceprevir was assessed in mice and rats following oral administration.

Hepatocellular adenomas were found in female mice in the 2-year carcinogenicity study.

Boceprevir was not found to be carcinogenic in a 2-year rat study. The AUC-values of boceprevir (SCH 503034) and the active metabolite SCH 534128 at high dose in rats were slightly below the human AUC-values at the intended dose.

Reproductive and developmental toxicity

The effect of boceprevir on fertility and early embryonic development was assessed in female mouse, male and female rats and in female rabbits.

Boceprevir induced reversible effects on fertility and early embryonic development in female rats at 150 mg/kg. In males a decreased fertility and testicular degeneration was shown at 150 mg/kg. The NOAEL was 75 mg/kg. In embryo-foetal toxicity studies of rats, there were no boceprevir-mediated effects on reproductive parameters (e.g. resorptions, foetal viability), or foetal weight, nor were there any test article-related malformations or variations. The NOAEL for maternal toxicity in rats is <150 mg/kg (based on the decrement in gestational body weight gain) and the NOAEL for embryo-foetal toxicity in rats is 600 mg/kg. Rabbits showed maternal toxicity at 50 mg/kg, but embryo-foetal toxicity or teratogenicity was not observed up to 600 mg/kg.

In pre/postnatal toxicity study in rats, there were no boceprevir related effects on pregnancy, parturition and lactation of the maternal animals (F0) or on the growth, viability, development or reproductive performance of the F1 generation. Survivability of the F2 generation was unaffected. The NOAEL for F0 and F1 generations was found 150 mg/kg.

Juvenile rats showed after 3 months exposure to boceprevir lower mean body weights and body weight gains, delayed attainment of male developmental landmarks at 150 mg/kg, hyperplasia of thyroid gland follicular cells, hypospermia in the epididymides, and vacuolation of the seminiferous epithelium and degeneration in the seminiferous tubules at dosage levels of 75 and 150 mg/kg. The NOAEL for F1 systemic toxicity was 25 mg/kg (AUC about 0.2 times the intended human adult exposure). Thyroid gland hyperplasia seems to be specific for juvenile rats, as it was not observed in adult rats, or in mice.

Toxicokinetic data

Toxicokinetic data were obtained after a single and repeated oral administrations of boceprevir.

From toxicokinetc data obtained after a single dose, gender-related differences in systemic exposure were evident in rodents with females more exposed than males given the same boceprevir dose (up to 3-fold in mice and rats). In addition, there was some variability from one study to another regarding the exposure levels measured at the same dose level in each sex, particularly at high doses.

In mice, AUC levels were decreased after repeated doses compared to those measured following single dose.

Local Tolerance

No study was performed since boceprevir is intended to be administered orally.

Other toxicity studies

Standard immunotoxicity endpoints including white blood cell counts, differentials lymphoid organ weights, lymphoid tissue histopathology and bone marrow cellularity were assessed in general toxicity studies and did not indicate a need for specific immunotoxicity or antigenicity studies to be conducted. Idiosyncratic adverse reactions are not expected.

Additional studies were performed to elevate mechanisms concerning testicular toxicity, hormone levels during pregnancy, estrogenicity, thyroid hypertrophy, heamolysis and APTT. Also some *in vivo* combination studies have been performed.

The testicular toxicity shown in repeated dose studies in male rats was not accompanied by changes in serum levels of LH, FSH and testosterone.

In female rats, the observed decrease in pregnancy was not accompanied by changes in serum concentrations of LH, FSH, P4 and E2. In vitro tests showed that boceprevir has no estrogenic activity and no antagonistic activity on the androgen receptor.

Boceprevir showed no effect on red blood cell osmotic fragility in human blood and no effect on APTT (activated partial thromboplastin time) in cynomolgus monkey blood.

In rats, the combination of ribavirin with boceprevir did not increase the toxicity of boceprevir in a 3-month study. Administration of diflunisal, ritonavir and ribavarin caused more toxicity in a 3-month study in rats with thymus, adrenal gland, kidneys and thyroid glands as targets. Co-administration of boceprevir, ribavirin and ritonavir increased dose normalized exposure to boceprevir at steady state approximately 2 to 6-fold (in females) or 4 to 9-fold (in males).

The combination of PEG-Intron and ribavirin with boceprevir showed mild effects which were only attributable to PEG-Intron and ribavirin.

The applicant performed a number of 1-month repeated-dose studies in rats with exposures to different batches of boceprevir containing relatively high amounts of impurities and degradation products. Based upon systemic exposure, clinical observations, body weight, food consumption, ophthalmology, clinical pathology and pathology/histopathology data/findings, there was no toxicologically significant difference found between the batches tested and pure boceprevir.

2.3.5. Ecotoxicity/environmental risk assessment

An ERA according to CHMP guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00,) was submitted.

The $PEC_{SURFACEWATER}$ value determined in the phase I risk assessment exceeds the action limit value by a 1200-fold factor. Therefore, it is agreed that boceprevir should enter into phase II Tier A risk assessment. Further data is required to substantiate the outcome and complete the programme as such the study report on log Kow and the study reports related to the phase II assessment should be provided.

2.3.6. Discussion on non-clinical aspects

Pharmacology

Boceprevir is a serine protease inhibitor, which inhibits NS3, a viral protease which is involved in further cleavage of the viral polyprotein into downstream nonstructural proteins. Boceprevir binds covalently, yet reversibly, to the NS3 protease active site serine through a ketoamide functional group, thereby inhibiting the cleavage of the viral polyprotein into functional units, thereby inhibiting HCV replication.

In replicon assays with the human hepatoma cell line Huh7 transfected with RNA based on HCV genotype 1b, IC50 was 200 – 900 nM and IC90 was 400 – 1400 nM. In the presence of human serum, IC50 was 500 nM. In an enzyme assay, Ki was 14 nM for genotype 1a and 1b, and 39 nM and 25 nM for genotypes 2a and 3a respectively. *In vitro* studies showed that mutations emerge at concentrations up to 10 µM. Mutations are therefore expected to emerge at human exposures if boceprevir is used as monotherapy.

In replicon assays, boceprevir induced an up to 6-12 fold increase in IC90 after 8-10 passages and an up to 8-48 fold increase after approximately 30 passages. A156T conferred the highest level of resistance (increase in IC90 80-fold), but also significantly reduced replicon fitness. In a replicon assay, the combination of boceprevir at 6xIC90 (2.5 µM) and interferon alpha at 1xIC90 (1 IU/ml) reduced resistance from 0.14% to 0.005% of the cell population.

In HCV samples from Phase 1 and 2 patients (genotype 1 non-responders), post-baseline RAVs were detected in 15% of the subjects. 53% of patients who did not achieve sustained virologic response (SVR) had RAVs. More subjects with poor interferon response had RAVs (41%) compared to interferon responsive subjects (6%). The extent that baseline levels (higher or other types of RAVs) might jeopardize future treatment of treatment failures. The clinical consequence of the emerging mutations (in terms of response to boceprevir and impact to subsequent lines of therapies) need to be further substantiated.

Given that IC90 ranges from 400 - 1400 nM in *in vitro* studies the estimate of the required Cmin of 200 ng/ml (400 nM) seems rather low. Furthermore, clinical pharmacokinetic data show that in a large part of the patient population Cmin of 200 ng/ml was not even achieved. Moreover, this value represents the total fraction, as a result of which the freely available, non-protein-bound fraction is even lower. However, data show that higher dosing would not seem to increase Cmin substantially, and therefore a higher Cmin seems not likely achieved. Ultimately, the clinical response is the most important and clinical data point towards a significant effect of boceprevir in combination with peginterferon alpha and ribavirin compared to peginterferon alpha and ribavirin alone. Likely, the combination with peginterferon alpha and ribavirin contributes significantly to the efficacy

The activity of boceprevir was not investigated in animal studies. This is endorsed; robust *in vitro* cell culture systems are lacking and animal models for hepatitis C are not readily available, except

chimpanzees, and activity measurements in chimpanzees are not expected to add significantly to clinical data.

Boceprevir showed minimal cytotoxicity in several human cell lines (CC50 was 80 - >100 µM).

In secondary pharmacology studies Cross reactivity of boceprevir with an extensive panel of proteases, other enzymes and receptors was investigated *in vitro*. Only cathepsin L was inhibited by boceprevir to a substantial extent. This is considered not likely to have a relevant impact. Cathepsin L is only one of a large family of proteases, it is involved in nonspecific protein breakdown and most likely there will still be sufficient proteolytic pathways.

Concerning safety pharmacology studies, single oral doses of boceprevir did not induce adverse effects on the CNS, respiratory, renal and gastro-intestinal systems. However, the cardiovascular safety pharmacology programme raised some concern. The main criticism is that the concentrations tested *in vitro* (hERG and Purkinje fiber assay) were too low with regard to the clinical C_{max} free drug level. Nonetheless, a prolongation of the Purkinje action potential was observed at 0.5 Hz. The Applicant considers that the action potential prolongation is modest, but it must be kept in mind that this lengthening reached 42 to 82 msec (depending on the fiber) at a concentration corresponding to therapeutic concentrations. This effect being concentration-dependent and inverse rate-dependent, and probably amplified by hypokaliemia, such and effect cannot be ignored. Indeed, the dog Purkinje fiber is a well known sensitive and predictive model with very rare false positive results. In that context, it cannot be accepted that boceprevir is unlikely to prolong QT interval based on the lack of significant effect on hERG potassium channel in a study performed at concentrations in the range of the clinical Cmax. This opinion is justified notably by the fact many other ionic channels are involved in the repolarization of the action potential and that the Purkinje fiber model is a much more relevant, physiologic and predictive model.

The *in vivo* model was Cynomolgus monkey. At the top dose (200 mg/kg), an increase in heart rate was observed without any effect on QT interval. However, the Cynomolgus model is not a good model, as compared to dog for example, to investigate the potential effects of a drug on the ECG pattern. In fact, it is not very sensitive to detect an effect on the QT duration due in particular to the high basal heart rate in Cynomolgus monkeys and the absence of an ideal correction formula for that species. Therefore it is not surprising that no effect could be detected during the in vivo studies. The major human metabolite SCH 629144 was not tested. The applicant considers that due to the presence of the main metabolite in monkeys, its potential cardiotoxicity was evaluated during the in vivo studies. For the same reasons as above, this is not convincing.

Taking into account that the pharmacokinetics of boceprevir is highly variable and complex, and that the patients may present some pathophysiological conditions (e.g. electrolytic disturbances) that may potentiate a potential drug-related effect on cardiac physiology, there are some concerns regarding the results obtained in cardiovascular safety pharmacology studies. Therefore, even in the absence of a clear effect of boceprevir in healthy volunteers (with normal heart rate, no electrolyte disturbance, no co-administration of any other drug interacting with either the pharmacokinetics or the pharmacodynamics of boceprevir), there is still some doubt concerning the potential effects of boceprevir on QT prolongation, in particular in subjects presenting with low heart rates. Thus, the positive findings observed *in vitro* are mentioned in SmPC 5.3 to give adequate information to the prescriber. In addition, events possibly related to effects on the cardiovascular system (such as syncopes, unexplained deaths, and QT prolongation) will be monitored in the RMP.

Concerning pharmacodynamic drug interactions, IFNα and boceprevir showed additivity of effect in a replicon system. It was shown *in vitro* that IFNα decreased emergence of resistance to boceprevir. The interaction with ribavirin was not investigated preclinically. However, the combination of boceprevir with peginterferon-α and ribavirin is investigated clinically. No relevant pharmacodynamic interactions were observed with HIV protease inhibitors atazanavir, lopinavir and ritonavir.

Pharmacokinetics

Pharmacokinetic studies showed that the most important route of metabolism of boceprevir is via aldo-keto reductase (AKR) enzymes. The capacity of boceprevir to inhibit aldo-keto reductase enzymes was not investigated. AKRs 1C2 and 1C3 are dominantly expressed in hormone-associated tissue such as prostate, testis, uterus, and mammary gland. Thus, conversion of SCH 534128 and SCH 534129 to SCH 629144 will occur in liver and in extra-hepatic tissues, and local tissue concentrations of specific diastereomers may depend on the tissue distribution of the AKR1C isoforms. Further data provided by the applicant showed that AKR1C3 preferentially metabolised SCH 534128 to SCH 783007 and AKR1C2 preferentially metabolised SCH 534129 to SCH 783004. The applicant investigated only the inhibitory potential of boceprevir via AKR1C3 and not AKR1C2. Based on the provided data it can not be excluded that boceprevir inhibits AKR1C2. AKR isozymes are important in the endocrine hormone metabolism and interactions are as such a concern. The applicant has committed to evaluate endogenous steroids to evaluate whether their presumed interaction with the AKR isoforms is affected by the presence of boceprevir. If positive signals are detected, clinical studies can be designed to better understand the significance of the in vitro findings. This commitment is reflected in the RMP.

SCH 503034-K was also observed as metabolite of boceprevir. SCH 503034-K is a hydrolytic cleavage product and is also present as low-level impurity in the drug substance. Boceprevir is formed in the presence of SLS and under acidic conditions. In humans dosed with boceprevir as capsule, the circulating levels of SCH 503034-K relative to parent drug were lower than levels that may raise a safety concern

Qualitatively, the metabolites detected in humans were also detected in mice, rats, and monkeys. However, quantitatively, significant inter-species variability was noted. This is notably the case of the major human metabolite SCH 629144, which was a minor metabolite in the rat. This species is thus to be considered as not fully relevant for humans.

Preliminary pharmacokinetic data indicate that the exposure in juvenile rats is higher than in adult animals at similar administered dosages. The current application is for adult use only. However, off-label use in children cannot be excluded, therefore the SmPC states that the pharmacokinetic profile of boceprevir may be different in juvenile rats than in adult rats.

A single oral dose of ^{14}C-boceprevir, drug-derived radioactivity was rapidly transferred into the milk of lactating rats. No information was provided concerning the precise composition of radioactivity as found in rat milk samples. However the SmPC states that boceprevir and metabolites are excreted in rat milk.

Toxicology

The observed max. non-lethal oral acute doses in rat, dog and monkey were resp. 2000, 300 and 1000 mg/kg.

In repeat-dose toxicity studies boceprevir showed testicular degeneration in rats at systemic exposures lower than those in humans at the recommended human therapeutic dose. Such findings were observed neither in mice, nor in monkeys. Additional studies in rats suggest that Sertoli cell is probably the primary target of boceprevir toxicity, thus supporting inhibin B as a valid marker for this effect in clinical studies. There was no indication of altered testicular function in clinical studies, based notably on unaltered inhibin B levels in two phase 2 studies. The overall non-clinical and clinical data suggest that the testicular toxicity observed in rats only is not likely to be relevant for humans. However, no definitive mechanism is proposed to support the assumption that the testicular findings are rat-specific.

In juvenile rats, boceprevir caused reversible and reproducible follicular thyroid hyperplasia. This finding was not reported either in adults rats, or in mice. To better understand the thyroid hyperplasia observed, a hormone evaluation study in juvenile rats was conducted. However, it did not clearly support the hypothesis that thyroid effects in juvenile rats were the caused by boceprevir-related enhanced T3 and/or T4 clearance (phenobarbital-like mechanism) due notably to the lack of compelling data from the phenobarbital positive control.

Boceprevir induced a reversible decrease in the fertility in female rats at exposures 1.2-fold the human exposure at the recommended therapeutic dose. Decreased fertility was also observed in male rats, most likely as a consequence of testicular degeneration. Boceprevir was shown to be devoid of embryonic or teratogenic potential in both rats and rabbits at maternotoxic dose levels.

In the 2-year carcinogenicity study in female mice hepatocellular adenomas were found. However, considering the relatively low incidences of these findings, no genotoxicity, no hepatocellular adenomas in males, no association with increased malignancy, some induction of p450 enzymes, and no hepatocellular adenomas/carcinomas found in rats, the hepatocellular adenomas are considered to be due to enzyme induction and therefore not relevant for humans.

Administration of diflunisal, ritonavir and ribavirin caused more toxicity in a 3-month study in rats with thymus, adrenal gland, kidneys and thyroid glands as targets. Co-administration of boceprevir, ribavirin and ritonavir increased dose-normalized exposure to boceprevir at steady state approximately 2 to 6-fold (in females) or 4 to 9-fold (in males). This increase is considered to be due to the pharmacokinetic enhancement of the exposure to boceprevir by ritonavir. However data suggest that no toxicological effect due to a higher exposure of boceprevir during combination therapy is to be expected.

Anaemia was frequently reported as a treatment-related effect in humans. An *in vitro* assay in human blood did not provide any evidence of a haemolytic potential for boceprevir. Anaemia was not reported in mice, rats and monkeys, and bone marrow smears performed in the 6- and 12-month monkey studies did not show any treatment-related effect. Further investigations are required to understand the incremental anemia observed in clinical practice. The applicant has committed to perform further mechanistic studies.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical aspects of boceprevir have been adequately documented and meet the requirements to support this application.

Overall, the toxicological profile of boceprevir is acceptable.

Further investigations are required to understand the incremental anemia observed in clinical practice. The applicant has committed to perform further mechanistic studies

2.4. Clinical aspects

The applicant requested for accelerated assessment pursuant to Article 14 (9) of Regulation (EC) no 726/2004.

The application focused on HCV infection with genotype 1. For genotype 2 and 3 sustained viral response (SVR) around 70-85% can be achieved with pegylated interferon plus ribavirine after a 6 month treatment period, while after one year treatment SVR rates below 50% for genotype 1 are reached, with still lower SVR rates in some subpopulations. The low SVR rates in treatment naïve patients infected with genotype 1 results in a pool of treatment experienced patients for whom new treatment options are needed. In addition, because the SVR rates in treatment naïve patients infected with genotype 1 are low, there is also a medical need in these HCV genotype 1 infected patients for new drugs that improve response rates. Therefore there is an unmet medical need in HCV genotype 1 treatment naïve as well as pretreated patients. The addition of boceprevir to peginterferon + ribavirin therapy is expected to be of added value in two ways: first it will significantly increase Sustained Viral Response rates; second, it might shorten treatment duration.

The CHMP agreed to the applicant's request for an accelerated assessment for the evaluation of this product in November 2010.

The proposed indication for Victrelis (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.

The proposed treatment regimen is 800 mg of Boceprevir administered orally three times daily (TID) with food.

CHMP guidelines/Scientific Advice

The guideline on the Clinical Evaluation of Direct Acting Antiviral Agents intended for treatment of Chronic Hepatitis C EMEA/CHMP/EWP/30039/2008, is applicable.

On 20 May 2010 formal Scientific advice was given by the CHMP: EMEA/H/SA/1574/1/2010/II. This advice concerned quality aspects.

On the following dates Scientific Advices were given by the Member States:

Before start of the phase III studies:

France, 3 Sep 2008. Main comment: it was recommended to incorporate a stopping rule in phase III.

Sweden, 29 Feb 2008. Main points were: The MPA questioned the stopping rule at week 12 for experienced and after week 12 for naïve patients in phase III. MPA suggested earlier stopping in order to prevent resistance. Furthermore not randomizing patients with < 1 log reduction was recommended

in order to prevent resistance; the company decided to randomize these patients based upon the phase II results which cam available after this advice.

Before submission: United Kingdom, 26 May 2010, France, 12 April 2010, Sweden, 29 March 2010, The Netherlands, 15 April 2010. Phase III studies were still ongoing.

No clinical paediatric data was submitted as part of the application. A deferral was granted for clinical studies in the PIP.

2.4.1.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- overview of clinical studies

The clinical program mainly consists of

- two completed phase II studies: P03523/SPRINT 1 in treatment naïve patients, P03659/RESPOND 1 in treatment experienced patients
- two completed phase III studies: P05216/SPRINT 2 in treatment naïve patients, P05101/RESPOND 2 in treatment experienced patients

These studies were performed with peginterferon alfa 2b+ribavirin

A phase III study in combination with peginterferon alfa 2a + ribavirin (P05685) was also provided within the course of the procedure.

Ongoing Trials

A long-term follow-up study (P05063) of which interim results are presented.

Phase II: P05411: Boceprevir combination therapy is investigated in subjects co-infected with HIV.
Phase III: P05514 (PROVIDE): Boceprevir combination therapy is offered to non-responders or relapsers from PR control arm of boceprevir trials.

Phase III: P06086: Prospective evaluation of two strategies (ribavirin dose reduction only vs erythropoietin support) to manage anaemia associated with boceprevir/PR 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). • 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.	BOC 800 mg TID (or placebo) PEG2b 1.5 µg/kg QW RBV 600 to 1400 mg/day	404/403

		• 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

2.4.2. Pharmacokinetics

Twenty Phase I studies were submitted to support the pharmacokinetics of boceprevir. These included 13 studies in healthy subjects, five studies in subjects with chronic hepatitis C, and two special population studies, in hepatically impaired and renally impaired subjects. A total of 377 healthy subjects were included in these studies.

The clinical trials conducted in hepatitis C patients included genotype 1 interferon non-responder subjects and genotype 2/3 subjects, from which also pharmacokinetic data were obtained, next to one Phase 2 study (P03659) and two Phase 3 studies (P05216 and P05101) from which sparse sampling data were obtained for population pharmacokinetic analysis.

Additional information was obtained from studies submitted in the non-clinical part: animal data from studies DM27192, SN01556 and DM27296, protein binding data from study SN03368, in vitro Caco-2 data and absorption (including P-gp interaction) from study DM27866, diastereomer inter-conversion data from study SN04016, as well as data regarding CYP450 enzymes (substrate/inhibition) and other possible enzymes involved in the metabolism of boceprevir from studies SN03208, DM27292, DM27352 and DM27368.

Absorption

The absolute bioavailability of boceprevir has not been determined since no IV formulation was available. Boceprevir was shown to be a substrate as well as an inhibitor of P-gp using the Caco-2 bi-directional permeability assay (DM27866). Bi-directional permeability was concentration-dependent and saturable.

Bioavailability and bioequivalence

An original dry-blend capsule formulation (50 and 100 mg strength) was used in phase 1 and early phase 2 clinical studies. For further phase 2 and phase 3 studies, a higher dose capsule was required. Consequently, a clinical image formulation i.e a wet capsule (200 mg strength) was developed in study P03533.

One part of a study evaluated the effect of formulation on the bioavailability of boceprevir. The objective of this study was to determine whether a formulation containing SLS improved the bioavailability compared to the original formulation (400 mg single dose 4-period cross-over study

with original, 0% SLS, 3% and 6% SLS commercial formulation under fasted condition, n=44). The results are reported in the Table below.

Table 2: Mean (CV%) pharmacokinetic parameters of boceprevir following administration of Boceprevir (400mg, single dose) as original formulation or as capsules containing 0%, 3% (commercial formulation), or 6%SLS in fasted healthy adult subjects (P03533)

Treatment	n	AUC(0-t) (ng.hr/ml)	Cmax (ng/ml)	Tmax[a] (hr)
Original	12	1930 (45)	672 (55)	1.50 (1.00-3.00)
0% SLS	12	1510 (49)	364 (67)	2.25 (1.00-8.00)
3% SLS (commercial formulation)	12	2540 (40)	865 (35)	1.50 (1.00-4.00)
6% SLS	12	2750 (50)	1020 (61)	1.50 (1.00-5.00)

[a] *Median (range)*

Table 3: Relative systemic exposure of boceprevir following administration of Boceprevir (400mg, single dose) as original formulation or as capsules containing 0%, 3% (commercial formulation), or 6% SLS to fasted healthy adult subjects

Comparison	n	AUC (0-t) (ng.hr/ml)		Cmax (ng/ml)	
		Ratio Estimate (%)	90% CI	Ratio Estimate (%)	90% CI
0% SLS vs Original	12	76	62-94	51	39-68
3% SLS (commercial formulation) vs Original	12	135	109-167	139	106-183
6% SLS vs Original	12	140	113-174	147	112-193

These results show that the bioavailability of boceprevir was improved with formulations containing 3 and 6% SLS compared to the formulation containing 0% SLS and to the original formulation. The difference in bioavailability between the 2 formulations containing SLS was marginal. Similarly, PK changes were observed with the active diastereoisomer SCH 534128. Accordingly, the applicant selected the capsule containing 3% SLS for clinical trials.

The commercial formulation proposed for marketing (same composition and same manufacturing process as clinical image formulation used in phase 2 and 3) only differs by the colour of the capsule shell. No bioequivalence study was performed to demonstrate the bioequivalence between the clinical image formulation and the commercial image formulation which were considered to be similar by the applicant.

The original formulation has been used in several Phase I trials, while the commercial formulation has been used in the Phase II and III trials. The most important studies, like dose proportionality, food interaction, QTc effects, and drug-drug interaction studies have been carried out with the commercial formulation.

Effect of food

The food effect has been evaluated for the original formulation and for the commercial formulation.

The effect of high fat and non fat meals on the bioavailability of boceprevir was investigated with the original formulation in a three period single dose (600 mg) crossover study (n=12) (fasted, standard high fat breakfast and standard non-fat breakfast). The bioavailability of boceprevir increased

substantially when administered with food. The mean ratio estimate for AUC was 317% (high fat meal) and 182% (low fat meal) relative to the fasted state. The corresponding values for Cmax were 223% and 129% respectively.

The second study was a single dose two-period crossover study (administration of 600 mg in a fasted state and immediately after consumption of a standard high-fat breakfast) (n=20). The results indicated that in the fed state the peak was delayed (3hrs later) and the bioavailability increased (217% for AUC and 162% for Cmax) relative to the fasted state.

Three more studies were performed to evaluate the effect of food on the bioavailability of the commercial formulation.

One study was designed to determine the effect of a low fat meal on the bioavailability of boceprevir administered as the commercial capsule formulation (400 mg) single dose 3-way cross over followed by two treatments in a fixed sequence exploring food effect with original and commercial formulation, n=44). For the commercial formulation, boceprevir (and its diastereomers) AUC and Cmax increased by about 65% (2x200mg) due to intake of a low fat meal.

A second study investigated the effect of the timing of a low fat standard breakfast on the bioavailability of boceprevir commercial formulation. This was a single dose (400 mg) four period cross over study (fasted, administration 5 min before meal, after consumption of half meal and within 5 min of meal completion)(n=12). The capsules (2x200mg) were administered in fasted state, immediately before intake of a low-fat breakfast, during intake of a low fat breakfast (taken at about 50% of meal consumption) and immediately after the intake of a low-fat breakfast. The meal contained 21 g fat and had a caloric content of 450 kcal. The timing of the meal administration did not notably affect this increase in bioavailability.

The third study evaluated the PK of boceprevir after single doses administration under fasted and fed conditions in Japanese and Caucasian subjects. There were 3 dose groups (200, 400 and 800 mg). Each group included 3 periods: period 1 after an overnight fast, period 2 with a FDA standardized high fat breakfast and period 3 with a Japanese low fat meal. Twelve subjects (Japanese n=6, Caucasian n=6) were enrolled in each dose group.

In Caucasians, the effect of food on boceprevir AUCt increased for the 200, 400 and 800 mg strength from 16, 48 to 59%. For Cmax no effect was observed at the 200 mg dose, but this increased about 50% at the 400 and 800 mg dose. The overall food effect was 40% for AUC and 28% for Cmax. A similar trend was observed in Japanese subjects, although the effect of food was higher, especially on Cmax.

As reflected in the posology, the drug is to be administered with food, Administration without food could be associated with a net loss of efficacy due to insufficient exposure.

Distribution

Animal data indicate that high concentrations were observed in liver, bladder wall, kidneys, and various glandular tissues. In addition, boceprevir was not measurable in brain, indicating that it does not cross blood-brain.

Furthermore, preclinical data indicate that boceprevir crosses the placenta and is excreted in mother's milk.

In vitro protein binding studies using human plasma indicate that boceprevir is approximately 82% bound to plasma proteins at a concentration of 50 ng/ml and 69% at of 25000 ng/ml, indicating a slight concentration dependent binding. This was confirmed in vivo, where a protein binding of 74% was measured in plasma obtained from healthy volunteers. In addition, the protein binding of SCH629144 was about 70%, and a comparable protein binding for boceprevir and SCH629144 was observed in plasma from end stage renal disease patients.

Boceprevir is not actively taken up in red blood cells.

Population pharmacokinetic analysis indicated a central volume of distribution of 94 l., Vd/F was estimated to be about 772 l

Elimination

A study with ^{14}C boceprevir showed that a mean total of 88.2% (range 85%-91.6%) of the radioactive dose was recovered in the urine (mean 9.3%, range: 7.3%-11.8%) and in feces (mean 78.9%, range:75.8%-83.5%) over 168 hrs after a single administration dose of 800mg oral suspension in 3% (w/w) SLS (P03588). Approximately 3% and 8% of the dosed radioactivity was eliminated as unchanged boceprevir in urine and faeces, respectively.

In an ascending single dose study, plasma boceprevir concentrations declined in a biphasic manner with a mean terminal half-life of 7 to 15 hrs for doses ranging from 100 to 800 mg. In a multiple dose study (800 mg tid), the mean terminal half-life was 10.2 hrs (CV 98%) and 4.5 hrs (CV 53%) in Caucasian and Japanese subjects respectively. In pooled studies the mean steady-state half-life was 3.4 hrs (CV 90%). The half-life of the active diastereoisomer was found to be ranging from 1.5 to 5 hr across doses and studies.

The AUC values across the clinical studies and doses suggest that the plasma clearance of the inactive diastereoisomer SCH 534129 was greater than that of the active diastereoisomer SCH 534128. The ratio of diastereoisomer concentrations (active:inactive diastereoisomer) in humans varies with time approaching a steady-state ratio of about 2:1.

In vitro and in vivo data indicate that boceprevir undergoes extensive metabolism, mainly by the aldoketoreductase pathway and by CYP3A4/5 metabolism. The main part of the drug-derived radioactivity exposure in plasma was due to SCH 783004, SCH 783006, and SCH 783007 (together grouped as SCH 629144), which are formed by the aldoketoreductase pathway.

Dose proportionality and time dependencies

After a single dose, boceprevir shows a more than dose proportional increase over the 200 – 800 mg dose range; however this was not observed after t.i.d. dosing. At higher doses AUC and Cmax clearly increased less than dose proportional, probably due to limited solubility and absorption.

No unexpected accumulation occurred for boceprevir, with accumulation factors below 2. Also based on the population predicted AUC and Cmin levels no unexpected accumulation was identified. In addition, there was no indication that the elimination half-life was dependent on dose or affected by repeated administration. Steady state was achieved within about 2 days.

Special populations

Specific phases I studies evaluating renal and hepatic functions were conducted. Other data related to age, gender and race were derived from population PK analyses.

A study was carried out on subjects with end stage renal disease and haemodialysis, who received an 800 mg single dose of boceprevir. Obtained boceprevir pharmacokinetics at day 1, when patients were not dialysed, indicated that AUCt and Cmax were comparable between the end stage renal disease patients and healthy volunteers with ratio's of 0.90 (90% CI 0.47 – 1.74) and 0.81 (90% CI 0.38 – 1.74), respectively.

To evaluate the effect of dialysis, these patients received at day 4, when they underwent dialysis, an additional single 800 mg dose under fed conditions. Pharmacokinetics at day 4 and day 1 were comparable (ratio AUCt 0.99, ratio Cmax 0.88).

The effect of impaired liver function on the pharmacokinetics of boceprevir was investigated in study P03747. Subjects with mild hepatic impairment (Child-Pugh score 5 – 6), moderate hepatic impairment (Child-Pugh score 7 – 9) and severe hepatic impairment (Child-Pugh score 10– 12) were included.

Boceprevir was administered at a dose of 400 mg under fasting conditions. Blood samples were taken up to 72 h after dosing.

Mild to moderate hepatic impairment did not affect the pharmacokinetics of boceprevir after a single dose of 400 mg. Severe hepatic impairment increased AUC and Cmax by 42 and 61%, respectively.

Population pharmacokinetic analyses did not reveal any significant effect of gender, weight, race or age. No data were obtained in children and adolescents patients or children

Pharmacokinetic interaction studies

In vitro studies showed that boceprevir is primarily metabolised via aldoketoreductase isoforms (AKR1C2 and AKR1C3) and to a minor extent via CYP3A4/5-mediated oxidation.

Boceprevir is a substrate for P-gp. Furthermore, boceprevir inhibited the efflux of digoxin, with an estimated IC50 of 25 µg/ml.

Using human liver microsomes and incubations with P450 probe substrates with selectivity for CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5, boceprevir was demonstrated to be an inhibitor of CYP3A4/5 . A Ki of 7.7 µM (about 4 µg/ml) was observed and inhibition was time-dependent.

In vitro, using cultured human hepatocytes, no relevant induction by boceprevir was observed for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4/5 after incubation at a concentration of 1, 10 and 100 µM (520 – 52,000 ng/ml)

Concomitant drugs effecting boceprevir pharmacokinetics in vivo:

- In studies with ketoconazole (a strong CYP3A4 inhibitor and P-gp inhibitor) the AUCt and Cmax of boceprevir increased by about 130 and 40% respectively.

- Ritonavir (strong CYP3A4 inhibitor and weak P-gp inhibitor) affects the elimination of SCH629144 (110% increase in AUC). The precise mechanism of this interaction is not clear.
- Data provided suggest that the effects of AKR inhibitors (NSAIDs diflunisal or ibuprofen) are unlikely to be of any clinical relevance if co-administered with boceprevir.
- Efavirenz (a CYP3A4 inducer) decreased Cmax, Cmin and AUCtau of boceprevir (800 mg t.i.d.) statistically significant by 8, 44 and 19%, respectively.
- Tenofovir did not affect the pharmacokinetics of boceprevir. A small but statistically significant increase in SCH629144 Cmax and AUCtau of about 10% was observed.
- Boceprevir pharmacokinetics (200-400 mg t.i.d.) were not affected by peg-interferon-α (1.5 µg/kg).

Boceprevir effects n the pharmacokinetics concomitantly administered drugs:

- No effects on the pharmacokinetic parameters of diflusinal were observed when co-administered with boceprevir
- Concomitant administration of boceprevir with midazolam increased the Cmax and AUC of midazolam by 177 and 430%,
- Boceprevir coadministration increased the Cmax and AUC of efavirenz by 11 and 20%, respectively, which was statistically significant
- Boceprevir increased the Cmax and AUC of tenofovir (P-gp substrate, and renal hOAT1 and hOAT3 substrate)by 32 and 5%, respectivelyNo dose adjustments is required for the co-administration with tenofovir.
- Boceprevir (800 mg t.i.d.) caused a statistically significant increase of Cmax and AUC of drospirenone, by 57 and 99%, respectively, after administration of drospirenone/ethinyl estradiol 3mg/0.02 mg (Yaz) o.d. For ethinyl estradiol no effect on Cmax was observed; however AUC decreased 24%. Alternative contraceptives should be considered for these patients.
- Peg-interferon-α pharmacokinetics (AUC) were unaffected by boceprevir (200-400 mg t.i.d).

Pharmacokinetics using human biomaterials

2.4.3. Pharmacodynamics

The pharmacodynamic properties of boceprevir were investigated in isolates obtained from HCV patients enrolled into the phase I and III studies. In the following these data are presented along with a brief summary of virological data. In addition, information from the QTc study in healthy subjects and the integrated PK/PD analyses is described.

The mechanism of action underlying the antiviral activity, and aspects of drug resistance are also discussed in the section"Non- Clinical aspects "Pharmacodynamics".

Mechanism of action

The mechanism of action involves boceprevir covalently, yet reversibly, binding to the NS3 protease active site serine (Ser139) through a ketoamide functional group. Upon binding to the NS3 protease active site serine, boceprevir prevents the HCV protease from cleaving the intermediate viral polyprotein into functional units, thereby effectively inhibiting HCV replication.

Primary and secondary pharmacology

The inhibitory concentrations producing a 50% response (IC50) and a 90% response (IC90) for suppression of the HCV replicon (genotype 1b) in a 72-hour culture were approximately 200 nM and 400 nM. In 50% human serum, the replicon IC50 value for boceprevir was 500 nM.

In Phase Ib dose finding combination study of boceprevir administered in combination with PegIFN there appears to be a dose response relation ship: higher total daily doses seem to result in higher response rates.

Effect on the QTc interval

A Phase 1, four-way crossover, placebo and positive (moxifloxacin) controlled QTc study to evaluate QT/QTc interval prolongation and proarrhythmic potential for boceprevir at a clinically therapeutic dose (800 mg TID) and at a supratherapeutic dose (1200 mg TID) was conducted in healthy adult subjects. Neither the therapeutic nor supratheraputic doses of boceprevir were associated with clinically relevant effects upon cardiac conduction. Nevertheless a signal (see non clinical discussion) on electrophysiological data warrants attention of physicians in patients at risk of QT prolongation (hypokalemia, long congenital QT).

Pharmacokinetic/pharmacodynamic (PK/PD) relationship

An analysis from phase II data of the total daily dose versus the maximum viral load drop with standard deviation was performed. In general for monotherapy, total daily dose was a predictor of response.

A concentration-response analysis was performed. The results indicated that maximal HCV-RNA drop correlated best (larger correlation coefficient value, R=0.653) with trough concentrations of boceprevir; a modestly less robust relationship was noted for Cmax (R=0.466) and AUC (R=0.511) of boceprevir

A PK/PD quartile analysis was performed to evaluate the relationships between mean boceprevir Cmin at Week 5 (corresponding to 4 weeks of boceprevir treatment) for each Cmin quartile and its relation to the effect of boceprevir+peg2b+RBV combination therapy as measured by median log10 HCV-RNA change at Week 5 or median of maximum log10 HCV-RNA decline during Week 5. There was a consistent moderate positive correlation between boceprevir Cmin and reduction in viral load.

In the Phase 3 PK/PD analysis, potential relationships between boceprevir and RBV PK parameter values and selected treatment outcomes (such as SVR and viral response at week 8, 12, 24 and end of treatment) were quantitatively explored using multivariate logistic regression. No clear associations of viral response with boceprevir PK were seen, including the primary endpoint of SVR

PK/PD quartile analysis was performed to evaluate the relationships between mean boceprevir Cmin at Week 5 (corresponding to 4 weeks of boceprevir treatment) for each Cmin quartile and its corresponding responsiveness to combination treatment as measured by median log10 HCV-RNA change at Week 5 or median of maximum log10 HCV-RNA decline during Week 5.

There was a consistent moderate positive correlation between boceprevir Cmin and reduction in viral load. Subjects who had a lower Cmin at Week 5 (mean Cmin=34.9 ng/mL in the lowest Cmin quartile) had a smaller viral load reduction (median log10 HCV-RNA change from baseline of -1.46), while

subjects who had higher Cmin at Week 5 (mean Cmin=193 ng/mL in the highest Cmin quartile) had greater viral load reduction (median log10 HCV-RNA change from baseline of -3.84)

Pharmacokinetic interactions with other medicinal products or substances

As stated above, nonclinical data indicate that boceprevir is metabolized primarily by aldoketoreductase (AKR) and to a lesser extent by via CYP3A4/5-mediated oxidation.

Among the CYP3A4/5 substrates, no events suggesting increased exposure to the substrates were observed. While subjects exposed to CYP3A4/5 inhibitors such as the macrolides did experience increase rates of gastrointestinal events compared those not receiving macrolides, so did subjects receiving standard of care in addition to a macrolide. There was no evidence to suggest that the theoretical changes in exposure for drugs that share CYP3A4/5 metabolism manifested as clinically important events.

Genetic differences in Pharmacodynamic response

A genetic variant near the gene encoding interferon-lambda-3 (*IL28B* rs12979860, a C to T change) is a strong predictor of response to peginterferon alfa-2b/ribavirin. This genotypic marker was not identified at the time of the initiation of the phase III trials and could only be studied retrospectively in patients that specifically gave their informed consent (see Clinical Efficacy section of this report). More recently, a genetic variant leading to inosine triphosphatase (ITPA) deficiency has been associated with risk of ribavirin-related anaemia during PR therapy. A retrospective subgroup analysis has been carried out and is presented in the Clinical Efficacy section of this report.

2.4.4. Discussion on clinical pharmacology

The dose rationale for boceprevir is mainly based upon the clinical outcome. The protein-binding unadjusted IC50 value for the hepatitis C virus genotype 1b in the replicon system is 200 ng/ml, and would thus be higher than the free boceprevir trough values. However, boceprevir is distributed to the liver, the target organ, and concentrations at the primary site of action may be higher. Applying a higher dose is considered not useful, taking into account the less than dose proportional increase in exposure.

A t.i.d. dose scheme is to be applied. With respect to adherence to dosing interval, subjects in all three clinical key studies providing efficacy and safety data were instructed to dose boceprevir every 7 – 9 h.

Maximal boceprevir peak plasma concentrations after oral administration are observed after about 1 - 2 h. Boceprevir absorption increased by up to 60% at the 800 mg three times daily dose when administered with a meal, relative to the fasting state. Consequently the SmPC states that the capsule should be taken with food and information is provided that food increases AUC up to 60%, regardless of food type and timing. Pharmacokinetics after t.i.d. dosing over the 200 – 800 mg dose range increases dose proportionally. At higher doses (i.e. 1200 mg t.i.d.) a less than dose proportional increase in exposure is clearly observed

In subjects with various degrees of stable chronic hepatic impairment, there was a trend toward an increase in the mean boceprevir Cmax and AUC with decreasing liver function, particularly in the group with severe hepatic impairment. The boceprevir ratio estimates for mild, moderate and severe hepatic

impaired subjects, compared with healthy subjects, were 91%, 114% and 149% for AUC0-t and 100%, 107% and 161% for Cmax, respectively.

The applicant originally proposed that boceprevir be contraindicated in patients with a Child-Pugh score > 6 i.e with moderate and severe hepatic impairment. However, this contra-indication seems based on the need to co-administer boceprevir with pegylated IFN and ribavirin, which are contraindicated for use in patients with moderate and severe hepatic impairment, rather than justified by the impact of hepatic impairment on the boceprevir PK parameters. Overall, the limited impact of moderate hepatic impairment on boceprevir PK parameters does not by itself warrant a strict contraindication of boceprevir.

For patients with renal impairment no dose adjustment is advised, which is acceptable considering the almost completely non-renal elimination of boceprevir and the lack of an effect on pharmacokinetics in patients with end stage renal disease on haemodialysis.

No data are available for children/adolescents. The SmPC states that safety, efficacy and pharmacokinetics of boceprevir in children < 18 years have not yet been established. Regarding gender, weight, race and older age, no precautions are necessary based upon population pharmacokinetic analysis.

The effect of AKR inhibitors (NSAIDs diflunisal or ibuprofen) seems moderate on boceprevir concentrations. However, with ibuprofen, boceprevir plasma exposure is not altered in a significant manner whereas with diflunisal, boceprevir plasma exposures tend to increase. The Applicant was asked to discuss these conflicting results and their clinical relevance. The limitations of the investigations were acknowledged and overall, given the limited use of AKR inhibitors in clinical practice, no mention of this is made in the SmPC.

The combination of boceprevir 400 mg TID with ritonavir 100 mg BID has been studied in comparison with boceprevir 400 mg TID. No significant impact is observed. On the basis of these study results the applicant had considered that interaction studies with boosted PI were not required. However, in order to clarify the net effect of ritonavir in combination with boosted protease inhibitors on boceprevir plasma exposure, interaction studies with boosted PIs were deemed necessary .tThe Applicant has committed to perform clinical studies with boosted protease inhibitors, including atazanavir/ritonavir, darunavir/ritonavir and lopinavir /ritonavir.

Ketoconazole co-administration leads to a two-fold increase in boceprevir AUC. The Applicant was asked to discuss the clinical relevance of such PK variations. There is no clear relationship between Cmin and boceprevir adverse events. However the CHMP considers that the 2-fold increase in boceprevir plasma exposure measured with AUC is relevant and a warning is inserted in the SmPC concerning co-administration with ketoconazole. In general, an increase in boceprevir exposure would be anticipated with other concomitant azol antifungals. As such the warning is extended to other drugs of this class, including itraconazole, voriconazole and posaconazole.

Furthermore, since the CYP3A4 pathway is marginally involved in boceprevir metabolism, the mechanism behind this increase needs to be further addressed, and the respective role of P-gp and CYP3A4 inhibition should be precisely assessed. This may be of importance so as to define which inhibitors may be of concern: CYP3A4 or P-gp inhibitors. The applicant has committed to further substantiate the interaction profile of boceprevir with studies for methadone, simvastatin, atorvastatin, immunosuppressive drugs used post transplantation (ciclosporin and tacrolimus) that are CYP3A

substrates and drugs which are P-gp substrates (such as digoxin, dabigatran) or inhibitors (such as ciclosporin).

Tenofovir was not found to have a significant effect on boceprevir concentrations, and vice versa.

Efavirenz, due to its drug-metabolizing enzyme inducing properties, decreased AUC of boceprevir by 19% and Cmin by 44%. These results, together with the lack of a complete understanding of the elimination pathways of boceprevir, warrant alerting the attention of physicians in case of co-administration although it is admittedthat efavirenz is a moderate rather than a potent CYP3A4 inducer as compared to rifampicin, phenobarbital or carbamazepine.

Midazolam AUC increased 5-fold after the addition of boceprevir. Therefore, the combination of boceprevir with midazolam is contraindicated and caution recommended with midazolam IV.

The effect of boceprevir on oral contraceptive drugs is complex. Boceprevir increased drospirenone exposure substantially. Drospirenone metabolism only involves CYP3A4 to a minor extent. Therefore, the observed interaction with boceprevir is unexpected. Boceprevir may affect other metabolic pathways, however it remains unclear which ones. A study is being conducted with boceprevir and a combination oral contraceptive containing norethindrone and ethinylestradiol, to identify if the effect on drosperinone is relevant also for norethindrone. The results of the study will be provided to the CHMP. Attention of physicians will be alerted on the need for alternative contraceptives.

No significant effects on the pharmacokinetics of the pegylated interferons were observed with boceprevir.

Concerning clarithromycin, the design of the study does not allow drawing any conclusions on the impact of co-administration.

2.4.5. Conclusions on clinical pharmacology

Boceprevir is the first representative of protease inhibitor in the HCV treatment. Boceprevir inhibits NS3 protease at low nanomolar concentrations. The inhibitory concentration (IC50 and IC90) values for boceprevir in a HCV genotype 1b replicon assay were approximately 200 nM (n=25) and 400 nM (n=25), respectively. In 50% human serum, the replicon IC50 value for boceprevir was 500 nM.

The applicant has committed to further substantiate the interaction profile of boceprevir with additional interaction studies (with boosted HIV protease inhibitors notably of importance in the context of HIV-HCV co-infection).

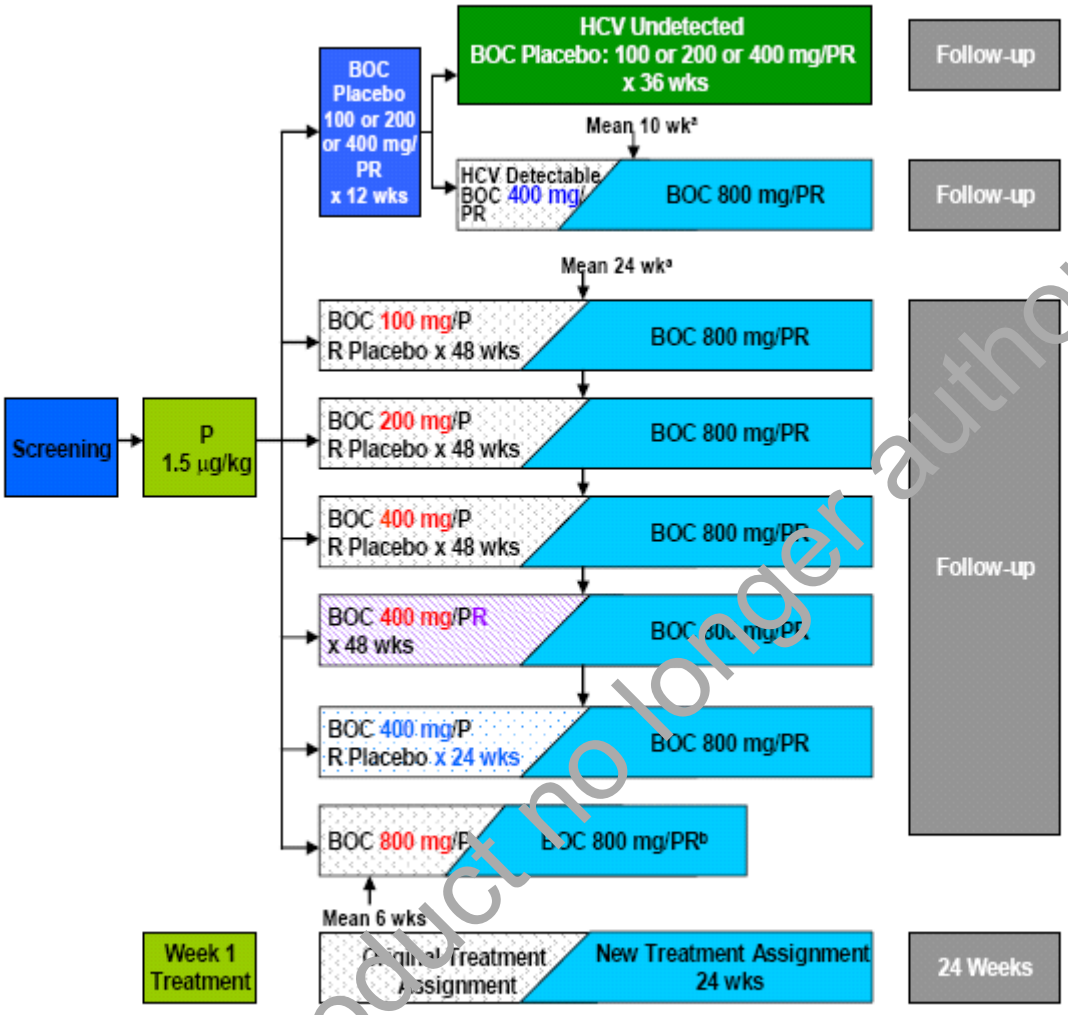
2.5. Clinical efficacy

2.5.1. Dose response studies

There were two phase IIb studies. 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:

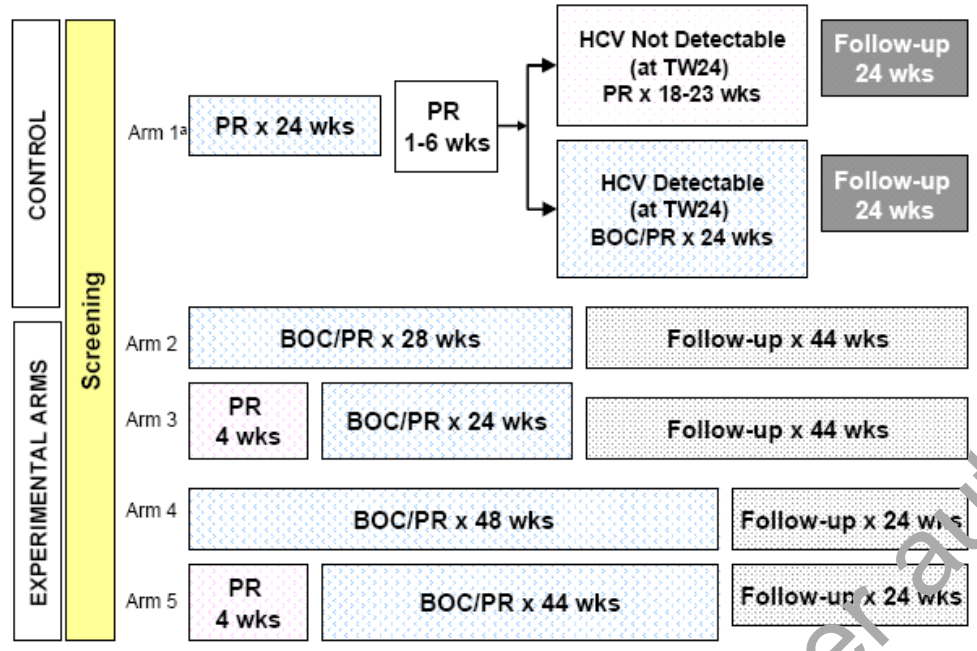
- ribavirin is needed to prevent viral breakthrough with resistant variants

- 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.

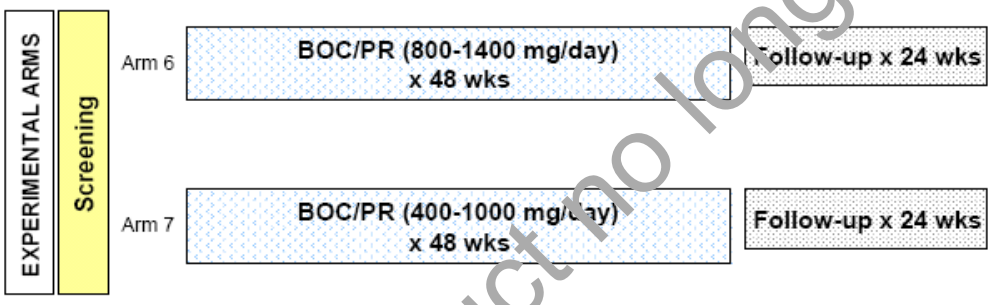
- SPRINT-1 was an open-label, randomized safety and efficacy trial in adult, treatment-naïve CHC subjects with genotype 1 infection. The study compared standard-of-care PEG2b (1.5 µg/kg) plus ribavirin (800 to 1400 mg/day) for 48 weeks to five treatment strategies containing boceprevir with only one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

The study design was as follows:

Part 1 Study Design Diagram

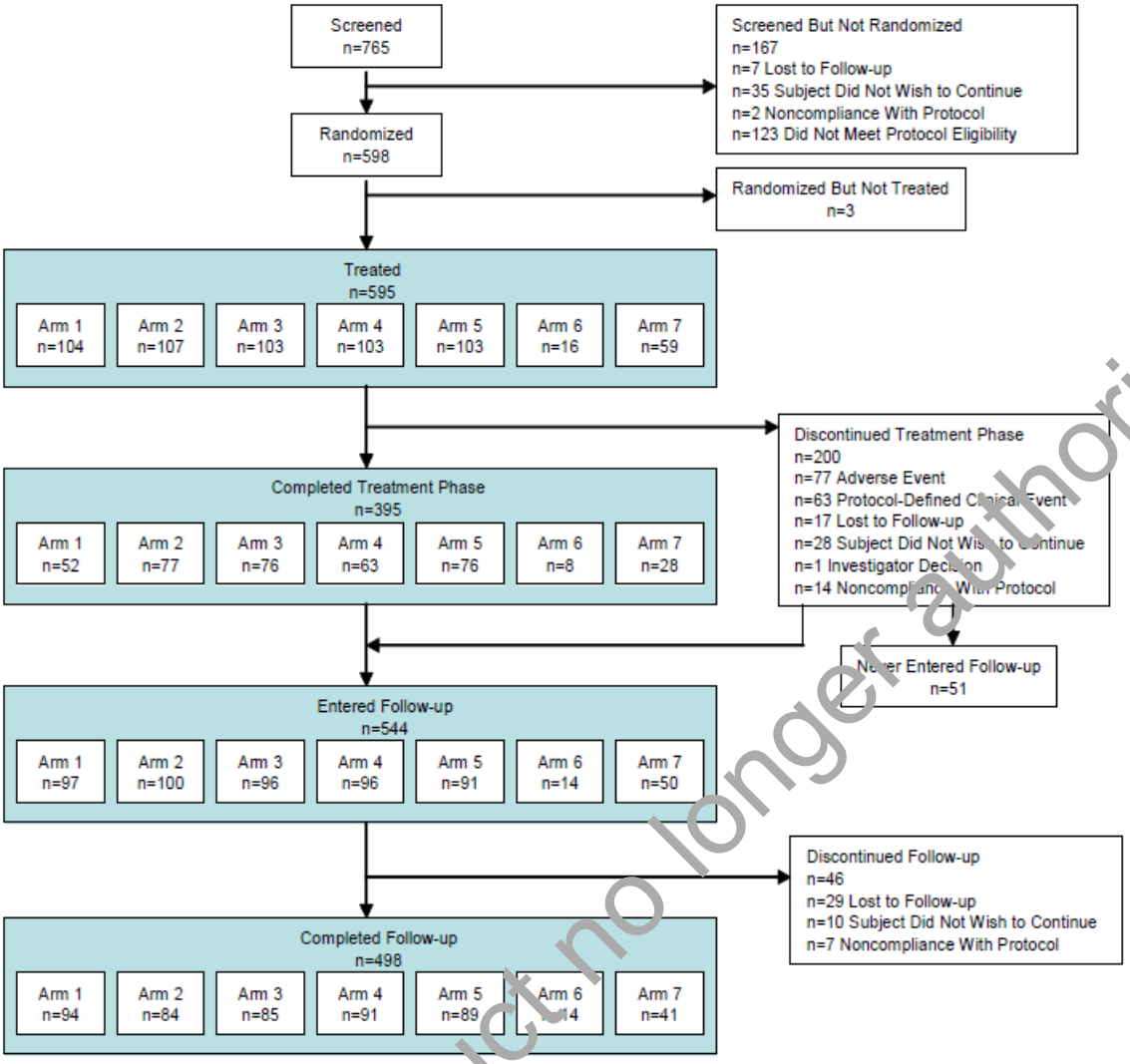


Part 2 Study Design Diagram



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 $\log_{10}$ 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 4: 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% versus 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 5: 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 6: 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.

2.5.2. 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: Duration of Run-in phase: Duration of Extension phase:	Approximately 22 months not applicable 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.
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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=52	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
Relaps[f] 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 Δ	--	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 RGT 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 24 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
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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 (31.2)	114 (70.4)	124 (77.0)
SVR, n (%)	17 (21.2)	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 centers 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.

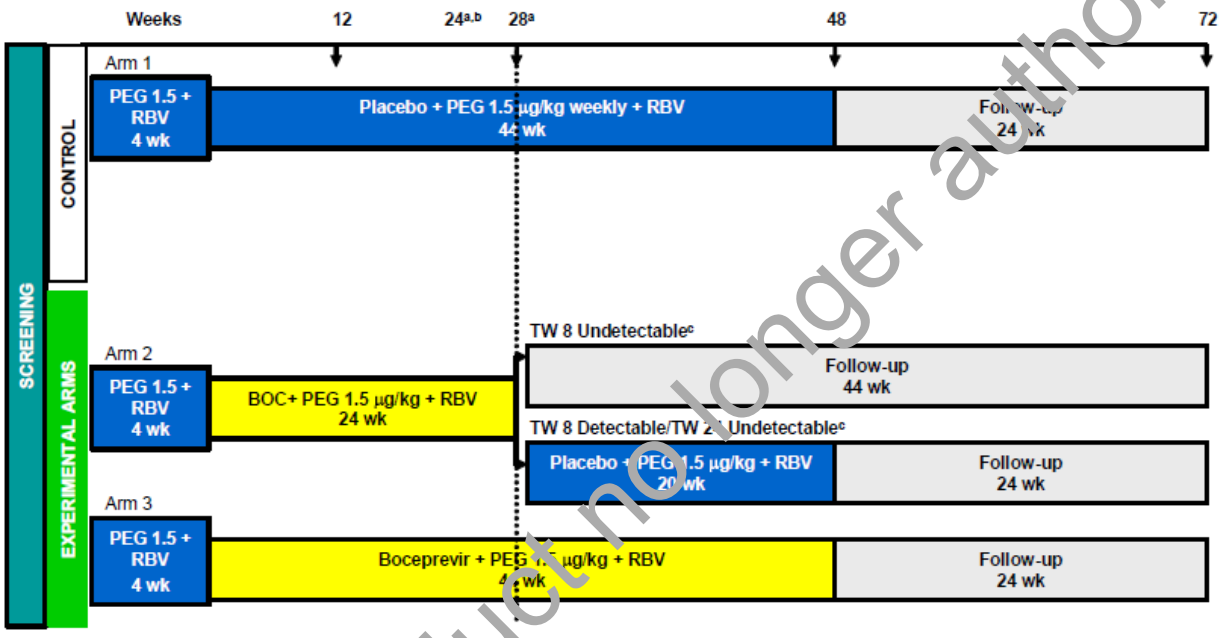
• **Arm 3** (BOC/PR48): PR for 4 weeks followed by boceprevir + PEG2b 1.5 µg/kg + RBV (weight-based dose, 600 to 1400 mg PO daily) for 44 weeks with 24 weeks posttreatment follow-up.

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)

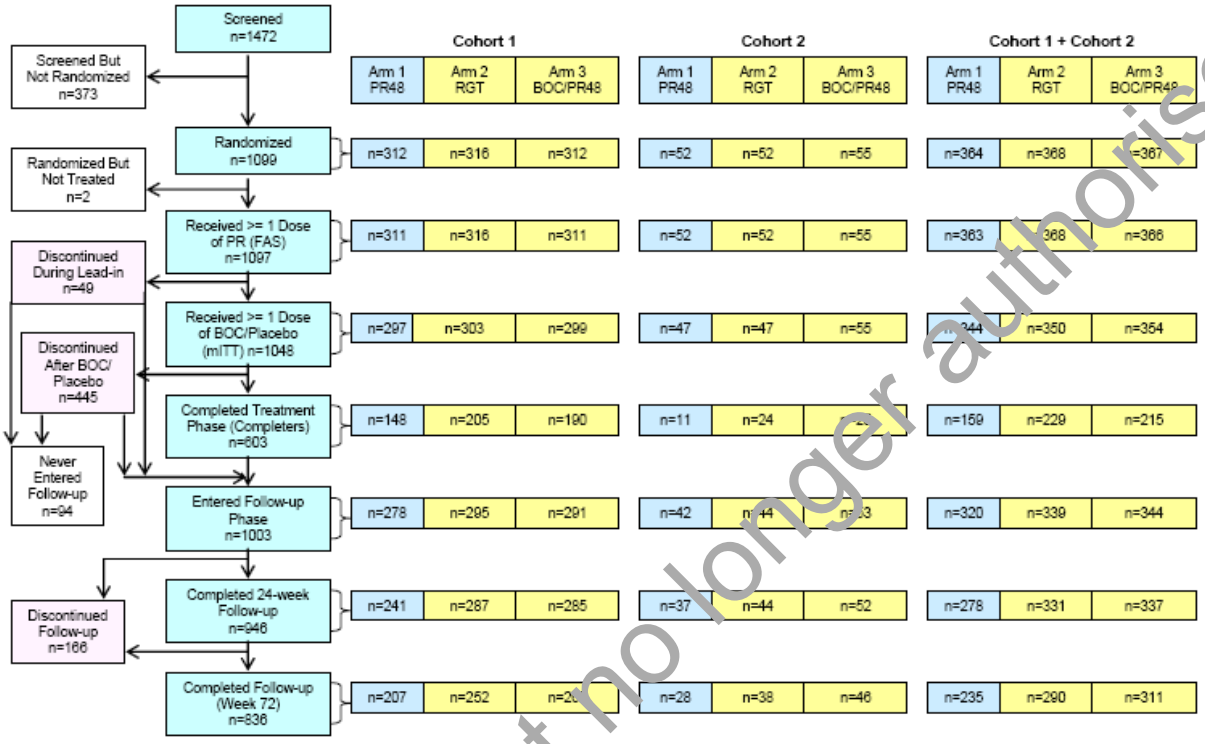
This was a double-blind study in which the sponsor, investigator, study personnel, and study participants were to be blinded with respect to boceprevir treatment. The randomization schedule for blinding of treatments was maintained by the sponsor, provided to the IVRS, and disclosed only after study 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 7: 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)	51.3 (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 (5.1)	29.8 (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	15	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	964 (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], n (%)									
1	177 (14)	22 (10)	199 (14)	31 (10)	7 (10)	38 (10)	146 (16)	15 (9)	161 (15)
1a	560 (45)	135 (60)	695 (47)	117 (38)	33 (49)	150 (40)	443 (47)	102 (64)	545 (50)
1b	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 8: 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 - 52.3
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%)	170 (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 36% 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 9: 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=55	*%*
SVR [a]	125	*40.2*	211	*66.8*	213	*68.5*	12	*23.1*	22	*42.3*	29	*52.7*
- Δ SVR			**26,6**		**28,3**				**19,2**		**29,7**	
- 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	*12.0*	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 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.

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 10: 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)	48/54 (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 11: 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(191 /303)
	<=400,000	80.8(21 /26)	78.1(25 /32)	88.0(/25)
	>400,000	34.4(116 /337)	61.9(208 /336)	64.5(/331)
Sex	Male	35.0(72 /206)	65.1(149 /229)	65.(/221)
	Female	41.4(65 /157)	60.4(84 /139)	66.(/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(/12)	57.1(4 /7)
Baseline Weight	<75 kg	45.9(67 /146)	62.(/131)	63.4(83 /131)
	>=75 kg	32.3(70 /217)	(/237)	67.7(159 /235)
BMI	<=25	46.5(60 /129)	58.4(59 /101)	67.5(83 /123)
	25-30	33.1(49 /148)	74.6(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(/27)	54.5(18 /33)	52.6(20 /38)
	>150,000 IU/mL	38.4(/29 /3)	64.2(215 /335)	67.7(222 /328)
Fibrosis[c]	0	47. /17)	85.0(17 /20)	60.0(6 /10)
	1	39.0(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[c] 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)

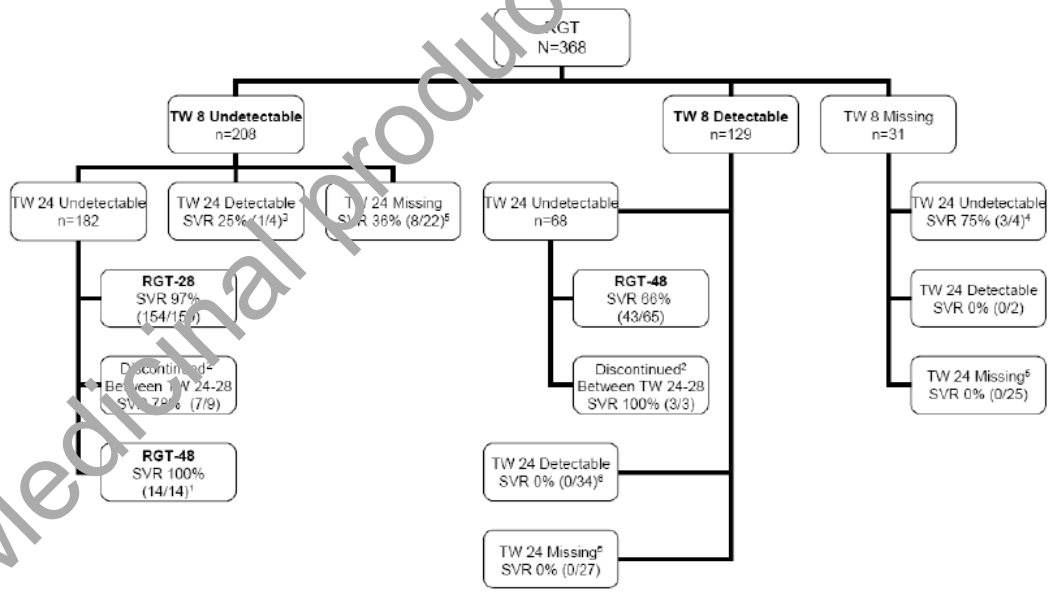
c Liver histology based on the central pathologist's reading.
d HCV subtype as determined by TRUGENE HCV 5NC assay was used for subject stratification.
e HCV subtype as determined by Virco assay based on sequencing of domain p329bp in the NS5B polymerase gene; all samples unavailable for retesting were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

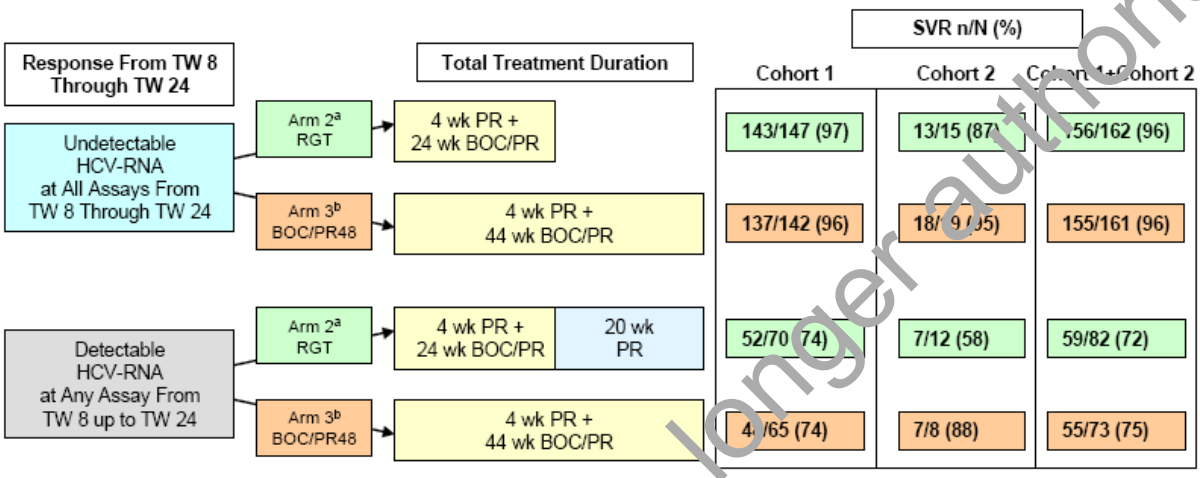
Comparison of outcomes in early and late responders in the RGT and BOC/PR48 arms

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 12: 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)	-
Relapse	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 13)

Table 13:

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.

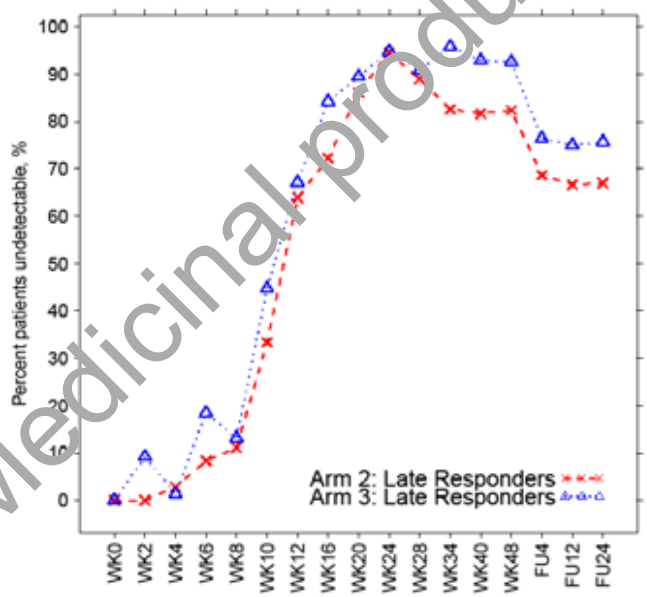
Table 14: Sustained Virologic Response in Late Responders (IVRS), P05217

	RGT	BOC/PR48	
All Subjects			
SVR, % (n/N)	*66% (45/68)	75.3 (55 /73)	-9.2[-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 15: 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 (1:2:2 ratio)

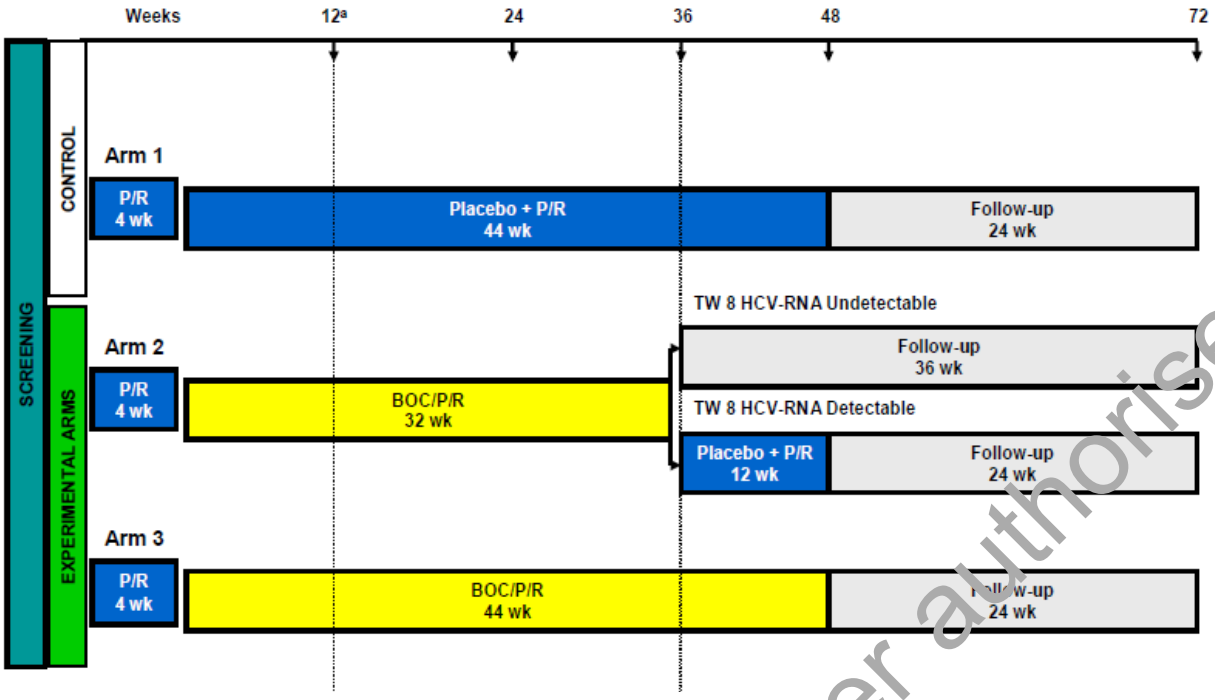
Control
Arm 1 (PR48): PR= standard of care therapy consisting of Peginterferon alfa-2b PEG2b (1.5 µg/kg sc once weekly) plus ribavirin (weight-based dose 600 to 1400 mg) po daily) for 4 weeks followed by placebo (matched to boceprevir) + PR for 44 weeks with 24 weeks post-treatment follow-up.

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

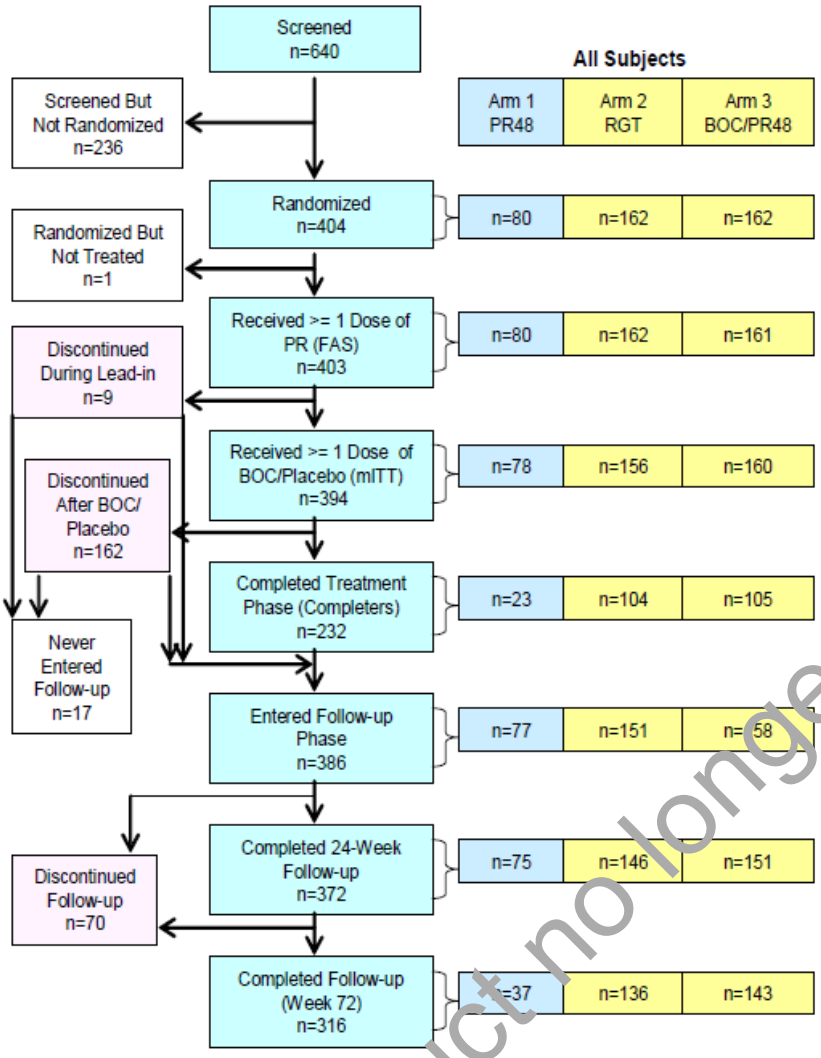


Table 16: Demographics and baseline characteristics

	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	29.3
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)	94 (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, 31 of whom being exposed to BOC). A large majority of patients had high viral load >800 000 UI/ml (82%) 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 17:

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 18:

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*	36	*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	*100*	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 (BT): 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 19: 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)	3/5 (60.0)	5/7 (71.4)
40 - 64 y	16/70 (22.9)	84/146 (57.5)	95/146 (65.1)
≥65 y	1/8 (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	4/17 (23.5)	20/42 (47.6)	34/44 (77.3)
≥75 kg	13/63 (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)
Statin Use			
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)

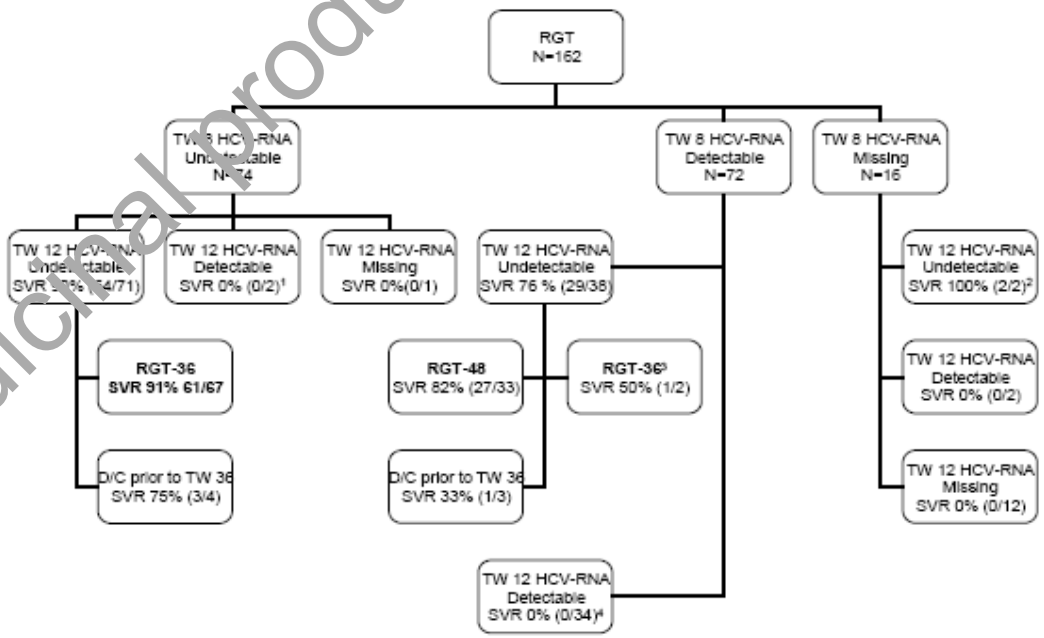
Baseline Viral Load (IU/mL)			
≤800,000	6/15 (40.0)	12/15 (80.0)	16/20 (80.0)
>800,000	11/65 (16.9)	83/147 (56.5)	91/141 (64.5)
≤400,000	3/6 (50.0)	7/7 (100)	5/7 (71.4)
>400,000	14/74 (18.9)	88/155 (56.8)	102/154 (66.2)

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)	47/77 (61.0)
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)	44/66 (66.7)	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			
0/1/2	14/61 (23.0)	77/117 (65.8)	81/119 (68.1)
3/4	2/15 (13.3)	14/32 (43.8)	21/31 (67.7)
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: 20: 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 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 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 21: 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*.

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 (0/48)
	F3/4	14.3 (1/7)	0 (0/18)
	Missing	20.0 (1/5))	0 (0/5)

In the subgroup of patients that were late responders and reached 36 weeks fo 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 pharmacogenomics (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 22 below.

Table 22: 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

[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.

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 23: 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 a planned study to be performed by the applicant. A protocol is to be submitted by the applicant for validation by the CHMP before the study starts.
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.

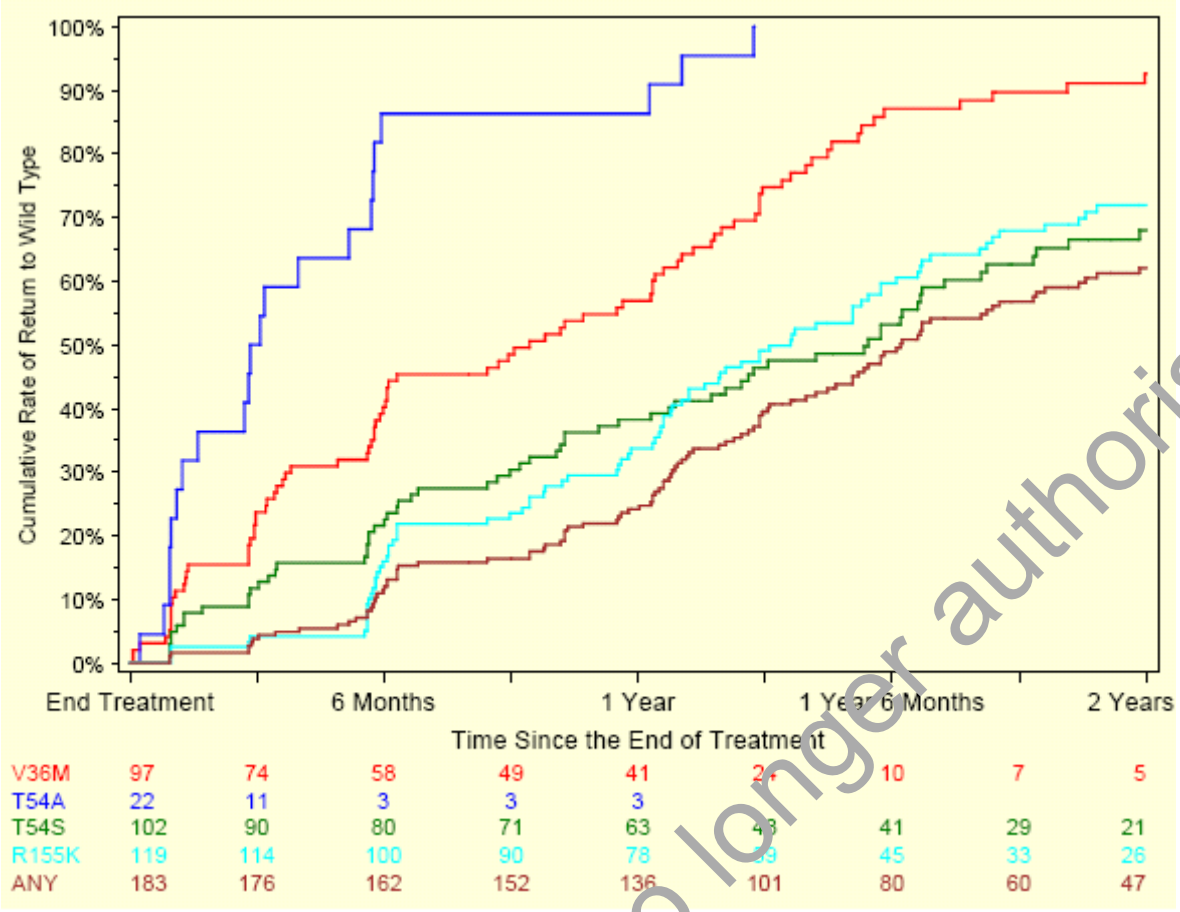


Figure: Kaplan-Meier for the Rate of Return to Wild Type

P05685: A Phase 3 Efficacy and Safety Study of Boceprevir in Combination With PEG-α2a and Ribavirin in Subjects with Chronic Hepatitis C Genotype 1 Who Failed Prior Treatment With Peginterferon/Ribavirin.

P05685 was conducted to confirm the efficacy benefits of boceprevir when administered in combination with the other marketed pegylated interferon product, peginterferon alfa-2a (Pegasys) and ribavirin (PEG2a/R).

Protocol P05685 was a multi-center, double-blind, randomized (in a 1:2 ratio), placebo-controlled Phase 3 study in adult patients (≥18 years of age) with CHC genotype 1 infection who had failed previous PR treatment. Eligibility criteria were similar to RESPOND-2 (P05101). Randomized treatment assignment was stratified based on the patient's previous response to therapy (partial responder or relapser) and on HCV genotype (1a or 1b infection) as determined by the TRUGENE assay. Patients randomized to PEG2a/R received 48 weeks of peginterferon alfa-2a 180 mcg administered subcutaneously weekly (labeled dosage of Pegasys) and oral ribavirin using weight-based dosing from 1000 to 1200 mg/day divided BID, plus placebo TID starting at TW 5. The dosing regimen for peginterferon alfa-2a/ribavirin is the regimen listed in the relevant product circulars.

Patients randomized to BOC/PEG2a/R received peginterferon and ribavirin for a 4-week lead-in period, followed by the addition of oral boceprevir 800 mg TID for 44 weeks.

Treatment duration in this study was the same as in the BOC/PR48 arm of RESPOND-2. This regimen was chosen to obtain the maximum duration of therapy for the assessment of safety. HCV-RNA levels were tested using the same assay as in the RESPOND-2 study: the TaqMan 2.0 assay (Roche Diagnostics) with a lower limit of detection of 9.3 IU/mL and limit of quantitation of 25 IU/mL. In both treatment arms, patients with detectable HCV-RNA at TW 12 were discontinued for futility. These patients were considered failures in the efficacy analysis. The primary efficacy endpoint was SVR, defined as undetectable HCV-RNA at follow-up week 24, in all randomized patients receiving at least one dose of study medication (FAS).

Efficacy

Sixty-seven patients were randomized to the PEG2a/R arm and 134 to the BOC/PEG2a/R arm. SVR rates were 21% in the PEG2a/R arm and 64% BOC/PEG2a/R arm . SVR rates were nearly similar to the SVR rates observed in the PR48 control and BOC/PR48 arms of RESPOND-2 (21% and 66%, respectively).

Table 24: Sustained Virologic Responses (SVR) with Boceprevir Added to Peginterferon Alfa-2a Plus Ribavirin, P05685

Protocol No. P05685

	FAS		mITT	
	PEG2a/R n=67	BOC/PEG2a/R n=134	PEG2a/R n=67	BOC/PEG2a/R n=130
SVR, n (%)	14 (20.9)	86 (64.2)	14 (20.9)	86 (66.2)
Δ SVR (%)	-	43.3	-	45.3
95% CI for Δ	-	30.6, 56.0	-	32.6, 57.9
P-value	-	<0.0001	-	<0.0001
EOT (Undetectable HCV-RNA), n (%)	28 (41.8)	99 (73.9)	28 (41.8)	99 (76.2)
Relapse, n/N (%)	7/21 (33.3)	11/95 (11.6)	7/21 (33.3)	11/95 (11.6)

Cross-Study Comparison of Sustained Virologic Response and Relapse Rates:

Table 25: P05101 (RESPOND-2) and P05685

	P05685		P05101	
	Arm 1 PEG-α2a/R48[a] n=67	Arm 2 BOC/PEG-α2a/R48[a] n=134	Arm 1 PR48[b] n=80	Arm 3 BOC/PR48[b] n=161
SVR[c], n (%)	14 (20.9)	86 (64.2)	17 (21.3)	107 (66.5)
95% CI	(11, 31)	(56, 72)	(12, 30)	(59, 74)
P value[d]	--	<0.0001	--	<0.0001
Relapse[e], n/N (%)	7/21 (33.3)	11/95 (11.6)	8/25 (32.0)	14/121 (11.6)
95% CI	(13, 54)	(5, 18)	(14, 50)	(6, 17)
P value[f]	--	0.013	--	0.009

[a] Arm 1 (PEG-α2a/R48) = PEG-α2a + RBV for 48 weeks.
Arm 2 (BOC/PEG-α2a/R48) = PEG-α2a/R lead-in for 4 weeks, then BOC/PEG2a/R for 32 weeks.

[b] Arm 1 (PR48) = PEG-α2b + RBV for 48 weeks.
Arm 3 (BOC/PR48) = PR lead-in for 4 weeks, then BOC/PR for 44 weeks.

[c] SVR (Sustained Virologic Response): The last available value in the period at or after FW 24. If there is no such value, the FW 12 value was carried forward. SVR_{24} rates (SVR with "missing=failure" approach) were nearly identical (P05685:

11/67 [16.4%] Control, 84/134 [62.7%] BOC/PEG2a/R; P05101: 17/80 [21.3%] PR Control, 106/161 [65.8%] BOC/PR48.)

[d] Versus PR control arm. P values were calculated using the two-sided Cochran-Mantel Haenszel (CMH) Chi-square test adjusted for the baseline stratification factors: previous treatment response (nonresponder vs relapser) and genotype (1a vs 1b).

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

[f] Versus PR control arm. P values were calculated using the two-sided Chi-square test.

5.1.1. Discussion on clinical efficacy

The applicant conducted two pivotal phase III studies in 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 applicant 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, the applicant proposes 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 applicant 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. The applicant added a specific site amendment 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<0.0001) 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 CHMP requested the applicant to further address this issue. The applicant 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. As such the applicant as committed to carry out a prospective study in this regard. The protocol will be provided in July 2011 and final results are expected by May 2014. 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 applicant 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 applicant was asked to further discuss this issue and has proposed the following futility rule that would be applicable for both treatment naïve and prior treatment failure patients: 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 applicant 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 applicant highlights that there is a close correlation between the historical week 12 response to 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 34%, 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 refected in section 4.4 (the section 4.1 will cross-refer to this statement) to reflect the limitations of the data set and that the *optimal management of null responders remains to be established.*

Co-administration with pegylated interferon alfa 2a

Both Phase III SPRINT 2 and RESPOND 2 studies were conducted with PegIFN alpha 2b
The applicant provided results from a newly submitted double blind multi center study (P05685) with boceprevir combined with Peg-IFN alfa 2a+ribavirin vs Peg-IFN alfa 2a+ribavirin in subjects with HCV genotype 1 who failed prior treatment with PEG/RBV (overall approx 200 patients were included with a ratio 2:1).

Overall the efficacy results are consistent with the clinical data derived from the study P05101 and adequately substantiate that boceprevir could be used either with Peg-IFN alfa 2b (main data) or Peg-IFN 2a. Moreover, in theory, given the respective pharmacokinetics of alfa 2a and 2b, the extrapolation from the clinical data with alfa 2b to alfa 2a is more conservative than the contrary. (see also safety part as regards the combination with alfa 2 a as compared to alfa 2b).

Assessment of paediatric data on clinical efficacy

No clinical studies in paediatric patients have been carried out.

5.1.2. 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 limitation 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. The applicant has committed to carry out a prospective study 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.

The CHMP questioned the co-administration of boceprevir with pegylated interferon alfa 2a given that the pivotal phase III trials used instead peginterferon alfa 2b. The applicant provided further data and adequately demonstrated that efficacy results are consistent when boceprevir is used in combination with Peg-IFN 2a . Overall the indication allows for use in is combined with both peginterferons, alfa 2b and alfa 2a (see also safety part as regards the combination with alfa 2 a as compared to alfa 2b)

5.2. 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 26 below.

Table 26: Distribution of Treatment Duration By Dose of Boceprevir in the Phase 2 Through 3

	Number (%) Subjects			
	Boceprevir Daily Dose[a] (mg)			
Treatment Duration[b]	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	1
Maximum	206	215	207	396

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 27: Distribution of Treatment Duration in the Key Studies:

	Number (%) of Subjects					
	Treatment Naïve P03523/P05216		PEG/PR Treatment Failure P05101		All Subjects	
Treatment Duration[b]	PR[a] n=467	BOC/PR n=1225	PR n=80	BOC/PR n=323	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 (85)	974 (80)	25 (31)	238 (74)	424 (78)	1212 (78)
TW 48	214 (46)	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 27). 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 28: 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-naïve 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 29: 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)	400 (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)	75 (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)	47 (15)	108 (20)	302 (20)
Insomnia	154 (33)	403 (33)	16 (20)	93 (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)	100 (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 30: 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.

Response guided therapy in the phase III Studies P05216 and P05101

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/m2). 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 1 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 ¾) 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 29 below.

Table 31: 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%	1%
Use of EPO	30%	47%	21%	46%
Dysgueusia	25%	39%	11%	45%
Neutropenia as AE	18%	**31%**	10%	14%
Neutrophils<750/mm3 Grade3-4	18%	**28%**	9%	20%
Neutrophils<500/mm3 Grade4	3%	**14%**	1%	7%
Thrombocytopenia as AE	6%	7%	0%	6%
Platelets < 50 (Grade3)	7%	10%	0	5%
Platelets <25 (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 32: 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)	11	(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

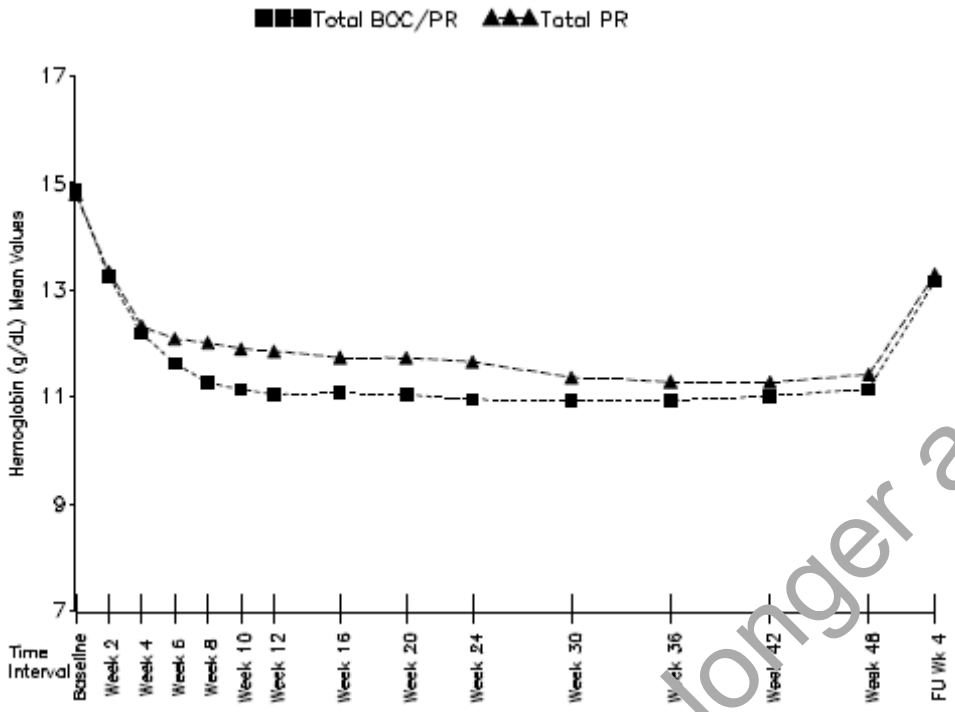
Subjects with Hgb values of <10 g/dL were considered anaemic whether or not the investigator assigned an AE of anaemia. The proportion of subjects reporting anaemia /hemolytic anaemia was higher in the boceprevir arms (49%) compared with the control arms (29%). Dose modifications due to anaemia/hemolytic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

Table 33: 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 34:

	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)	151 (20)	118 (15)
Respiratory, Thoracic, and Mediastinal Disorders	52 (34)	78 (20)	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.

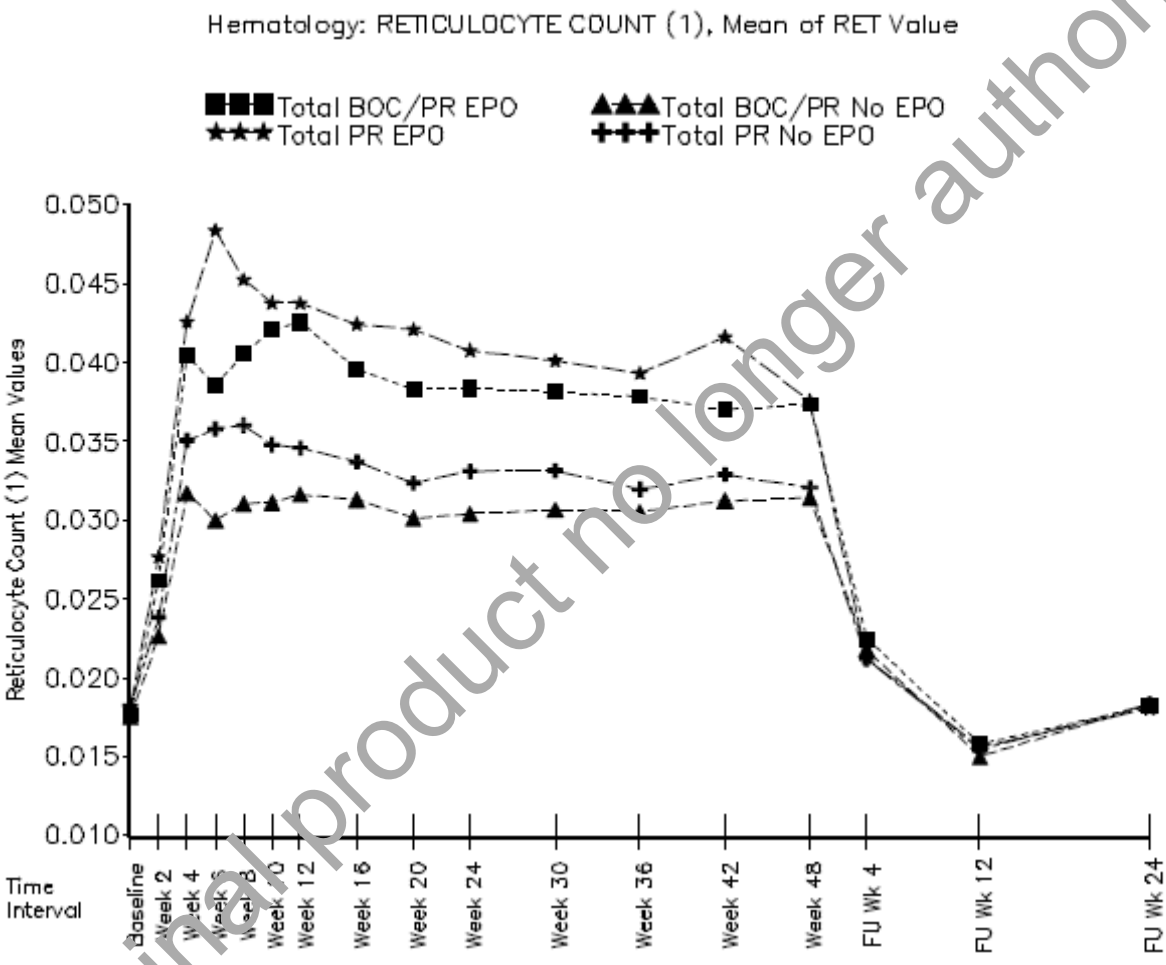
Medically important AEs potentially attributable to the use of erythropoietin, such as cardiovascular events, thrombotic or thromboembolic events were evaluated. These events occurred with similar frequency in subjects who received EPO and those who did not (4% and 6%, respectively).

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 arm3 (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 35 below

Table 35:

	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 36:

	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/mm3 Grade3-4	18%	**28%**	9%	20%
Neutrophils<500/mm3 Grade4	3%	**14%**	4%	7%
Thrombocytopenia as AE	6%	7%	0%	6%
Platelets < 50 (Grade3)	7%	10%	0	5%
Platelets <25 (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 37: 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=1225	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.

Boceprovir 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 34 below:

Table 38: 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)	289 (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 event.

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 1400mg/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 35 below:

Table 39: 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]	NA	23	(25)	23	(25)
<8.5[d]	NA	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[c]	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/mm3 including 3% who had Grade 4 decreased neutrophils < 500/mm3. There were no grade 4 decreased platelets during the study. However, 4% of patients experienced decreased platelets < 50/mm3.

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 40:

	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 41:

	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.

5.2.1. Discussion on clinical safety

The safety profile of Boceprevir was investigated in over 2800 subjects. At the proposed dose for marketing, 800 mg three times daily, 1900 subjects have been exposed in Boceprevir including 66% of them for at least 24 weeks.

The Key Studies Integrated for Safety Assessment included one Phase 2 study performed in naïve population (SPRINT1) and two Phase 3 studies, respectively conducted in naïve patients (SPRINT-2) and in patients who had failed previous therapy (RESPOND 2).

Safety data from these three studies were presented pooled and separated according to the analysed population (naïve and pretreated). Overall, 1548 subjects were exposed to boceprevir in these studies.

Globally, the addition of boceprevir to standard of care 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, i.e 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 < 10g/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 1g/dl versus -2.5 to 3.5g/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 by the applicant. However, it is important that the applicant makes further efforts to better investigate the mechanism behind the higher rate of anaemia reported in patients treated with the tritherapy of boceprevir/peginterferon and ribavirin. The applicant has made a commitment in this context as reflected in the RMP.

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 applicant 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.

The applicant was asked to discuss to what extent the anaemia associated with boceprevir plus pegIFN/ribavirin could be managed without resorting to the use of EPO considering the need for sufficient ribavirin exposure and, taking into account that the use of EPO raises safety concerns that could impact on the benefit risk balance.

The Applicant has provided data that show rates of sustained virologic response by anaemia management in the pivotal studies. Patients managed with RBV dose reduction only conserved a high sustained virologic response (78% and 83% in studies P05216 and P05101 respectively) which remain comparable or higher than those whom anaemia was managed by erythropoietin only (74% and 80% respectively). The data is difficult to interpret since very few patients had only ribavirin dose reduction in both studies P05216 and P05101.

It is important to underline that the efficacy and safety results with and without EPO could only have been reliably interpreted if a randomization would have been performed according to EPO.

It is also noteworthy that as mentioned in the recently available European Association for the Study of Liver Disease (EASL) Clinical Practice Guidelines on the management of hepatitis C virus infection in clinical practice (released April 2011), erythropoietin is "broadly" used worldwide to manage the anaemia associated with peginterferon and ribavirin (PR) therapy in patients with chronic hepatitis C. The applicant highlighted that EPO is used in Europe but there is considerable variation in the use of erythropoietin within Europe.

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. Results of the ongoing P06086 comparing RBV dose reduction and EPO use for the management of anaemia could

help to address this issue . The results of this study are expected by April 2012 , no interim analysis is planned.

The addition of boceprevir to standard of care was also associated to an increased risk of developing neutropenia and Grade3/4 neutropenia and, in a lesser extent, to an increased risk of developing thrombocytopenia.

Due to the potential increased risk of Grade3/4 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. This is reflected in the SmPC .

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 SmPC as are the reported AEs goitre, hypo- and hyperthyroidisms. Thyroid neoplasm has been included in the RMP as potential risk.

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 applicant 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 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 the applicant was asked to make a thorough review for any signal of potential proarrhythmic effect of boceprevir. 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 applicant 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. Close monitoring will be carried out on this area in future PSURs. This aspect is reflected in the RMP. The SmPC reflects the pre-clinical data and alerts physicans to these findings.

The safety profile of boceprevir should be further investigated in sensitive populations, such as HIV-HCV co-infected patients and patients with cirrhosis or advanced liver fibrosis. At this stage, although the safety data appear globally comparable in these populations compared with the general population, it is important to get more information from the ongoing clinical studies to formally conclude on this issue. Long term safety in previously-treated patients with boceprevir should also continue to be more investigated.

Assessment of paediatric data on clinical safety

Victrelis has not been studied in paediatric patients.

5.2.2. Conclusions on the clinical safety

Globally, the addition of boceprevir to 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.

It is therefore considered compulsory that, in order to establish the most rational management of anaemia, additional investigations be performed by the applicant to better understand the causes (and consequently possible patient characteristics) and potential negative consequences of the management of the high rate of anaemia (as a result of the incremental risk with boceprevir) in patients receiving the triple therapy with boceprevir plus ribavirin plus peginterferon. As such the applicant has committed to investigate the mechanism underlying the observed increase of anaemia, and to a lesser extent neutropenia and thrombocytopenia in patients co-administered boceprevir with PR standard of care, which is suggested as being the result of an additional suppressive effect on bone marrow hematopoietic processes.

Furthermore the potential impact on efficacy of lowering the dose of ribavirin in the management of anaemia will be investigated. In particular the data generated should provide further insight into the impact on the most optimal treatment regimen and duration and the characterisation of the potential patient population for which ribavirin dose reduction might be an option to manage the anaemia. To this effect the applicant has committed to provide results of the ongoing Study P06086.

Finally the anaemia management in patients treated for hepatitis C in the EU in the presence of boceprevir in clinical practice will be monitored by a drug utilization study to be put in place and an Educational Programme to inform health care professionals about the risk of haematological disorders (notably anaemia) associated with boceprevir.

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.
Table Summary of the risk management plan

Table 42: Summary of the Risk Management Plan

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimization Activities
Anemia	**Routine PV** • Routine Pharmacovigilance. **Additional PV Evaluation:** Monitor reports of anemia from comparative trial of erythropoietin versus ribavirin dose reduction for anaemia management (P06086) Monitor reports of anaemia from other ongoing clinical trials (P05514, and P05411). Mechanistic study for anaemia A postmarketing drug utilization study will be conducted to further assess boceprevir utilization under conditions of routine clinical use (including management of anemia) in Europe	**Routine Risk Minimization** Section 4.4, Special warnings and precautions for use, of the SmPC. Section 4.8, Undesirable effects, of the SmPC. Communicated in the PIL, PPI. Physician specific labeling-Professional labeling. **Additional Risk minimization activity:** • Physician educational materials will be developed and made available.
Neutropenia	**Routine PV** Routine Pharmacovigilance. **Additional PV Evaluation:** Ongoing studies: P05411, P06086 and P05514. A postmarketing drug utilization study will be conducted to further assess boceprevir utilization under conditions of	**Routine Risk Minimization** Section 4.8, Undesirable effects, of the SmPC. Section 4.4, Special warnings and precautions for use, of the SmPC. Communicated in the PIL, PPI. **Additional Risk Minimization Activity**

Table 42: Summary of the Risk Management Plan

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimization Activities
	routine clinical use in Europe.	Physician educational materials will address the safety profile of boceprevir including neutropenia.
Thrombocytopenia	**Routine PV** Routine Pharmacovigilance. **Additional PV Evaluation:** Ongoing studies: P05411, P06086 and P05514. A postmarketing drug utilization study will be conducted to further assess boceprevir utilization under conditions of routine clinical use in Europe	**Routine Risk Minimization** Section 4.8, Undesirable effects, of the SmPC. Communicated in the PIL, PPI. **Additional Risk Minimization Activity** Physician educational materials will address the safety profile of boceprevir including thrombocytopenia.
Drug-Drug interaction (CYP3A4/5)	**Routine PV** Routine Pharmacovigilance. **Additional PV Evaluation:** Planned studies: P08371, P08123, P08124, P08335, P08383, P08431 Investigator initiated studies of omeprazole and etravirine Evaluation of the potential for inhibition of AKR 1C2 by boceprevir Ongoing studies: P05411, P06086, P05514, and P05685.	Section 4.5, Interaction with other medicinal products and other forms of interaction, of the SmPC. Product Information a. Patient product information will inform regarding potential drug interactions and instruct patient to discuss with their HCP. Patient product information will inform regarding potential drug interactions and instruct patient to discuss with their HCP.
Resistance-associated amino acid variants	**Routine PV** Routine Pharmacovigilance. **Additional PV Evaluation:** P05063 -A long-term follow-up study allowing subjects who participated in one Phase 1, 2, or 3 studies to be enrolled. Subjects are followed for 3.5 years after the end of treatment in the previous BOC treatment study. No treatments are administered. The study will provide information to confirm durability of virologic response, characterize natural history of HCV sequence variants, and characterize long-term safety in subjects who previously participated in studies with	**Routine Risk Minimization** Section 4.4, Special warnings and precautions for use, of the SmPC.

Table 42: Summary of the Risk Management Plan

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimization Activities
	boceprevir.	
Impact of dysgeusia on quality of life or treatment discontinueation	**Routine PV** Routine Pharmacovigilance. **Additional PV Evaluation:** Ongoing studies: P05411, P06086 and P05514.	Section 4.8, Undesirable effects, of the SmPC.
Medication errors	**Routine PV** Routine Pharmacovigilance.	Section 4.2, Posology and method of administration, of the SmPC.
QT interval prolongation	**Routine PV** Routine Pharmacovigilance.	Section 4.4, Special warnings and precautions for use, of the SmPC. Section 5.3, Preclinical safety data, of the SmPC.
Thyroid neoplasm (thyroid nodule)	**Routine PV** Routine Pharmacovigilance	Section 4.8, Undesirable effects, of the SmPC.
Potential exposure during pregnancy	**Routine PV** Routine Pharmacovigilance. Participation in the Ribavirin Pregnancy Registry.	**Routine Risk Minimization** Section 4.6, Fertility, pregnancy and lactation, and section 5.3, Preclinical safety data, of the SmPC.
Exposure during lactation	**Routine PV** Routine Pharmacovigilance.	**Routine Risk Minimization** Section 4.6, Fertility, pregnancy and lactation, of the SmPC.
HCV/HIV coinfection	**Routine PV** Routine Pharmacovigilance **Additional evaluations:** P05411-A Phase 2, double-blind, placebo-controlled, study in HCV-treatment-naïve subjects coinfected with human immunodeficiency virus (HIV) and chronic HCV genotype 1. The MAH has committed to discussions with the AIDS Clinical Trial Group (ACTG) to explore establishing studies in the HIV/HCV coinfected population. The MAH is working with the ANRS (Agence Nationale de Recherché sur le SIDA) who is conducting a study in the HIV/HCV coinfected population.	**Routine Risk Minimization** Section 4.4, Special warnings and precautions for use
HBV/HCV coinfection	**Routine PV**	**Routine Risk Minimization**

Table 42: Summary of the Risk Management Plan

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimization Activities
	Routine Pharmacovigilance	Section 4.4, Special warnings and precautions for use.
HCV genotype 2/3/4	**Routine PV** Routine Pharmacovigilance **Additional investigations:** For HCV genotype 2/3, results from clinical trial P03648 Pilot studies under Merck investigator initiated study program are going to be conducted.	**Routine Risk Minimization** Section 4.4, Special warnings and precautions for use.
Patients with previous tritherapy boceprevir - PR treatment failure.	**Routine PV** Routine Pharmacovigilance	**Routine Risk Minimization** Section 4.2, Posology and method of administration, of the SmPC.
Exposure in patients with severe cirrhosis (Child-Pugh > 6, Class B & C	**Routine PV** Routine Pharmacovigilance	**Routine Risk Minimization** Section 4.2, Posology and method of administration, of the SmPC.
Exposure in organ transplant patients	**Routine PV** Routine Pharmacovigilance **Additional PV Evaluation:** -National Diabetes, Digestive and Kidney Disease /National Institute of Health, Working Group on Liver Transplant has selected Merck to collaborate on a pre-transplantation study, protocol under development. - ANRS has selected Merck to collaborate on a pre-transplantation study.	**Routine Risk Minimization** Section 4.4, Special warnings and precautions for use.
Exposure in the pediatric population	**Routine PV** Routine Pharmacovigilance. **Additional PV evaluation** A pediatric investigation plan for boceprevir has been developed to study treatment in children and adolescents from 3 years of age to less than 18 years of age with genotype 1 chronic HCV infection without liver decompensation. The pediatric study, P07614, is deferred until after submission of the MAA. It is scheduled to begin in SEP 2011. The Phase 3 pediatric study, P08034, is scheduled to begin in 2012	**Routine Risk Minimization** Section 4.2, Posology and method of administration, of the SmPC. Section 4.5, Interaction with other medicinal products and other forms of interaction, of the SmPC. Section 4.8, Undesirable effects, of the SmPC. Section 5.2, Pharmacokinetic properties, of the SmPC.

Table 42: Summary of the Risk Management Plan

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimization Activities
	following the determination of dose(s) from study P07614.	
Exposure in elderly patients	**Routine PV** Routine Pharmacovigilance. **Additional PV Evaluation:** Ongoing clinical trials (P06086, P05514 and P05063).	**Routine Risk Minimization** Section 5.2, Pharmacokinetic properties, of the SmPC.
Exposure in patients with hemoglobin < 13 g/dL (male) or < 12 g/dL	Refer to proposed pharmacovigilance activities for anemia.	Refer to proposed risk minimization activities for anemia.
Exposure in patients with psychiatric disorders.	**Routine PV** Routine Pharmacovigilance.	**Routine Risk Minimization** Section 4.8, Undesirable effects, of the SmPC.
Long term therapy	**Routine PV** • Routine Pharmacovigilance.	**Routine Risk Minimization** Section 4.2, Posology and method of administration, of the SmPC.

The CHMP, having considered the data submitted in the MA application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product:

The Marketing Authorisation Holder shall ensure that all physicians who are expected to prescribe or use Victrelis are provided with a healthcare professional educational pack containing the following at launch:

- The Physician Educational Materials (PEM)
- The Summary of Product Characteristics (in full)
- The Patient Information Leaflet

The PEM should contain the following key elements:

- Detailed information about the risk of haematological disorders (notably anaemia) associated with Victrelis, consisting of factual description of the haematological disorders in terms of frequency and time to onset and related clinical symptoms

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

5.3. 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.

Based on these results boceprevir is regarded as representing a significant therapeutic advance that justifies the principle of an accelerated review as decided by the CHMP in November 2010.

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 BOC 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, the applicant is requested to resolve the uncertainties of the added value of boceprevir to the bitherapy in those patients having good predictive factors for interferon responsiveness. This requirement is subject to condition of the marketing authorisation.

ATaking into account that 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 vicrelis 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. These considerations are reflected in section 4.4 of the SmPC.

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. This is reflected in the SmPC.

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 < 10g/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.

It is therefore considered compulsory that, in order to establish the most rational management of anaemia, additional investigations be performed by the applicant to better understand the causes (and consequently possible patient characteristics) and potential negative consequences of the management of the high rate of anaemia (as a result of the incremental risk with boceprevir) in patients receiving the tritherapy with boceprevir+ribavirin+peginterferon. To this effect the provision of results of a study comparing EPO versus ribavirin dose reduction as measures of managing anaemia is a condition of the Marketing Authorisation.

The clinical consequence of resistance to boceprevir (in terms of response to boceprevir and impact to subsequent lines of therapies) is unknown and will have to be further substantiated as part of the RMP

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.

5.3.1. Risk management plan

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns the following additional risk minimisation activities were required:

The Marketing Authorisation Holder shall ensure that all physicians who are expected to prescribe or use Victrelis are provided with a healthcare professional educational pack containing the following:

- The Physician Educational Materials (PEM)
- The Summary of Product Characteristics
- The Patient Information Leaflet

The PEM should contain the following key elements:

- Detailed information about the risk of haematological disorders (notably anaemia) associated with Victrelis, consisting of factual description of the haematological disorders in terms of frequency and time to onset and related clinical symptoms

5.4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Victrelis in the treatment of treatment of Chronic Hepatitis C was favourable and therefore recommended the granting of the marketing authorisation subject to conditions. In line with the current conditions of prescription for the bitherapy with interferon and ribavirin, treatment with Victrelis should be initiated and monitored by a physician experienced in the management of patients with hepatitis C.