Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Boceprevir

Proprietary Product Name: Victrelis

Sponsor: Merck Sharp & Dohme (Australia) Pty Ltd

April 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New Chemical Entity
Decision:	Approved
Date of Decision:	22 December 2011
Active ingredient(s):	Boceprevir
Product Name(s):	Victrelis
Sponsor's Name and Address:	Merck Sharp & Dohme (Australia) Pty Ltd Level 4, 66 Waterloo Road North Ryde NSW 2113
Dose form(s):	Capsule
Strength(s):	200 mg
Container(s):	Blister pack
Pack size(s):	84 & 336 capsules
Approved Therapeutic use:	Victrelis (boceprevir) is indicated for the treatment of Chronic Hepatitis C (HCV) genotype 1 infection, in combination regimen 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.
Route(s) of administration:	Oral
Dosage:	800 mg (4 capsules) three times daily
ARTG Number (s)	179059

Product Background

This AusPAR describes an application for the registration of Victrelis (boceprevir, BOC), a new, orally administered NS3/4A serine protease inhibitor of the hepatitis C virus (HCV). HCV is a global public health issue with approximately 180 million people infected; the associated mortality is noted by the World Health Organisation (WHO) as >350,000/year.[1] The most common subtype of hepatitis C in Australia is genotype 1; this is also the most difficult to treat and effect a sustained clearance (eradication) of the virus. Current standard of care (SOC) therapy consists of PEG-interferon alpha (PEG-INFa) and ribavirin (PR) with clearance rates at best of 40-50%. This means that approximately half the patients treated do not clear their HCV and remain at risk of the long term complications including liver cirrhosis, decompensated liver disease, hepatocellular carcinoma and premature death.

BOC is a new, orally administered NS3/4A serine protease inhibitor of HCV for use in combination with PEG and PR for the treatment of adults aged ≥18 years who have

[1] World Health Organisation, "Fact Sheet Number 164: Hepatitis C", June 2011, Web, accessed 29 February 2012 < http://www.who.int/mediacentre/factsheets/fs164/en/>.

chronic hepatitis C (CHC) with HCV RNA (ribonucleic acid) genotype 1 without liver decompensation, in two different settings:

i) previously untreated (treatment naïve) patients;

ii) those who have failed previous interferon based therapy (treatment failures).

The aim of this new class (protease inhibitors) of anti HCV agent is as adjuncts to SOC therapy with the aims of augmenting the eradication of HCV and averting the long term consequences of chronic hepatitis C (CHC).

Regulatory Status

Victrelis (boceprevir, BOC) has received marketing approval in the United States, the European Union, Canada, Brazil and Switzerland (Table 1). Numerous international filings for BOC are also currently under review (Table 2). BOC is the first HCV protease inhibitor proposed for registration in Australia.

Table 1: International marketing approval for Victrelis (boceprevir).

COUNTRY	FILING DATE	APPROVAL DATE	INDICATION
United States	10 November 2010	13 May 2011 *Priority Review*	VICTRELIS (boceprevir) is indicated for the treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients (18 years and older) with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy.
European Union	23 November 2010	18 July 2011 *Accelerated Assessment*	Victrelis is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease who are previously untreated or who have failed previous therapy.
Canada	21 December 2010	29 July 2011 *Expedited Review*	VICTRELIS (boceprevir) is indicated for: The treatment of Chronic Hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alfa (PegIFN)/ribavirin (RBV), in adult patients (18 years and older) with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous therapy.
Brazil	28 January 2011	25 July 2011 *Fast Track Review*	
Switzerland	28 February 2011	2 November 2011 *Fast Track Review*	

Table 2: International filings currently under review for Victrelis (boceprevir).

Country	Filing Date	Application Details
Australia	15 January 2011	
Colombia	28 January 2011 (Clinical phase) 24 October 2011 (quality phase)	
Mexico	28 March 2011	
Russia	19 April 2011	
Singapore	14 June 2011	Priority Review Abridged Route
Israel	15 May 2011	Priority
Malaysia	27 May 2011	Priority review
South Africa	28 June 2011	Regular Review
Morocco	24 August 2011	Regular

Product Information

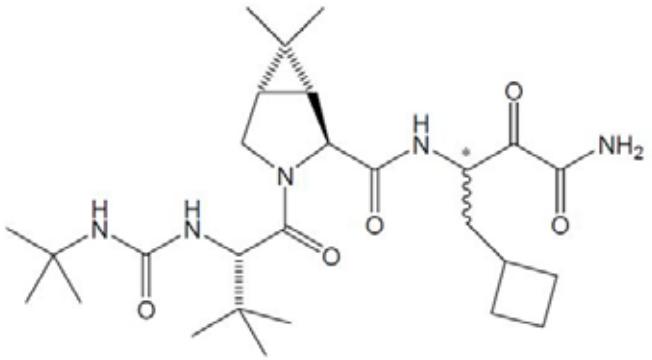
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

The structure of the drug substance is shown in Figure 1.

Figure 1: Structure and chemical information for boceprevir.



Molecular formula: $C_{27}H_{45}N_5O_5$
Molecular weight: 519.7
CAS No.: 394730-60-0
Solubility in water 1.5 mg/mL

There are five chiral centres, four of which are controlled as a specific stereoisomer. The drug substance is a mixture of two stereoisomers with a ratio of about 53:47. The major stereoisomer (SCH 534128) is the therapeutically active moiety, while the minor stereoisomer (SCH 534129) is inactive.

There are no functional groups that are ionisable within the physiological pH range. No polymorphs are known, and the drug substance is produced as an amorphous powder.

BOC is BCS (Biopharmaceutics Classification System) Class III[2] based on the capsule strength (200 mg). If the calculation were based on the highest single dose (800 mg), then it would be considered BCS Class IV. Its aqueous solubility is about 1.5 mg/mL (0.15%).

The levels of impurities contained within BOC exceed the applicable International Conference on Harmonisation (ICH) qualification threshold of 0.05% and were therefore referred to the Medicines Toxicology Evaluation Section at TGA for assessment.

The drug substance has to be stored under refrigeration for stability reasons. Under these conditions, the proposed retest period of two years is considered appropriate.

Drug Product

The capsule contents are manufactured by a conventional process with a conventional formulation.

The proposed limits for specified degradants in the finished drug product were referred to the Medicines Toxicology Evaluation Section at TGA for assessment.

The finished product expiry specifications are deficient in that the proposed assay limits for BOC (90.0-105.0%) do not comply with the requirements of Therapeutic Goods Order (TGO) 78 (92.5-107.5%).

The proposed shelf life for the capsules is 24 months with storage at 2-8°C, which may include a period of three months at temperatures up to 30°C after dispensing to the patient.

Biopharmaceutics

The capsules proposed for registration were used in clinical trials from Phase II onwards.

An absolute bioavailability study was not performed because of the lack of availability of a suitable intravenous (IV) formulation. BOC is poorly soluble in aqueous media and the dose (800 mg) is reasonably high, so a suitable intravenous formulation could not be developed.

A low fat meal was shown to increase the bioavailability of the proposed capsule by about 50%. An earlier study had shown that relative to a low fat meal, a high fat meal increased the area under the plasma concentration time curve (AUC) of the Phase I capsule by about 65%. However, the PI simply states that the capsules should be given with food, without providing information on the effects of different types of food. This has been brought to the attention of the Delegate.

Quality Summary and Conclusions

The application was considered at the 138th meeting of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) on 23 May 2011. The

[2] The Biopharmaceutics Classification System (BCS) is a guidance for predicting the intestinal drug absorption provided by the US Food and Drug Administration. According to the BCS, drug substances are classified as follows:

Class I: high permeability, high solubility;

Class II: high permeability, low solubility;

Class III: low permeability, high solubility;

Class IV: low permeability, low solubility.

PSC endorsed the questions that had been raised by the TGA. A recommendation that the half life of the active metabolite should be included in the PI was based on misinformation. The major stereoisomer of BOC is the clinically active moiety, and the metabolites are inactive.

At the time of evaluator review, the application was not approvable in respect of Chemistry, Manufacturing and Controls because of the non compliance of the finished product assay expiry limits with TGO 78.

III. Nonclinical Findings

Introduction

This AusPAR describes an application by Schering Plough Pty Limited to register boceprevir (BOC) for the treatment of hepatitis C virus (HCV) infection, to be supplied in 200 mg capsules (Victrelis) for oral administration of 800 mg three times daily. BOC is purported to inhibit HCV replication by impairing the activity of the serine protease that mediates cleavage of the HCV polyprotein to the functional proteins essential for viral propagation.

The current nonclinical submission was extensive, comprehensive, well documented and included studies that addressed all aspects expected for a new chemical entity. However, all of the toxicity studies involved a once daily oral (PO) dosing regimen, which resulted in animals being variably exposed, poorly exposed and/or unexposed to the individual components of BOC (diastereomers and main human metabolites in particular) for a large part of each day, when compared with continuous exposure proposed for humans. In a letter from the TGA (dated 30 June 2011), the sponsor was requested to justify the dose regimen used for nonclinical studies and to comment on the adequacy of exposure of animals to BOC and the main human circulating metabolites.

Pharmacology

Activity and mechanism of action *in vitro*

BOC rapidly and readily penetrates hepatic cells, where equilibrium is achieved within 40 min, and it is retained within these cells for prolonged periods. A liver distribution study in humans also supports rapid and extensive penetration and good retention of BOC in target (hepatic) cells.

Crystallography studies confirmed that BOC forms an adduct at the active site serine on HCV NS3. The time taken for new NS3 formation is about 50% shorter than the time taken for BOC-NS3 to dissociate, hence the bond is considered effectively irreversible, or covalent. The formation of a bond between BOC and the active site on the protease is thought to impair the proteolytic activity of the HCV protease.

Inhibition of HCV replication by BOC was demonstrated against the isolated viral protein strain 1b (equilibrium binding constant, Ki* 19.8 nM) (Study D46276) and in a cell based system where human hepatoma Huh7 cells are transfected with clone 16 HCV replicon; IC_{50} and IC_{90} (measures of the concentration of drug needed to inhibit 50% and 90%, respectively, of viral growth) values were 200 nM and 400 nM, respectively, after incubation for 72 h. Inhibition by BOC was concentration and time dependent, was associated with almost complete loss of replicon RNA (< 1 copy/cell remained after 15 days' exposure to 6 x IC_{50}), and resulted in reduced synthesis of new replisomes. BOC mediated inhibition of replicon RNA followed first order kinetics with a t½ of 12 h.

BOC is a mixture of two diastereomers, with SCH 534128 claimed to be active and SCH 534129 claimed to be inactive against HCV. In response to a request from TGA (letter

dated 30 June 2011) for data to substantiate the claim regarding differences in diastereomer potency, the sponsor provided a textual description and graphs from a study with recombinant proteases (Study SCH 503034PK016). The full report of this study was not provided in the response; however, the extracted data were consistent with the claims and therefore this issue is considered resolved.

The main human circulating metabolites of BOC are claimed to be inactive against HCV; for example, the proposed PI states that 'studies *in vitro* indicate that BOC primarily undergoes metabolism through the aldoketoreductase (AKR) mediated pathway to ketone reduced metabolites that are inactive against HCV'. However, no studies with metabolites were provided in the submission.

In response to a request from TGA (letter dated 30 June 2011) for data to substantiate the claim regarding metabolites, the sponsor reported that the inhibitory constant (Ki*) for SCH 629144 in the replicon assay was > 450000 nM and the metabolites do not have the required chemical moiety to form a covalent bond with the NS3 protease active site. The full report of the (preliminary) study of Ki was not provided for evaluation data and the argument based on chemical structure is theoretical. However, the response is considered acceptable and this matter will not be further pursued. The sponsor also indicated that no other studies have been done with main BOC metabolites.

Effect of HCV genotype on boceprevir activity

BOC showed similar activity against NS3 proteases from genotypes 1, 2 and 3 in enzyme based assays: the Ki* at genotype 1a and 1b proteins (derived from H77S and Con1 replicons) was 14 nM, and at genotype 2a and 3a proteases (obtained from HCV infected patient plasma) it was 39 and 25 nM, respectively (Study D-67130).

Effects of interferon-α, HIV protease inhibitors, human serum on boceprevir activity

BOC and interferon-α showed additive inhibition of HCV replication when these drugs were incubated together over the IC_{50}-IC_{90} range for each drug with HCV replicon bearing cells (Study D46282). Co incubation with the HIV protease inhibitors atazanavir, lopinavir or ritonavir had no effect on BOC activity, and BOC had no effect on the anti-HIV activity of these protease inhibitors (Study D55995). BOC activity was reduced three fold in 50% human serum *in vitro* (Study D55850).

The combined effects of BOC, interferon-α and PR (mimicking proposed clinical use) on HCV replication were not investigated. In response to a request from TGA (letter dated 30 June 2011) on whether these were available, the sponsor advised that PR has a cytostatic/cytotoxic effect on HCV replicons *in vitro*[3] that would therefore confound replication studies. This response is accepted.

Cytotoxicity

BOC had negligible effects on the viability of Huh-7 cells, and Huh-7 cells harbouring HCV replicon clone 16, at concentrations up to 10x the IC_{90} for replicon inhibition. BOC had no cytotoxic effects on human peripheral blood mononuclear cells (PBMCs), baboon primary hepatocytes (Study D-46285), human melanoma (A2058), pancreatic carcinoma (Miapaca), colon cancer (HT29) and mammary epithelial (MCF12A) cell lines, and primary human hepatocytes, and minimal cytotoxic effects on a human T cell line (PM-1) (Study D55850).

[3] Zhou S, et al. The effect of ribavirin and IMPDH inhibitors on hepatitis C virus subgenomic replicon RNA. *Virology* 2003; 310:333-342.

Activity *in vivo*

No *in vivo* nonclinical efficacy studies were submitted for BOC. This is acceptable in view of the US Food and Drug Administration (FDA) draft Guidance for Industry: Chronic Hepatitis C Virus Infection[4] which states that "demonstration of anti-HCV activity in an animal model is not needed".

Resistance

A major challenge to successful HCV treatment is the emergence of drug-resistant virus. Due to the high replication rate (~10^{12} virions per day) and high mutation frequency of HCV, it has been estimated that every possible variant of the virus is produced every day in an infected individual, leading to the circulation of genetically distinct, but closely related subpopulations, or "quasi-species", in an infected individual.[5]

A number of studies using biochemical and cell based HCV replicon assays assessed the development of mutations that render HCV resistant to BOC, including studies with samples from genotype 1 non responders in a BOC Phase II clinical trial. Replicon studies were conducted with human hepatoma Huh-7 cells and an HCV subtype 1b strain. Increases of 1.5-2 fold or more in the assays were regarded as the threshold for differences in resistance.

An early biochemical and HCV replicon study (D-46282, 2003), in which resistant replicons were selected by culture with BOC concentrations up to 2.5 μM, identified three resistance associated variants (RAVs), with amino acid substitutions A156S, A156T and V170A. These RAVs were associated with respective increases of 19, 290 and 12 fold in Ki*, respectively, compared to the wild type, and negligible or minor decreases in catalytic efficiency, suggesting that the mechanism of resistance was a reduction in enzyme affinity for BOC. V170A and A156S appeared early and conferred low levels of resistance. Mutation A156T became dominant with increased duration of exposure or at higher BOC concentrations, and conferred the highest resistance. Replication fitness of replicons bearing the A156T mutant was lower than those containing V170A or A156S (Study D46283). RAVs remained sensitive to interferon-α.

A later biochemical and replicon study (D55147, 2008) characterised additional BOC RAVs (Table 3) that were identified in clinical studies to be early generation HCV protease inhibitors. The identified resistance loci V36, Q41, F43, T54, R155, A156 and V170 were near the inhibitor binding site.

[4] Food and Drug Administration, "Guidance for Industry Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Agents for Treatment", September 2010, Web, accessed 29 February 2012 < http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM225333.pdf>.

[5] Susser S, et al. Characterization of resistance to the protease inhibitor boceprevir in hepatitis C virus-infected patients. *Hepatology* 2009; 50:1709-1718.

Table 3: Fold change in Ki* for boceprevir against mutant proteases.

Mutation	Fold increase in boceprevir Ki* compared with wild type (16-66 nM in most assays)
A156T (A156V was also identified as an important RAV in other studies)	300
T54C, R155I	32-45
A156S, R155G, R155T	17-20
V170A, V36M + R155K, T54S + R155K	10-14
F43C, T54A, V55I, R155M, (F43S was also identified as an important RAV in other studies)	4-10
V36A, V36M, Q41R, T54S, V170T, R155K, R155Q, V55A, V158I, V36I	2-3.5
D168V, V158M, V163L, V36L	< 2 (Not resistant)

A number of RAVs identified *in vitro* in nonclinical studies were also identified in clinical trials. Additional variants identified in clinical study P03523 were V36I, T54C, V55I, and R155/I/M/Q/G/T, with R155I showing a 45 fold increase in Ki* (Study D-57130).

Another resistance study (D55176) used a computational selection pressure based method to calculate the selection pressure for all codons in the HCV protease region (amino acids 1-181). This selection pressure (K_a/K_s) is the ratio of the number of non synonymous substitutions per non synonymous site (K_a) to the number of synonymous substitutions per synonymous site (K_s), and can be used as an indicator of selective pressure acting on a protein coding gene. The study identified previously known major resistance mutations, and three pairs of correlated changes.

In addition to the biochemical and replicon studies, a recent study (D-57129, October 2010) used a secreted alkaline phosphatase assay to characterise the putative RAVs identified in preclinical and clinical trials. This phenotyping assay measured BOC potency against HCV NS3 in Huh-7 cells over 24 h. BOC half maximal effective concentration (EC_{50}) fold changes for each RAV were consistent with biochemical and replicon assays. Confirmed BOC RAVs in the context of NS3 from genotype 1a were: V36A/M, F43S, T54A/S, V55A, R155K/T, A156S/T/V, I170A/T, V36A + R155K, T54S + R155K, V36M + R155K and V36A + T54S + R155K. In the context of NS3 from genotype 1b, confirmed RAVS were: V36A/M, F43S, T54A/S, V55A, R155K/T, A156S/T/V, V170A/T, T54S + A156S, V36M + R155K and T54S + R155K.

The combined effects of BOC, interferon-α and PR (mimicking proposed clinical use) on the emergence of RAVs *in vitro* were not investigated in studies submitted. In response to a request from TGA (letter dated 30 June 2011) on whether these have been done, the sponsor indicated that such studies were not feasible because PR is toxic to HCV replicons *in vitro.*[3] This response is accepted.

Cross resistance

BOC (SCH 503034) and telaprevir (VX-950) are both ketoamide inhibitors of the HCV NS3 protease. Most identified NS3 mutants affected both BOC and telaprevir in biochemical

and replicon assays, but the levels of resistance showed some differences, which probably reflected subtle differences in the binding characteristics of these drugs.[6]

Secondary pharmacodynamics and safety pharmacology

An extensive battery of *in vitro* assays, covering numerous receptors, proteases, and other enzymes, suggested that BOC (generally at 10 μM or ~5 μg/mL) is unlikely to interact with biological systems or biochemical processes other that its intended target at these concentrations. The drug also showed low potential for cytotoxicity in various cell lines at concentrations ≥ IC_{90} for HCV; and it did not interact *in vitro* with HIV protease inhibitors, either in terms of cytotoxicity or viral inhibition.

BOC inhibited the activity of the human proteases cathepsins B (IC_{50} 9-10 μM), G (IC_{50} 2.2 μM) and L (IC_{50} 8-11 μM); and of acyl CoA-cholesterol acyltransferase from rat liver (IC_{50} 1.7 μM; although no effect was found at rat HMG-co-A reductase activity). The potential significance of this inhibition and whether the concentrations are clinically relevant is unclear and was not explored in nonclinical studies. Interestingly, an increase in cholesterol and triglyceride levels was observed in repeat dose toxicity studies in monkeys, while fatal doses of BOC in rats were associated with marked decreases in cholesterol and triglyceride levels (the latter falling below the detection limit of the assay).

It is not clear if these effects are associated with an interaction between BOC and acyl CoA-cholesterol acyltransferase; however, consideration may be given to reviewing cholesterol and triglyceride levels in clinical trial patients receiving BOC to determine if post market monitoring is warranted.

A standard battery of *in vivo* and *in vitro* safety pharmacology studies (including cardiovascular safety) also did not identify potential target organs for secondary activity, at single doses of BOC up to 50 mg/kg/day in dogs or 200 mg/kg in rats and monkeys. Exposure to the active BOC diastereomer and to the main human metabolites of BOC was probably lower than or similar to that expected in humans at these doses.

Pharmacokinetics

General

BOC is a 1:1 mixture of two diastereomers, SCH 534128 and SCH 534129 that interconvert to some extent *in vitro* (≤ 40% in plasma from all species studied including humans) and *in vivo* (about 10% of each diastereomer converts to the other in rats). Total BOC and single diastereomer (mainly SCH 534128) concentrations were measured in most studies that included toxicokinetics assays and diastereomer ratios remained stable once equilibrium was achieved, which reduced potential difficulties associated with estimating exposure to the individual components. Plasma concentrations of BOC were highly variable between individuals and across studies and were not dose proportional, making it difficult to extrapolate or predict parameters across studies.

Species differences in the duration and extent of exposure to BOC and its metabolites after PO dosing limited the value of animals (particularly mice and rats) as human models for investigating the potential toxicity of BOC.

Plasma kinetics

The oral absorption of BOC in animals is poor (~35% in rodents, 12% in monkeys) but rapid (the time to reach maximum (peak) plasma concentration following drug administration (T_{max}) was generally 0.5 h- 4 h), is improved by food (shown in monkeys, as

[6] Tong X, et al. Characterization of resistance mutations against HCV ketoamide protease inhibitors. *Antiviral. Res.* 2008; 77:177-185.

in humans) and appears to be saturable, which probably contributes, at least partly, to non dose proportional PO pharmacokinetics. Oral bioavailability in animals is also low (26-35% in rodents, 4% in monkeys) due to extensive and rapid first pass metabolism and total drug is hepatically cleared fairly rapidly in all species tested, with no apparent accumulation of parent or metabolites occurring with repeated once daily dosing.

Half life values for BOC or its diastereomers were generally <2 h in all species including humans, although these increased with dose. In rodents at a given PO dose, higher plasma concentrations were achieved in females than in males, but (as in humans) there were no sex differences in monkeys, which is a more relevant species than rodents in terms of human BOC kinetics. Increases in exposure were not dose-proportional and were dose limited at the higher doses tested in animals.

In rodents and monkeys, levels of BOC or its diastereomers declined rapidly after the maximum plasma drug concentration (C_{max}) was achieved (consistent with a relatively short terminal half life ($t_{½}$)) and were close to or below the detection limit by 8 h after dosing or by 24 h at the highest doses used. A similar situation is reported after a single dose in humans and this appears to have prompted the need for a three times daily(TID) dosing regimen to continually maintain effective anti viral concentrations. The clinical regimen aims to achieve plasma BOC levels that exceed the *in vitro* IC_{90} at HCV of 400 nM.

Because of metabolic differences, the ratio of active to inactive BOC diastereomer in plasma varied amongst species, but it remained stable over time within each species. Based on AUC, the plasma concentration ratio of SCH 534128 to SCH 534129 was approximately 2:1 in humans, 0.17:1 in monkeys and about 1:1 in rodents. Therefore, for a given total BOC concentration, the concentration of the active diastereomer will be 50% lower in rodents and about 12 times lower in monkeys, when compared with the human concentration of SCH 534128.

Distribution and plasma protein binding

BOC and related compounds were distributed to all tissues in rats, except brain and spinal cord. Highest concentrations of radioactivity relative to those in blood were observed in the liver, intestines, prostate gland, epididymides, thyroid gland, pancreas, pituitary gland and bone marrow. Drug associated material was cleared from all tissues by 8 h after a single PO dose, with the exception of the lymph nodes, excretory organs, pituitary gland and bone marrow where it persisted for up to 24 h. There was no evidence for drug retention in pigmented tissues. Whole body tissue distribution studies after repeated dosing were not done and therefore it is not known if drug accumulates in particular tissues with repeated dosing.

BOC was found to cross the placenta and distribute to the foetus and was also excreted in milk during lactation.

In monkeys, liver concentrations of BOC diastereomers after 6 months of repeated PO dosing with BOC were 2-9 times higher than corresponding levels in plasma, again indicating good distribution to this organ.

In vitro studies found that BOC and/or associated compounds were moderately bound to plasma proteins (specific protein(s) not identified) in all species investigated: free drug fractions were about 15-20% for human plasma, up to about 30% in rat, rabbit, mouse and monkey samples, and only about 10% in dog samples. Therefore, the free fraction does not need to be taken into account when calculating animal/human exposure multiples.

Metabolism

The metabolism of BOC diastereomers in all species examined including humans is complex, involving reduction, oxidation, cleavage, dimerisation and various combinations of these reactions to produce a wide array of > 60 metabolites that are excreted predominately via the bile in faeces. The main metabolic enzymes are predominantly cytoplasmic AKR, which occur in hepatic and non hepatic tissues; and, to a lesser extent, CYP450 isoforms 3A4 and 3A5, although other CYP isoforms appear to also be involved to a minor extent. Phase II metabolism (glucuronidation) apparently does not feature in the metabolism of BOC.

In addition to BOC diastereomers, the main circulating substances in humans are M28 (produced by AKR mediated reduction of SCH 534128) and M30 and M31 (produced by AKR mediated reduction of SCH 534129). These ketone reduced metabolites are three of the four respective isomers of metabolite SCH 629144 (the fourth isomer is below assay detection limits in all species) and are also formed to varying extents in monkeys and mice, but they are only minor metabolites in rats. SCH 629144 isomers have short half lives (generally < 2 h).

At least thirty other metabolites have been detected in human plasma after a PO dose of BOC, but with the exception of M0BA (also called SCH 503034-K) they occur at minor or trace levels and are similar in nature to those detected in various matrices in rodents or monkeys. M0BA is a hydrolytic cleavage product formed by sodium lauryl sulphate catalysed hydrolysis in the stomach and is also an important circulating component in humans (reportedly up to ~20% of drug related material at certain times). M0BA is also a degradation product in the Victrelis finished product and is considered in the context of impurities.

The extent to which BOC diastereomers are metabolised, the rate of individual diastereomer metabolism and the relative importance of metabolic pathways (that is, by oxidation or by AKR) varies amongst species, resulting in important inter species differences in the nature and extent of the main circulating diastereomers and metabolites. Reduction by AKR appears to be a major pathway in monkeys and humans, although SCH 534129 is cleared faster than SCH 534128 in humans while the reverse is true for monkeys. In rodents, BOC appears to be metabolised predominately by CYP mediated oxidation rather than AKR mediated reduction and only minor amounts of the main human metabolites (M28, M30 and M31) are detected in the circulation of these species. These differences result in rodents being of limited value as models for humans in terms of the main circulating BOC metabolites.

There were no nonclinical studies of BOC metabolites included in the current submission and the sponsor has indicated that such studies have not been done.

Excretion

In all species examined including humans, < 10% of a BOC dose is excreted as unchanged parent drug and ≤ 5% of a dose is excreted in urine after IV (or PO) dosing, consistent with drug clearance being mainly (> 80%) biliary following metabolism. In animals, faecal excretion of unchanged BOC accounted for a small proportion (generally < 10%) of the drug related material despite poor oral absorption, suggesting the possibility of local metabolism of unabsorbed drug. Biliary recirculation of BOC associated compounds occurs to a small extent (< 10% of an absorbed dose) and small secondary peaks in diastereomer concentrations after C_{max} have been observed in animals. BOC metabolites found in animal faeces and urine are comparable to those found in human excreta. Therefore, animals are adequate human models in terms of route and extent of drug excretion.

Kinetic interaction studies with boceprevir

BOC is a substrate and an inhibitor of CYP3A4/A5. The parent drug and/or its metabolites inhibit (monkeys) or induce (rats) a range of CYP isoforms. BOC is a substrate and an inhibitor of the P glycoprotein transporter; its metabolism by AKR or by CYP450 is affected by drugs that inhibit or induce the activity of these enzymes. The effect of BOC or its metabolites on AKR activity was not investigated and the possibility of an inhibitory or inducing effect cannot be ruled out. *In vivo* studies found that co administration of BOC with PR, PEG-INF, ritonavir and/or diflunisal appeared to affect exposure to one or more of the co administered drugs, but it was not possible to conclusively define the interactions.

Overall, there is a strong indication that exposure to BOC and/or its metabolites will affect and be affected by a wide range of drugs, and this will warrant post market monitoring of individual drug levels, particularly for drugs with a low therapeutic index.

Adequacy of exposure of animals to boceprevir and metabolites in toxicity studies

All of the animal toxicity studies involved once daily PO dosing with BOC; given the short half life of BOC and the main human metabolites (~2 h or less), this may be expected to result in animals being underexposed (compared with the expected human exposure) for much of the day and unexposed to BOC and related material for up to 16 hours each day (when the final quantifiable sampling time (tf) = 8 h). This could provide an opportunity for recovery of drug associated effects (if any) before the next dose is administered and may limit the value of the animal studies in terms of investigating and predicting the potential toxicity of BOC under conditions mimicking those in humans (that is, continuous exposure).

For most animal studies, selection of dose and dosing regimen was not justified and there was no discussion of whether more frequent dosing should be done to at least match the regimen proposed for humans. In monkeys, exposure at 1000 mg/kg did not greatly differ from that at 500 mg/kg/day; this suggested that absorption was probably dose limited, and highlighted the need to have considered more frequent daily dosing or to supplement PO dosing with parenteral dosing.

As mentioned above, inter species differences in BOC metabolic rate and/or pathways resulted in important differences in the nature and extent of the main circulating diastereomers and metabolites amongst species, which compounded deficiencies in exposure to these as a result of a once daily dosing regimen.

Table 4 provides an indication of exposure to the main circulating substances after PO administration of BOC to humans when compared with exposure at doses close to the highest used most often in the main animal toxicity studies:

Table 4: Exposure comparisons on the basis of individual diastereomers and metabolites after administration of boceprevir.

	Human **800 mg TID** **(~50 mg/kg/day)**	**[1]Monkey M + F** **300 mg/kg/day**	**[2]Rat M / F** **200 mg/kg/day**	**[3]Mouse M / F** **600 mg/kg/day**
	$AUC_{(0\text{-}24\ h)}$ µg.h/mL	**$AUC_{(0\text{-}24\ h)}$ µg.h/mL (animal to human exposure ratio)**		
Boceprevir	16.9	32.3 (2)	28.2 / 63.9 (1.7 / 3.8)	44.2 / 68.4 (2.6 / 4)
SCH 534128	11.3	4.8 (0.4)	15.3 / 23.4 (1.3 / 2)	25.0 / 34.5 (2 / 3)
SCH 534129	5.6	27.5 (5)	12.9 / 30.4 (2.3 / 5)	19.2 / 33.9 (3 / 6)
SCH 629144	76	226 (3)	0.963 / 2.69 (0.01 / 0.03)	23.2 / 61.7 (0.3 / 0.8)

1: Day 84 data from Study 04080.
2: Day 30 data from Study 10080.
3: Day 82 data from Study 04320.
Exposure ratio is the ratio between the animal AUC and human AUC.
Note: tf (final quantifiable sampling time) in animals is mainly at 8 h.

In monkeys, highest doses used generally did not achieve plasma levels of SCH 534128 (active) similar to those expected in humans and monkeys remained unexposed to this diastereomer for a large part of each day. Total daily exposure to the inactive diastereomer and to the ketone reduced metabolites was generally higher in monkeys but as with SCH 534128, exposure to these substances was likely to have been intermittent and/or variable rather than stable and continuous as expected in humans.

Based on AUC over 24 h, total exposure of rodents to either diastereomer was generally higher than in humans; however, exposure to the ketone reduced metabolites was very low or negligible. This limits the value of studies performed in these species (including the carcinogenicity and reproductive toxicity studies) for defining the toxicity profile of BOC.

In a letter from TGA (dated 30 June 2011), the sponsor was requested to comment on the limitations of the animal studies (in terms of extent and duration of daily exposure) for assessing the potential toxicity of BOC at concentrations that are continuously sustained (as proposed for humans). The sponsor was also asked to indicate whether any nonclinical studies are available or planned using a more frequent daily dosing schedule or using other methods (that is, parenteral dosing) to supplement daily single bolus PO dosing, particularly in monkeys.

In a letter dated 28 July 2011, the sponsor advised that the "animal toxicity and safety studies were designed to ensure adequate exposure to BOC in support of clinical trials ... [and] ... to provide sufficient exposure for identification/evaluation of potential BOC-related toxicities".

It appears that the optimal clinical dosing regimen may not have been finally decided at the time the nonclinical studies were designed, which adequately explains the use of a once versus three times daily dosing regimen.

In response to concerns over poor exposure to BOC components in animals, the sponsor provided graphical evidence that, at the highest doses used, plasma concentrations of total

BOC in some of the animal studies remained higher than human concentrations after TID dosing over a 24 h period. The sponsor also contends that the toxicity profile of BOC was adequately evaluated in the nonclinical studies; that the toxicities in animals have not been observed in humans; and that exposure to the main human metabolites was higher in at least one animal species. The sponsor advises that no additional nonclinical studies are planned using a more frequent daily dosing schedule or using other methods.

The sponsor's comparison of exposure on the basis of total BOC concentration is not considered valid because, as mentioned above under the section 'Plasma kinetics', the ratio of active:inactive diastereomer varies substantially amongst species resulting in marked species differences in the exposure to the individual diastereomers, even if exposure to total BOC is similar. Exposure comparisons on the basis of individual diastereomers and metabolites (Table 4) illustrate the differences in exposure among the various drug components between species.

It is accepted that at least one animal species was exposed to a component of BOC at a level higher than that expected in humans. The evaluator maintains however, that the dosing schedule was not adequate to explore the full potential toxicity profile of BOC. This view is reinforced by the fact that dose limiting toxicity was not identified in animals and that even the anticipated toxicities (such as haematological changes observed clinically) were not observed in animals (see the *Toxicology* section).

Toxicology

General

The main toxicity studies were done in mice, rats and monkeys, with BOC administered PO once daily as a suspension in 0.4% (w/v) aqueous methylcellulose. Only an acute toxicity study was done in dogs and this species was not adequately characterised pharmacokinetically. No studies were done with the proposed capsule formulation but it contains common excipients and interactions between BOC and these are not expected.

The duration of studies in monkeys (1-12 months), mice (3 months) and rats (3-6 months) was appropriate to support chronic use of medicines in humans, as recommended in relevant guidelines (CPMP/ICH/300/95).[7] However, as mentioned above, exposure to BOC related material was limited. Doses used for monkeys were not high enough to elicit frank toxicity, while in rodents many of the observed effects were difficult to interpret in terms of potential effects of BOC in humans because of interspecies differences in metabolic profile.

According to the clinical overview, anaemia and to a lesser extent neutropenia and thrombocytopenia are observed adverse effects (AEs) of BOC in humans. These effects were generally not observed in the animal studies, which tends to reinforce doubts over the relevance of the animal models and/or the adequacy of the dosing (including dose level and regiment) used for the animal toxicity studies.

Overall, the toxicology program with BOC provided limited information on potential toxicity during uninterrupted exposure to BOC and its metabolites. Tables showing exposure of BOC components in animals when compared with humans are provided in the sections below and illustrate these limitations.

[7] ICH Topic S4. Duration of Chronic Toxicity Testing in Animals (Rodent and Non Rodent Toxicity Testing). Note For Guidance On Duration Of Chronic Toxicity Testing In Animals (Rodent And Non Rodent Toxicity Testing (CPMP/ICH/300/95).

Findings in monkeys

Doses of BOC used in monkeys caused only minimal effects; gastrointestinal disturbance (diarrhoea and emesis, on occasion after 1000 mg/kg), increased cholesterol and triglyceride levels, suppression of hepatic CYP450 enzymes, prolonged activated partial thromboplastin time (APPT), and minimally reduced red blood cell (RBC) parameters. No target organs for toxicity were clearly identified and no conclusions about the potential toxicity profile of BOC can be drawn from these studies because exposure to the active diastereomer was low, and was probably variable and intermittent when compared with that expected in humans.

There was no information on possible mechanism(s) underlying the effects on lipids and CYP450 enzymes and it is not possible to comment on whether these effects might progress or intensify with a dosing schedule mimicking that proposed for humans. Prolonged APPT findings were consistent across studies and further investigations were performed (see below), but these were not informative.

The no adverse effect level (NOAEL) in monkeys was 200 mg/kg/day across the 1-12 month studies, while the highest dose (1000 mg/kg/day for two months following treatment at 300-500 mg/kg/day for one month) was also a NOAEL in terms of systemic toxicity. At these doses, total daily exposure, particularly to the active diastereomer, was less than or did not substantially differ from that expected in humans as shown in Table 5 (monkey-to-human exposure (AUC) multiple is shown in brackets).

Table 5: Drug exposure for individual diastereomers of boceprevir comparing monkey and human.

		SCH 534128	**SCH 534129**	**SCH 629144**
Monkey (200 mg/kg)	C_{max} µg/mL	0.3-0.5	1.7-2.5	~20
	AUC µg.h/mL	2-2.8 (0.2)	16-19 (2.8-3.4)	~150 (2)
Monkey (1000 mg/kg)	C_{max} µg/mL	0.9	7.7	44.5
	AUC µg.h/mL	~10 (0.9)	75 (13.4)	457 (6)
Human (800 mg TID)	C_{max} µg/mL	~1.5	~1	~5.4
	AUC µg.h/mL	11.3	5.6	76

Note: animal-to-human exposure (AUC) multiple is shown in brackets.

These studies are unlikely to provide good information about the potential for cumulative, progressive or exacerbating toxicity of BOC with repeated dosing because in addition to relatively low exposure, the drug was most likely effectively cleared for several hours before the next dose was administered.

Prolonged APPT findings in monkeys

Special investigations were performed to further investigate the (consistent) findings of prolonged APPT with BOC in monkey studies. These did not shed light on a possible mechanism and no abnormalities were found in individual intrinsic and contact factor coagulant activities (Factors VIII, IX, XI and XII, prekallikrein and high molecular weight kininogen). Haematology abnormalities apart from prolonged APPT were not found in any of the monkey studies but it would be of interest to determine whether these would occur at exposure levels at least comparable to those expected in humans. A decrease in platelet

counts was observed in the mouse repeat dose toxicity studies but the significance of this is not clear.

Overall, the nonclinical studies do not provide a clear understanding of whether or not BOC affects haematology. It is acknowledged that coagulation and APPT were specifically monitored in clinical trials and this can be continued in the post market setting if warranted.

Findings in rodents

BOC treatment in rodents was associated with relatively limited effects but as with the monkey studies, this may be due to relatively low and intermittent exposure (relative to that expected in humans) rather than to a benign toxicity profile. The liver was identified as a target organ in rodents, with increases in alanine transaminase (ALT) and aspartate transaminase (AST) enzymes observed in life, and histopathological changes consisting of Kupffer cell hypertrophy, increased neutrophil infiltration and hepatocyte necrosis in mice; and multinucleated hepatocytes and hepatocyte necrosis in rats. Unlike monkeys, where hepatic enzymes were suppressed, CYP450 enzyme induction was observed in mice, which is probably associated with CYP450 mediated metabolism of BOC being prominent in mice (and rats).

The potential human relevance of the liver changes in rodents is equivocal because the major metabolic pathway for BOC in rodents (mainly by CYP450) differs from that in humans (or monkeys; mainly by AKR), and therefore the liver burden caused by BOC will be much greater in rodents. Liver effects observed with BOC in rodents are often observed with drugs extensively metabolised by CYP450, with the exception of necrosis and neutrophil infiltration. It is not clear if the latter changes were a consequence of drug metabolism or if they reflect a direct hepatotoxic action of BOC and/or its metabolites; however, the relevance of the findings to humans remains equivocal.

Male reproductive tissue toxicity

Male reproductive tissues were a prominent target organ for BOC toxicity in rats but not in mice or monkeys, with the changes characterised by Sertoli cell vacuolation, spermatid degeneration and atrophy of seminiferous tubules in the testes; and luminal cellular debris and hypospermia in the epididymides. The effect was considered to occur primarily as a result of effects on the Sertoli cell but the precise biochemical/molecular mechanism(s) underlying the changes and whether there is an association with BOC diastereomer(s) and/or metabolites or bothwere not explored.

Reproductive tissue toxicity in males was independent of rat age and was not associated with measurable changes in follicle stimulating hormone (FSH), luteinizing hormone (LH) or testosterone levels. Reproductive tissue toxicity in males was dose dependent in terms of severity, had a very rapid onset (changes set in train from the first dose), and was very slowly reversible. Functionally, histopathological changes were associated with marked reductions in sperm counts and motility and a dramatic impairment of fertility. Studies to determine if reproductive function was restored were not done, although there was evidence of very slow recovery of tissue changes.

There is no information on a possible underlying mechanism(s) for BOC associated effects on male reproductive tissues. In the absence of this information and given the limitations of the rat as a model for BOC pharmacokinetics in humans, it is not clear if BOC induced toxicity to male reproductive tissues is of potential relevance for humans. It is noted that special monitoring of testicular function markers was conducted in males in clinical trials of BOC. The latter have been ceased in consultation with the FDA [from the nonclinical overview: “In clinical studies, inhibin B levels as a surrogate marker of testicular function

do not appear to decline after the start of BOC. BOC did not appear to have an effect on testicular function. The testicular effects seen in nonclinical studies in rats with BOC are thus likely to be species specific. The FDA has agreed that further inhibin B monitoring is no longer required."] In view of the above, it is not considered necessary to request the sponsor conduct further investigations of BOC induced reproductive tissue toxicity in male rats.

Exposure at no effect levels in rodents

Highest no adverse effect levels in mice were 600 mg/kg/day for 3 months in females and 250 mg/kg/day for males or females for up to 3 months. In rats, highest NOAELs were 125 mg/kg/day for up to 6 months (150 mg/kg/day for 3 months) in females, and 15-25 mg/kg/day for 3-6 months in males. At these doses, total daily exposure, particularly to the active diastereomer and to the main metabolites, was less than or did not substantially differ from that expected in humans (Table 6).

Table 6: Drug exposure for individual diastereomers of boceprevir comparing rodents and human.

		SCH 534128	**SCH 534129**	**SCH 629144**
Female mouse (600 mg/kg)	C_{max} µg/mL AUC µg.h/mL	8-12 40-63 (3-6)	8-10 39-66 (7-11)	22 63 (0.8)
Male mouse (250 mg/kg/day)	C_{max} µg/mL AUC µg.h/mL	4.6 7.5 (0.7)	3 5 (0.9)	Data are not available, but are likely to be substantially less than that shown in cell above.
Female mouse (250 mg/kg/day)	C_{max} µg/mL AUC µg.h/mL	6.4 10 (0.9)	5 8.8 (1.6)	
***Female rat (150 mg/kg)**	C_{max} µg/mL AUC µg.h/mL	3 7 (0.6)	3.8 8 (1.4)	0.1 0.28 (0.004)
Male rat (20 mg/kg)	C_{max} µg/mL AUC µg.h/mL	0.3 0.8 (0.07)	0.2 0.6 (0.1)	Data not available but are likely to be substantially less than that shown in cell above.
Female rat (20 mg/kg)	C_{max} µg/mL AUC µg.h/mL	0.1 0.4 (0.03)	0.1 0.3 (0.05)	
Human 800 mg TID	C_{max} µg/mL AUC µg.h/mL	~1.5 11.3	~1 5.6	~5.4 76

*data from neonates
Note: animal-to-human exposure (AUC) multiple is shown in brackets.

General conclusions from the repeat dose toxicity studies

Overall, toxicity studies in monkeys were limited by poor selection of dose and dosing schedule and provided very little information on the potential toxicity profile of BOC. In rodents, the liver (mice and rats) and reproductive tissues (male rats) were identified as major target organs but the relevance of these for human use of BOC is equivocal.

Toxicity studies with boceprevir impurities

Several one month repeat dose toxicity studies in rats and *in vitro* genotoxicity studies were conducted with BOC batches containing varying levels of impurities in order to justify the specification limits for Victrelis finished product. Findings were consistent with those in the main toxicology studies and no new or additional information on the toxicity profile of BOC was derived from these studies. Limitations regarding rodent species relevance and adequacy of exposure to BOC associated material, as described above for the main studies in rats, apply to these studies. In fact, exposure to BOC after dosing with impurity spiked batches was consistently lower than after dosing with unspiked batches at equivalent doses (which were not adjusted for content of active), probably because there was substantially less active ingredient in the spiked batches.

These studies were adequate, however, for assessing whether proposed impurity levels can be qualified on the on the basis of nonclinical data.

Drug combination repeat dose toxicity studies

These comprised a one month study of PO BOC (mainly given once daily) in combination with PR and either ritonavir or the unregistered nonsteroidal anti inflammatory drug (NSAID) diflunisal in rats; a 3 month study of BOC and PR in male rats (reproductive tissue toxicity study); and a 1 month study of BOC with PR and PEG-INF in monkeys.

Findings were consistent with effects observed in previous or current studies of the individual components and no novel toxicities were identified. However, it was not possible to conclusively determine whether the effects of one component were altered by concomitant drugs or whether drug interactions (including pharmacokinetic) occurred.

There were no studies against a baseline of prior treatment with PEG-INF and PR or with BOC and erythropoietin (EPO) as intended clinically. However, studies of this type are more appropriately performed in humans as noted in the FDA draft Guidance for Industry.[4]

Overall, these studies are of limited predictive value of the potential toxicity when BOC is used in combination with PR and either PEG-INF or ritonavir.

In clinical trials, an additional decrease in red blood cells (RBC) was observed when BOC was used in combination with PR and PEG-INF but similar effects were not found in the monkey study. In a TGA letter dated 30 June 2011, the sponsor was requested to comment on this "discrepancy", to provide a rationale for dose selection in the monkey study and to comment on whether the study was of sufficient duration to detect a possible additional effect of BOC when administered to cynomolgus monkeys in combination with PR and PEG-INF.

In response, the sponsor advised that the study was designed with reference to the FDA Guidance for Industry: Nonclinical Safety Evaluation of Drug or Biologic Combinations[8] and International Conference on Harmonisation M3;[9] the study duration was based on indication (non chronic) and the "duration of dosing previously determined to be required to observe the known toxicities of the individual components of the drug combination. A

[8] Food and Drug Administration, "Guidance for Industry: Nonclinical Safety Evaluation of Drug or Biologic Combinations", March 2006, Web, accessed 29 February 2012 www.fda.gov/OHRMS/DOCKETS/98fr/05d-0004-gdl0002.pdf.

[9] European Medicines Agency, "Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals", June 2009, Web, accessed 6 March 2012 < www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002720.pdf>.

study of longer duration was considered inappropriate because of the generation of interferon neutralizing antibodies after repeated administration to monkeys. Dose levels were selected to achieve systemic exposures relevant to the intended clinical use (for example, higher than the clinical therapeutic level) and to allow for the detection of potential combination toxicities (for example, synergistic, additive and/or novel toxicities) ... No additional effect of BOC was detected."

It is accepted that the study duration was limited by the development of neutralising antibodies to PEG-INF (these developed by the end of treatment for one month study but not for two weeks). However, BOC dose selection was not adequately justified in view of the limited/negligible activity at the dose used. The sponsor contended that the "data were adequate and sufficient to support progression of clinical studies that further evaluated effects of the triple combination". The value of the study is considered to be limited to this context only. The study is not considered to have provided definitive information on potential toxicities with the drug combination.

Deaths with boceprevir

Note: Deaths associated with gavage accidents which occurred in most nonclinical studies were able to be defined as such. These are not included in the discussion below.

Deaths after single or repeated doses of BOC in rodent species were puzzling and quite striking. In many cases, an association with treatment could not be ruled out but information was not available to determine cause(s), target organs and potential relevance to humans using BOC.

Acute fatalities

In acute toxicity studies, the highest single PO dose given to dogs (300 mg/kg), monkeys (1000 mg/kg) and rats (2000 mg/kg) was virtually without effect except for transient gastrointestinal disturbance/salivation. In mice, a single 2000 mg/kg PO dose was fatal in the acute toxicity studies but it was associated only with clinical signs (respiratory difficulties) in the micronucleus study.

Where they occurred in mice, deaths were preceded by weakness, hypothermia, respiratory difficulties, dehydration and signs of gastrointestinal disturbance (abnormal stool after IP dose) and (for mice) marked abnormalities in clinical chemistry, especially liver and haematology parameters; however, the target organ/s and possible underlying mechanisms for acute, fatal toxicity was not clear from these studies.

In rats, a single 500 mg/kg PO dose of BOC was fatal within 20 min after administration to 7 day old neonates, but no pre mortal clinical signs or tissue changes at necropsy (limited to oesophagus, trachea and lungs, and thoracic cavity) were found and again there was no information on or discussion of possible target organs or cause of death. The next highest dose (250 mg/kg/day) did not cause overt toxicity apart from a slight decrease in body weight in neonates.

A relatively small margin between fatal and no adverse effect doses raises the possibility that BOC has a narrow therapeutic index; however, this was not able to be clearly defined on the basis of the animal studies.

Plasma drug concentrations after fatal doses were generally higher than those expected in humans, except in neonatal rats where concentrations of the active diastereomer were lower. Drug exposure of animals after single doses is shown in Table 7.

Table 7: Drug exposure of animals after single doses of boceprevir diastereomers.

		SCH 534128	SCH 534129	SCH 629144
Dog (300 mg/kg)	C_{max} µg/mL	8.8 (6)	7.9 (7.9)	No data
(no effect dose)	AUC µg.h/mL	65.8 (6)	56.5 (10)	
Monkey (1000 mg/kg)	C_{max} µg/mL	0.9 (0.6)	7.7 (7.7)	44.5 (8)
(no effect dose)	AUC µg.h/mL	~10 (0.9)	75 (13)	457 (6)
Rat (2000 mg/kg) PO **(no effect dose)**	Exposure data are not available and cannot be extrapolated or predicted from other studies because of non-dose-proportional kinetics at these levels and probably incomplete PO absorption			
21 day old rat (500 mg/kg)	*C_{max} µg/mL	~10 (6.7)	~10 (10)	~0.4 (0.07)
(fatal dose)	AUC µg.h/mL	~25 (2.2)	~25 (4.5)	~1 (0.01)
21 day old rat (250 mg/kg)	*C_{max} µg/mL	~5 (3.3)	~5 (5)	~0.2 (0.04)
(no adverse effect dose)	AUC µg.h/mL	~12 (1.1)	~12 (2)	~0.5 (0.006)
Mice M / F (2000 mg/kg) (fatal in one study, but not in another)	C_{max} µg/mL AUC µg.h/mL	21.6 / 27 (14 / 18) 300 / 176 (26 / 15)	17 / 22 (17 / 22) 196 / 128 (35 / 23)	60 / 67 (11 / 12) 316 / 412 (4 / 5)
Human 800 mg TID	C_{max} µg/mL AUC µg.h/mL	~1.5 11.3	~1 5.6	~5.4 76

* Data estimated from exposure at 150 mg/kg/day in neonatal males and females; these data provide an indication of the level of drug concentrations.
Note: animal-to-human exposure multiple is shown in brackets.

Fatalities with repeated PO doses of boceprevir

Target organs and primary causes of deaths were also not identified after repeated dosing with BOC. In female rats, BOC was relatively benign at doses of 125-150 mg/kg/day for up to 3 months; however, 200 mg/kg/day for 28-49 days was fatal. There was a rapid onset of changes in clinical chemistry and haematology parameters prior to death:

- marked lymphocyte depletion but increased (up to 4 fold) neutrophils;
- increases in liver function parameters;
- marked (up to 85%) decreases in cholesterol and triglyceride levels (the latter falling below the assay detection limit); and
- slight shifts in calcium, phosphorous, sodium and protein levels).

Findings at necropsy (adrenal cortex hypertrophy, hypocellularity and/or haemorrhage of bone marrow, lymphoid atrophy and/or necrosis in several lymphoid tissues, ovarian follicular atresia, uterine and vaginal atrophy) were not adequately explained in terms of target organs for BOC toxicity or possible underlying mechanism. The investigators suggested the changes reflected states of stress and dehydration but there was no attempt to explain underlying events that might have resulted in these states.

Deaths also occurred in pregnant rabbits given BOC ≥ 50 mg/kg/day PO for ≥ 13 days, and again possible causes and toxicity leading to death were not discussed. Only weight

reduction, decreased food consumption and decreased faecal output (suggestive of possible gastrointestinal effects) were reported prior to death/morbid sacrifice. A No effect level (NOEL) in pregnant rabbits was not established; interestingly, no adverse side effects were reported for non pregnant rabbits given 1000 mg/kg/day PO for ten days. Underlying reasons for these incongruous findings in pregnant and non pregnant rabbits were unclear but it is acknowledged that pregnant rabbits are more sensitive to toxins than non pregnant rabbits.

In pregnant mice, doses of 1000-2000 mg/kg/day for 2-4 days were fatal (with preceding signs similar to that described for other deaths), but doses of 900 mg/kg/day for up to three months were well tolerated.

Fatalities with BOC tended to occur at random and cannot be explained or predicted in terms of possible underlying mechanism of target organs for toxicity. Dose volumes (generally 5 or 10 mL/kg) were kept constant across all groups within each study, ruling this out as a possible contributor. Where plasma BOC levels in decedents were determined, these were reported to be similar to those found in animals that survived treatment, which adds to the uncertainty over BOC induced fatalities.

Overall, it appears that BOC has the potential to be fatal at clinically relevant exposure levels. However, a clear understanding of possible underlying mechanisms and target organs is not able to be determined from the nonclinical studies.

In response to a TGA request (letter dated 30 June 2011) to comment on fatalities in the nonclinical studies of BOC, the sponsor provided clarifying information that minimised concerns over inter study discrepancies. However, no light was shed on possible mechanism/s or causes of death due to BOC. The sponsor's contention that they occurred at "extremely high doses" is not reassuring given that exposure at fatal doses is not substantially higher than expected human exposure. The sponsor's statement that "extensive clinical monitoring/experience has identified no concerns" is acknowledged. The fact that no deaths occurred in monkey studies of BOC is also of some reassurance *albeit* limited because drug exposure was at best similar and mostly lower that that expected in humans.

Genotoxicity

A full and extensive range of standard genotoxicity assays were performed with BOC, all of which were negative. Exposure to both diastereomers in these assays was likely to be adequate since the two diastereomers equilibrate ~1:1 *in vitro*. However, it is unlikely that there was substantial, if any, exposure to the main human ketone reduced metabolites since these are not formed to any great extent by the metabolic activation system used in the assays (rat liver S9 fraction). Therefore, none of the *in vitro* assays with BOC provided complete information on the potential genotoxicity of this drug.

In response to request for comment on the above deficiency (TGA letter of 30 June 2011 refers), the sponsor commented that "this metabolite lacks the electrophilic moiety (ketoamide) present in BOC and would have less potential to react with activated nucleophiles than BOC. Since the parent has been comprehensively evaluated for potential genotoxic effects both *in vivo* and *in vitro*, and found not to be genotoxic or carcinogenic, SCH 629144 (composed of stereoisomers SCH 783004, SCH 783006, and SCH 783007) is considered not to be genotoxic or carcinogenic."

The sponsor's arguments are theoretically based and unsubstantiated. However, the sponsor also pointed out that the metabolites were present in the rodent carcinogenicity studies, both of which did not provide evidence for a carcinogenic risk to humans.

It is accepted that exposure to the individual components of BOC was higher in either the mouse or the rat at some stage during the carcinogenicity studies. The (unknown) risk of genotoxicity with BOC metabolites is considered low in the context of the proposed indication and the risks associated with the parent drug itself. Therefore, this matter will not be pursued for this application.

Carcinogenicity

Standard carcinogenicity studies were performed in mice (once daily doses up to 500 mg/kg/day for males, 650 mg/kg/day for females) and rats (once daily doses up to 125 mg/kg/day for males, 100 mg/kg/day for females). No effect levels were 250 mg/kg/day for male or female mice and 20 mg/kg/day for male or female rats. These studies suffered from the same limitations as described above for the repeat dose toxicity studies, that is, exposure to BOC diastereomers and to the main human metabolites was inadequate in terms of extent and duration each day (see Table 6). However, it is acknowledged that exposure to the individual components of BOC was higher in either the mouse or the rat at some stage during the carcinogenicity studies.

Findings were consistent with those in the studies of shorter duration and no additional target organs or pathological changes were identified, with the exception of presence of dark material in the gall bladder of mice. The latter finding was not associated with other changes and it is of equivocal toxicological significance (an association with enterohepatic recirculation of drug material which is prominent in this species may be a possibility).

Tumour findings consisted of a higher incidence of hepatic adenoma in female mice given the highest dose of BOC when compared with control females. This development is not unexpected given that the liver is a target in the mouse; as mentioned above, the human relevance of liver changes with BOC in rodents is equivocal.

Reproductive toxicity and embryofoetal development

A full range of reproductive toxicity studies, covering all segments, was performed in mice, rats, and rabbits given single daily PO doses of BOC. As with all other nonclinical studies, these were limited by relatively poor and intermittent exposure to the active diastereomer as well as to BOC metabolites in rodents. In rabbits, only total BOC levels were determined and no other pharmacokinetic information was provided for this species. Therefore, it is not known if rabbits are similar to humans in terms of processing BOC, which further limits the usefulness of the rabbit embryofoetal development studies. Concerns over the limitations of these studies are somewhat mitigated by the fact that BOC will be contraindicated in pregnancy because it will be coadministered with PR, a known teratogen.

Placental transfer and excretion into milk

A placental transfer study in pregnant rats found that BOC and its metabolites readily cross the placenta and distribute to fetal tissues (including the central nervous system (CNS)) after a single PO dose of 150 mg/kg radioactive carbon labelled (^{14}C)-BOC. With the exception of the embryonic sac, drug levels in all foetal tissues examined (cardiac blood, brain, heart, liver, kidneys, lung) were 3-20 times lower than corresponding maternal blood levels and were below detectable limits by 24 h after dosing. In the embryonic sac, levels were up to 13 times higher than those in maternal blood levels and prolonged retention (for at least 48 h after maternal dosing) was found, suggesting a potential for drug accumulation in foetal tissues with repeated dosing, which might be compounded under conditions of continuous daily exposure.

BOC and related compounds were also found in rat milk and in pup plasma after a single 30 mg/kg PO dose of ^{14}C-BOC was administered to lactating rats, at levels lower than those

in maternal plasma. Based on exposure to nursing rat pups and estimations of infant milk intake, the sponsor estimates that nursing human infants would be exposed to about 0.6% of a maternal dose of BOC (that is, up to ~14 mg/day) via milk.

Administration of BOC directly to neonatal rats was associated with impairment of male sexual development (see section below: 'Use in children - Studies in neonatal and juvenile animals'). The relevance of this finding for nursing infants is unclear because it is unlikely that infants would be exposed to high drug concentrations via breast milk.

Effect on fertility and early embryonic development

Treatment of male or female rats or female mice with BOC prior to mating or from Day 1 of gestation resulted in a striking decrease in fertility (male and female rats) and a substantial increase in early embryonic deaths (rats and mice). These effects were generally dose-dependent and were independent of overt maternal toxicity.

A decrease in fertility in treated male rats was predictable from testicular findings in repeat dose toxicity studies (see section above: 'Male reproductive tissue toxicity'). However, as already discussed, the underlying mechanism is not clear and was not investigated. Impairment of female fertility (in treated females paired with untreated males) was not predictable from repeat dose toxicity studies and it was not possible to determine whether pregnancy failures in treated females were due to impairment of maternal fertility, impairment of early embryonic viability, or both.

In rats, oestrous cycling during the mating period was unaffected by BOC treatment and there were no clear effects on LH, FSH, oestrogen and progesterone levels during pregnancy, although the latter assays were difficult to interpret. These findings do not add to the understanding of how BOC affects female fertility and/or early embryonic development. However, it is notable that doses causing early embryofoetal loss were without effect on the developing foetus if they were administered after implantation was completed (that is, from gestation Day 6 in rats).

Females treated with BOC recovered full reproductive capacity and had apparently normal early pregnancy parameters if a four week washout period was allowed after a three week treatment period. No studies were done to determine if reproductive capacity was restored in males, although evidence of very slow reversibility was shown for testicular tissue changes in the repeat dose toxicity studies. There were no studies assessing offspring development in animals that recovered from the effects of BOC.

The NOEL for impairment of male fertility was 75 mg/kg/day (for up to 10 weeks), which was associated with exposure to BOC diastereomers and main human metabolites lower than that expected in humans (see data for 150 mg/kg/day for rats in Table 6). This dose level is higher than the NOEL for similar histopathological changes found in the 3-6 month repeat dose toxicity studies (15-25 mg/kg/day), probably because of a very high sperm reserve capacity in rats.

The no effect dose for impairment of female fertility and early embryonic deaths was 75 mg/kg/day for female rats and 500 mg/kg/day for female mice, both of which are also associated with drug exposure lower than or similar to that expected in humans (see Table 6).

In response to a request of whether information was available to clarify the effects described above (TGA letter of 30 June 2011), the sponsor advises that "no additional investigative/mechanistic reproductive toxicity studies are considered warranted or currently planned", particularly since BOC will be administered in combination with drugs that are already contraindicated in pregnant females. This response was considered acceptable.

Embryofoetal and peri/postnatal development

BOC had no effect on the developing foetus if it was administered once daily to pregnant rats (up to 600 mg/kg/day) or rabbits (up to 300 mg/kg/day) during the period of organogenesis (from gestation day 6 or 7 until gestation day 17 or 19). There was also no effect on perinatal or postnatal development if it was administered to pregnant rats from gestation Day 7 until postnatal Day 20 (up to 150 mg/kg/day). The highest doses used for the main studies were associated with the following (approximate) drug concentrations (Table 8).

Table 8: Highest drug concentrations of boceprevir diastereomers used in main studies.

Female rat (600 mg/kg)	**SCH 534128**	**SCH 534129**
C_{max} µg/mL	6 (4)	5 (5)
AUC µg.h/mL	91 (8)	78 (12.8)
Female rat (150 mg/kg)	**SCH 534128**	**SCH 534129**
C_{max} µg/mL	4.4 (3)	4 (4)
AUC µg.h/mL	57 (5)	52 (9)
Female rabbit (300 mg/kg/day)	**Total boceprevir**	
C_{max} µg/mL	4.3 (1.7)	
AUC µg.h/mL	32.8 (1.9)	
Human 800 mg TID	**SCH 534128**	**SCH 534129**
C_{max} µg/mL	~1.5	~1
AUC µg.h/mL	11.3	5.6

Note: animal-to-human exposure multiple is shown in brackets.

As mentioned above for other nonclinical studies of BOC, the lack of effects in the embryofoetal and peri/postnatal development studies is of limited reassurance given the limitations of the animal models and the less-than-adequate exposure levels.

Pregnancy classification

BOC is proposed for use in combination with PR (Pregnancy Category X) and PEG-INF (Category D) and therefore Victrelis will be contraindicated in pregnancy. However, it is also necessary to assign a category for BOC in its own right. This is difficult without a basic understanding of whether and how BOC affects early embryofoetal development and in view of the limitations of the reproductive toxicology program with BOC.

In the draft PI for Victrelis, the sponsor proposes 'Category B' for use of BOC in pregnancy, without specifying the B subcategory. Given that the AE of BOC in animals appears to be restricted to fertility/early embryonic development and since there were no positive findings in the rat and rabbit fetal development (teratology) studies, Category B2 appears to be the most appropriate category because it also refers to inadequacies in animal studies:

> *"Category B2*
>
> *Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed.*

Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of foetal damage."

The above category also refers to an absence of findings in pregnant women taking BOC, which will require confirmation by the clinical evaluator/Delegate.

Modifications to the proposed statements on use in pregnancy and effects on fertility are suggested.

Use in children - Studies in neonatal and juvenile animals

An *in vitro* study comparing the metabolism of BOC in adult human liver samples with that in paediatric (2-17 years) liver samples showed no difference in the nature or quantity of metabolites (M28, M31 and oxidative metabolites) formed in S9 and cytosolic fractions.

A preliminary two week repeat dose toxicity study in rat pups aged six days found that BOC was fatal within 20 min after administration of a 500 mg/kg PO dose (see section above: 'Deaths with boceprevir') but had no overt effects apart from decreased weight gain at doses of 250 mg/kg/day.

In the main study, neonates (age Day 6) were given PO BOC 25, 75 or 150 mg/kg/day (which are similar to dose levels used in the adult repeat dose toxicity studies) and were monitored for clinical signs, changes in clinical chemistry, haematology and urine parameters, as well as sexual developmental landmarks (balanopreputial separation for males, vaginal patency for females) over a three month period. Full necropsy investigations were performed at the end of a four week treatment free period.

Notable findings consisted of AEs on male sexual development (increased time taken to attain balanopreputial separation) and associated AEs on reproductive tissues (as observed in adults) which were more severe after the four week recovery period than at the end of the treatment period. A no effect dose for these effects (25 mg/kg/day) was consistent with that found in adult male rats; it is not clear if the effects on sexual development are linked with testicular changes or whether they occur via a different mechanism.

Increased liver weights, but no associated tissue changes, were observed in males and females given 75 or 150 mg/kg/day; this is consistent with findings in adults. However, thyroid follicular cell hyperplasia was also observed in rats and this was not reported in any study of adult rats. Both the liver and the thyroid changes were reversed after a four week recovery period.

A one month study to further investigate the findings of thyroid cell hyperplasia in neonates given BOC 150 mg/kg/day showed some evidence for transient increases in plasma T3 and/or thyroid stimulating hormone (TSH) levels, but the findings were not conclusive and the validity of the study was questionable given that expected responses were not obtained in the positive control (phenobarbitone) group.

Since BOC was found to strongly induce CYP450 enzymes in rodents (mice), an effect on thyroid hormone levels may be expected. As noted in other areas of this assessment, BOC suppresses rather than induces CYP450 in humans (and monkeys) and therefore the potential clinical relevance of this finding is equivocal.

While findings in studies with neonatal rats were generally consistent with those in adult rats, all rodent studies of BOC are of limited value for defining the potential activity/toxicity profile of this drug when used in humans. Therefore, studies in neonatal/juvenile rats cannot be used to support the use of BOC in human children.

Impurities

Specifications for some individual degradants or impurities in the proposed formulation exceeded the limit acceptable without qualification or justification (0.15% for individual impurities in the finished product, for drug doses > 2 g/day).[10]

Various amounts of each of the impurities were present in batches used for *in vitro* assays of mutagenicity or clastogenicity, all of which were negative. Total drug concentrations used in these studies (up to 5000 µg, or levels limited by cytotoxicity/precipitation) are likely to have contained impurities greatly in excess of those expected to be delivered to humans via Victrelis.

Drug batches used for repeat dose nonclinical studies contained varying amounts of impurities and specific one month rats studies with spiked batches were also performed, where drug batches containing 4-9% (total) impurities were compared with batches containing ~50% lower levels of total impurities. No difference in the toxicity profile was detected between batches; although it is questionable whether the studies were sensitive enough to detect such differences if they existed.

Information from the toxicology tabulated summaries included in the submission was used to assess whether proposed impurity levels are qualified on the basis of total daily intake in the animal studies when compared with that expected in humans. After assessment on the basis noted above, limits for select impurities remained unqualified and required reduction, along with a reduction in total impurity levels, or further justification.

A request to amend or justify limits for impurities that remained unqualified was submitted to the sponsor in a letter from TGA dated 30 June 2011.

- Based on the sponsor's reply (dated 28 July 2011), limits for the above indicated SCH compounds are considered qualified on the basis that these substances are also metabolites of BOC.
- The limit proposed for individual dimers has been reduced at release and shelf life, with a reduced limit for total dimers. The sponsor justification for these limits on nonclinical grounds was considered acceptable.
- The sponsor provided adequate nonclinical qualification for the proposed total impurity levels for individual groups of compounds and for overall total impurity/degradation products.
- Reasons were provided to explain why further reductions in impurity and degradation limits were impractical/not possible.

Overall, the proposed, revised, specifications for impurities and degradation products (as stated in the sponsor's documents provided under cover of a letter dated 28 July 2011) were considered acceptable on nonclinical grounds.

Nonclinical Summary and Conclusions

- The submission from was Schering Plough Pty Limited extensive and generally compliant with all relevant nonclinical guidelines. However, a once daily (PO) dosing regimen was used for all animal studies, whereas the proposed human dose is three times daily. This resulted in animals often being variably exposed, poorly exposed

[10] European Medicines Agency, "ICH Topic Q 3 B (R2) Impurities in New Drug Products", June 2006, Web, accessed 7 March 2012 < www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002676.pdf>

and/or unexposed to the individual BOC diastereomers and/or its metabolites for a large part of each day, compared with continuous exposure proposed for humans via a three times daily dosing regimen. In addition, quantitative differences in metabolism between rodents (used for many key toxicity studies) and humans (or monkeys) limited the utility of rodents as models for exposure to the main circulating human metabolites of BOC.

- Deficiencies in animal exposure to the components of BOC, relative to expected human exposure, limit the value of the nonclinical program for predicting potential toxicities of potential human relevance.
- Primary pharmacology studies adequately demonstrated that BOC binds to the active serine site on HCV protease, with a dissociation rate about 2 times longer than the time taken for new NS3 proteins to form. Inhibition of HCV replication by BOC was demonstrated against the isolated viral protein strain 1b (equilibrium binding constant, Ki* 19.8 nM) and in human hepatoma cells transfected with clone 16 HCV replicon (IC_{50} and IC_{90} values 200 nM and 400 nM, respectively, after incubation for 72 h). Inhibition by BOC was concentration and time-dependent, was associated with almost complete loss of replicon RNA (< 1 copy/cell remained after 15 days' exposure to 6 x IC_{50}), and resulted in reduced synthesis of new replisomes. BOC mediated inhibition of replicon RNA followed first order (linear) kinetics, with a $t_{1/2}$ of 12 h.
- In cell based assays, the inhibitory effect against HCV replication (genotype 1 b replicon) was additive with the inhibitory effect of interferon-α and was unaffected by anti-HIV protease inhibitors. In enzyme based assays, BOC showed similar inhibitory potency at HCV genotype 1a and 1b proteins and at genotype 2a and 3a proteases.
- Studies have not investigated HCV activity with the dual combination BOC and PR, and/or with the triple combination BOC, PR and interferon-α.
- BOC is a mixture of two diastereomers, with SCH 534128 the main active component, and SCH 534129 at least 41-130x less active against HCV. The main human circulating (ketone reduced) metabolites of BOC are likely to be inactive against HCV, based on structural considerations.
- Resistance associated variants (RAVs) that render HCV resistant to BOC were assessed in cell based and enzymatic assays. Several resistance loci were identified, including some near the inhibitor binding site on HCV, at amino acids V36, V55, V158, Q41, F43, T54, R155, A156 and V170. Of the RAVs identified to date, greatest reductions in BOC potency were observed with A156T/S/V, T54C and R155I/G/T substitutions. RAVs remained sensitive to interferon-α and were cross-resistant to another ketoamide protease inhibitor, telaprevir.
- Studies have not been done on the emergence of RAVs with the dual combination BOC and PR, and/or with the triple combination BOC, PR and interferon-α.
- An extensive battery of *in vitro* assays, covering numerous receptors, proteases, and other enzymes, suggested that BOC (generally at 10 μM or ~5 μg/mL) is unlikely to widely interact with biological systems or biochemical processes other that its intended target at these concentrations. The drug also showed low potential for cytotoxicity in various cell lines at concentrations ≥ IC_{90} for HCV; and it did not interact *in vitro* with HIV protease inhibitors, either in terms of cytotoxicity or viral inhibition.
- BOC inhibited the activity of the human proteases cathepsins B (IC_{50} 9-10 μM), G (IC_{50} 2.2 μM) and L (IC_{50} 8-11 μM); and of acyl CoA-cholesterol acyltransferase from

rat liver (IC_{50} 1.7 μM; although no effect was found at rat HMG-co-A reductase activity). The potential significance of this inhibition is unclear and was not explored.

- A standard battery of *in vivo* and *in vitro* safety pharmacology studies (including cardiovascular safety) did not identify potential target organs for secondary activity, at single doses of BOC up to 50 or 200 mg/kg. Exposure to the active BOC diastereomer and to the main human metabolites of BOC was probably lower than or similar to that expected in humans at these doses.
- The oral absorption of BOC in animals is low (~35% in rodents, 12% in monkeys) but rapid (T_{max} generally 0.5 h- 4 h), is improved by food (shown in monkeys, as in humans) and appears to be saturable. For a given PO dose, higher plasma concentrations were achieved in female rats than in male rats, but there were no sex differences in monkeys (as in humans).
- Oral bioavailability in animals is also low (26-35% in rodents, 4% in monkeys) due to extensive and rapid first pass metabolism and total drug is cleared (by the liver) fairly rapidly in all species tested, with no accumulation of parent or metabolites occurring with repeated once daily dosing. Plasma concentrations of BOC are generally not dose proportional. Excretion is mainly (> 80%) as metabolites via the faeces in all species investigated.
- In adult rats, BOC and metabolites distributed to all tissues except the CNS (although drug was detected in fetal CNS tissues in a placental transfer study; see below). Highest concentrations in adult rats were observed in the liver, intestines, prostate gland, epididymides, thyroid gland, pancreas, pituitary gland and bone marrow. Drug associated material was cleared from all tissues by 8 h after a single PO dose, with the exception of the lymph nodes, excretory organs, pituitary gland and bone marrow where it persisted for up to 24 h. There was no evidence for drug retention in pigmented tissues after a single dose. BOC is moderately (≤ 70%) bound to plasma proteins.
- Whole body tissue distribution studies after repeated dosing were not done and therefore it is not known if drug accumulates in particular tissues with repeated dosing.
- The metabolism of BOC diastereomers in all species examined including humans is complex, involving reduction, oxidation, cleavage, dimerisation and various combinations of these reactions to produce a wide array of > 60 metabolites that are excreted predominately via the bile in faeces. In humans and monkeys, the main metabolic pathways involve (mainly cytoplasmic) aldoketoreductases (AKR), which occur in hepatic and non hepatic tissues; and, to a lesser extent, CYP450 isoforms 3A4 and 3A5. In rodents, BOC is metabolised mainly by CYP450 3A4/3A5 isozymes. Phase II metabolism (glucuronidation) apparently does not feature in the metabolism of BOC in primates or rodents.
- In addition to BOC diastereomers, the main (≥ 10% of drug related material) circulating substances in humans are M28 (produced by AKR mediated reduction of SCH 534128) and M30 and M31 (produced by AKR mediated reduction of SCH 534129). These are isomers of a metabolite designated SCH 629144 and are also formed to varying extents in monkeys and mice, but they are only minor metabolites in rats. SCH 629144 isomers have short half lives (generally < 2 h) in all species examined. There were no studies of BOC isolated metabolites.

- BOC is a substrate and an inhibitor of CYP3A4/A5; the parent drug and/or its metabolites inhibit (monkeys) or induce (rats) a range of CYP isoforms; BOC is a substrate and an inhibitor of the P glycoprotein transporter; and its metabolism by AKR or by CYP450 is affected by drugs that inhibit or induce the activity of these enzymes. The effect of BOC or its metabolites on AKR activity was not investigated and the possibility of an inhibitory or inducing effect cannot be ruled out.
- In *in vivo* studies, coadministration of BOC with PR, PEG-INF, ritonavir and/or diflunisal appeared to affect exposure to one or more of the coadministered drugs but it was not possible to conclusively define the interactions on the basis of the nonclinical studies.
- The main toxicology studies were done in monkeys (up to 12 months duration), mice (3 months) and rats (up to 6 months) using single daily PO doses of BOC. Based on total daily AUC, exposure to BOC diastereomers and to the major human circulating metabolites was generally lower than that expected in humans. Further, the once daily dosing regimen resulted in exposure at some dose levels being variable and negligible/non existent for a large part of each day.
- BOC caused minimal effects in monkeys: gastrointestinal disturbance (diarrhoea and emesis, on occasion after 1000 mg/kg), increased cholesterol and triglyceride levels, suppression of hepatic CYP450 enzymes, prolonged APPT, and minimally reduced RBC parameters. Target organs for systemic toxicity were not identified.
- In rodents, the main target organs for toxicity were the liver (possibly associated with extensive metabolism by CYP450) and reproductive tissues (male rats only).
- BOC was negative in a full and extensive range of standard genotoxicity assays. Exposure to both diastereomers in these assays was likely to be adequate since the two diastereomers equilibrate approximately 1:1 *in vitro*. However, it is unlikely that there was substantial, if any, exposure to the main human ketone reduced metabolites since these are not formed to any great extent by the metabolic activation system used in the assays (rat liver S9 fraction). Therefore, none of the *in vitro* assays with BOC provide complete information on the potential genotoxicity of BOC.
- Standard carcinogenicity studies were done in mice (once daily PO doses up to 500 mg/kg/day for males, 650 mg/kg/day for females) and rats (once daily PO doses up to 125 mg/kg/day for males, 100 mg/kg/day for females). As for other nonclinical studies, the once daily dosing regime was not associated with exposure to BOC diastereomers and metabolites substantially higher than that expected in humans.
- Tumour findings consisted of a higher incidence of hepatic adenoma in female mice given the highest BOC dose when compared with control females. Other (non neoplastic) findings in mice and findings in rats were consistent with those in studies of shorter duration and no additional target organs or pathological changes were identified, with the exception of presence of dark material in the gall bladder of mice, the toxicological significance of which is unclear.
- A full range of reproductive toxicity studies was performed in rats, mice and rabbits, with BOC administered PO once daily. The drug was found to cross the placenta and distribute widely to the foetus, including to the CNS. BOC and related material was also excreted in milk during lactation. Concentrations in foetal tissues and milk were generally lower than those found in maternal plasma and were cleared in parallel.

- Treatment of male or female rats or female mice with BOC prior to mating or from Day 1 of gestation resulted in a striking decrease in fertility (male and female rats) and a substantial increase in early embryonic deaths (rats and mice). These effects were generally dose dependent and were independent of overt maternal toxicity.
- Female rats treated with BOC recovered full reproductive capacity and had apparently normal early pregnancy parameters if a 4 week washout period was allowed after a 3 week treatment period. No studies were done to determine if reproductive capacity was restored in males, although evidence of very slow reversibility was shown for testicular tissue changes in the repeat dose toxicity studies. There were no studies assessing offspring development in animals that recovered from the effects of BOC.
- BOC had no effect on fetal development if it was administered after implantation was established in rats and rabbit and there were no effects on peri/postnatal development of offspring from treated rats.
- Repeat dose toxicity studies of BOC in neonatal rats showed increased liver weights, but no associated tissue changes, thyroid follicular cell hyperplasia, degeneration of male reproductive tissues, and increased time taken to attain balanopreputial separation. No effect doses were associated with exposure to BOC that was lower than that expected in humans.
- Repeat dose toxicity studies of drug combinations comprised a one month study of PO BOC (mainly once daily) with PR and either ritonavir or (the unregistered nonsteroidal anti inflammatory drug(NSAID)) diflunisal in rats; a three month study of BOC and PR in male rats (reproductive tissue toxicity study); and a one month study of BOC with PR and PEG-INF in monkeys.
- Findings were consistent with effects observed in previous or current studies of the individual components and no novel toxicities were identified. However, it was not possible to conclusively determine whether the effects of one component were altered by concomitant drugs, or whether drug interactions (including pharmacokinetic) occurred.
- Deaths associated with BOC treatment were reported in various studies within the entire toxicology program. These were not explicable in terms of underlying target organs for toxicity and remain puzzling.
- Levels of specific individual and total impurities proposed for Victrelis (as revised in the sponsor's response included with letter dated 28 July 2011) are qualified on nonclinical grounds.
- Overall, findings from nonclinical studies of BOC do not preclude the registration of BOC for the proposed indication; however, the nonclinical program has not sufficiently defined the potential toxicity profile of this drug.

Conclusions and Recommendations

Nonclinical studies provided adequate evidence that BOC effectively inhibits HCV replication *in vitro* at concentrations readily exceeded in the liver *in vivo*. Numerous resistance variants to BOC emerge with time and increasing drug concentration. These have variable impact on the potency of BOC and confer cross resistance to other ketoamide HCV protease inhibitors including telaprevir. It is noted that BOC is not indicated as monotherapy due to the propensity for resistance. Cross resistance with PEG-INF or ritonavir is not expected due to their differing mechanisms of action. BOC showed no significant activity against the HIV protease *in vitro*.

In vitro secondary pharmacology screens with BOC showed no evidence for interactions with a wide range of enzyme, non HCV protease, and neurotransmitter receptor systems, indicating selective activity.

The nonclinical toxicity studies were generally of adequate duration and did not identify any effects which would preclude registration, however there were some limitations of the nonclinical testing which should be taken into consideration for the risk-benefit analysis:

- All toxicity studies utilised once daily dosing whereas BOC will be administered three times daily in the clinic. Treatment of animals at least twice daily appeared feasible. Dose limiting toxicity (including haematological effects observed clinically) was not clearly identified in the animal studies.
- BOC is extensively metabolised by several processes to form a large number of metabolites in humans and animals. Although all identified human metabolites were formed in test animals, there were substantial quantitative differences in levels of metabolites between species. Levels of the main human metabolites were relatively low in rodents (the reproductive toxicity and carcinogenicity test species), and adequate in monkeys, whereas daily exposure to the active diastereomer (SCH 534128) was substantially lower in monkeys than in humans due to more rapid clearance.
- No toxicity studies were performed where exposure to the individual diastereomers and metabolites of BOC simultaneously and consistently matched or exceeded the exposure to these components expected in humans.
- The toxicity of BOC in combination with PR and PEG-INF was investigated in a single toxicity study in monkeys but this was limited to one month in durationdue to antibody formation.

Should BOC be registered on clinical grounds, numerous amendments to nonclinical statements in the proposed Product Information are recommended.

IV. Clinical Findings

Introduction

The key body of clinical data in support of this application consists of twenty Phase I studies; three Phase II studies (two completed, one ongoing); five Phase III studies (two completed, three ongoing); and one long term safety study.

The clinical studies in this application (Phase I, II, III) complied with CPMP/ICH/135/95, an internationally accepted standard for the design, conduct, recording and reporting of clinical trials.[11]

Pharmacokinetics

Background

The antiviral activity of BOC was evaluated using the HCV replicon system utilising an assay for slow binding inhibitors of NS3 protease. Using this replicon, the IC_{50} and IC_{90} for HCV were 200nM and 400nM respectively. BOC with PEG showed additive effects with respect to suppression of replicon RNA without synergy or antagonism. The drug substance exists as an approximately equal mixture of two diastereomers, SCH 534128 &

[11] European Medicines Agency, "Guideline for Good Clinical Practice", July 2002, Web, accessed 8 March 2012 < www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf>.

SCH 534129, the former is at least 41 to 130 fold more potent as an HCV protease NS3 inhibitor than SCH 534129. The diastereomer content has been consistent throughout development and does not change during drug product manufacturing. The molecular formula is $C_{27}H_{45}N_5O_5$ and the molecular weight is 519.7. Resistance to BOC was associated with the following amino acid substitutions: V36M, T54A, R155K and V170A; these mutations conferred a 2 to 10 fold reduction in response to BOC. A156T and A156V, conferred the greatest fold resistance to BOC (50 fold) but at a fitness cost (decreased replicative capacity) with the A156T mutation.

Nonclinical pharmacokinetic (PK) studies were conducted in five animal species (mice, rats, rabbits, dogs, monkeys) to describe the absorption, distribution, metabolism and elimination of BOC. The PK attributes of BOC include moderate absorption and oral bioavailability. Toxicokinetic data from toxicity studies demonstrated that exposure (C_{max}, AUC) to the active diastereomer and SCH 534129 increased with increasing dose; moreover, the species used received adequate exposure for toxicity evaluation. Exposure was greater in female than in male rodents but not in monkeys or humans. Exposure to the major circulating human metabolites, SCH 629144 (the total of the individual stereoisomers resulting from the main metabolic pathway), was also evaluated; adequate animal-to-human exposure multiples were achieved in mice and monkeys. BOC was distributed to tissues, crossed the placenta in rats and was excreted in the milk of nursing rats. Based on the results of *in vitro* and *in vivo* studies, the AKR 1C isoforms and CYP 3A4/5 were identified as the primary enzymes responsible for BOC metabolism.

Excretion of BOC derived material is mainly via the biliary/faecal route in animals and humans. BOC caused direct and time dependent inhibition of CYP 3A4/5, and co administration with the CYP 3A4/5 substrate midazolam (MDZ) in human subjects increased exposure to MDZ. BOC is also a substrate and moderate inhibitor of P-gp. Co administration with ketoconazole, a CYP 3A4/5 inhibitor and a P-gp inhibitor, increased exposure to BOC and SCH 534128 (the active stereoisomer) 2.3 fold and 2.5 fold, respectively. A total of twenty Phase I human PK studies were conducted.

Methods

Analytical methods

Two different methods have been used to assess plasma concentrations of BOC. Early on in the Phase I development program a validated chromatographic assay where the two diastereomers were co eluted was used and these data were provided as SCH 503034 concentrations (=BOC). Thereafter, a chromatographic assay was developed and validated; here the two diastereomers were resolved, plasma concentrations were measured as individual diastereomers (SCH 534128 and SCH 534129) concentrations and summed to provide BOC concentrations. The latter sum has been termed SCH 503034 or BOC in most clinical study reports using this analytical method. These two methodologies were cross validated. The tandem mass spectrometric method was utilised for determination of BOC levels (the two stereoisomers and the main metabolite, SCH 629144) in human plasma. Standard laboratory analyses of safety bloods; standard electrocardiograms (ECG) and grading of adverse events (AEs) was used in these PK studies.

Pharmacokinetic data analysis

Individual plasma concentrations for each time point and the derived PK parameters were listed for each subject for each treatment. PK parameters including AUC and C_{max}, were log transformed using a one way analysis of variance (ANOVA) model.

Statistical analysis

Safety: Demographics were summarised in the larger studies. Tabulated variables included AEs, clinical laboratory tests, vital signs and ECG. Summary statistics, including the mean, standard deviation and coefficient of variation were provided for each treatment. In the studies exploring changes in QT/QTc[12] interval, summary statistics were presented, and the average change in QTcF categorised as <0, 0 to 30, 31-60, >60 msec. Derived QTc intervals were separately analysed using an ANCOVA model for a 4-way crossover extracting the effects due to treatment, sequence, period, subject and baseline as a covariate.

PK: Where applicable, repeated measure analyses of variance model, extracting effects due to treatment, sequence, period and subject were fit. Point estimates of the mean difference between the treatments and the reference treatment(s) were calculated and 90% confidence intervals were provided were applicable. Steady-state analyses were performed using trough concentrations collected on Days 11 through to 14 in those studies of this duration; an ANOVA was performed on the data for Days 11 to 14 using day as a class variable. Steady state was concluded for Day 14 if the minimum observed plasma concentration or trough concentration at steady state (C_{min}) did not increase over the preceding days, and each 90% Confidence Interval (CI) of the ratio in the mean for that day versus preceding days of vice versa fell in the interval (0.8, 1.25).

Adsorption

Bioavailability

BOC dissolved (100%) within 60 minutes of consumption. Administration with food increased the oral bioavailability of the commercial formulation of BOC relative to the fasted state by 40% to 60% based on AUC (P03533, P04133, and P04488). Meal type (high fat versus low fat) and timing of meal administration did not notably affect the increase in exposure. Following administration with food, BOC is rapidly absorbed with a time to maximum observed plasma concentration (T_{max}) of 2.0-5.0 hours and eliminated with a mean terminal phase half-life ($t_{½}$) of ~3 to 5 hours with respect to metabolic clearance. Steady state mean BOC AUC, C_{max}, and C_{min} increased in a less than dose proportional manner and individual exposures overlapped substantially at 800 mg and 1200 mg (P04486, P04488, P04489, P04624, and P05880), that is, in healthy subjects further dose escalation from 800mg to 1200 mg TID only increased exposure from 27% to 38% and therefore a substantial increase in efficacy with a 1200 mg dose would not be expected. These data suggest diminished absorption at higher doses. In addition, a four times daily (QID) regimen compared with TID administration of BOC also did not markedly affect the mean values of C_{max} or AUC, though mean C_{min} values were somewhat increased (P04487).

The two diastereomers SCH 534128 (active) and SCH 534129 (inactive) exist in plasma in a ratio of approximately 2:1, which was not altered by food, concomitant medications or in special populations (see below).

Bioequivalence

In the Phase I bioequivalence program (PO3533 and PO4983), at least early on, the dry blend capsule formulations of 50mg and 100mg strengths were used. For the Phase II

[12] The QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death. QTc: The QT interval is dependent on the heart rate (the faster the heart rate, the shorter the QT interval). To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval QTc is often calculated.

studies, a 200mg high shear wet granulation formulation was developed. The Phase II and Phase III clinical formulation differ from the proposed commercial formulation only in the colour of the capsule shell.

Influence of food

Food substantially increased oral bioavailability of BOC (40%-60%) regardless of meal fat content or timing with respect to dose (5 minutes before, during, or immediately after a meal).

Distribution

BOC is not highly bound to human plasma proteins (mean unbound fraction of BOC and SCH 629144 in plasma was ~0.250). The steady state AUC, C_{max}, and C_{min} of BOC increased in a less than dose proportional manner over the dose range of 200 mg to 1200 mg TID. BOC was extensively distributed (approximate mean of apparent volume of distribution (Vd/F) of 772 L) with a mean apparent total body clearance (CL/F) of approximately 161 L/hr.

Elimination

Accumulation of BOC was minimal with multiple days of TID dosing (mean accumulation (R) values range: 0.773-1.45) and steady state was reached after ~1 day of TID dosing (P04488). The two diastereomers SCH 534128 and SCH 534129 had similar mean $t_{½}$ and a similar R value.

Excretion

In a clinical study with ^{14}C-BOC (P03588), 9.3% and 78.9% of the dose was recovered in urine and faeces respectively. Approximately 3% and 8% of the dosed radiocarbon was eliminated as BOC in urine and in faeces, respectively. These data support the primarily hepatic mediated clearance of BOC.

Metabolism/Interconversion and Pharmacokinetics of metabolites

BOC is extensively metabolised through both oxidative and reductive (AKR) pathways. Reduction of the diastereomers occurs at the ketone adjacent to the ketoamide. In humans, three (of the possible four) reduced ketone stereoisomers were identified as major circulating metabolites. Steady state metabolite-to-parent AUC ratios were approximately 4:1 in humans. In monkeys and humans, the metabolite-to-parent ratios were higher following repeated dosing than following a single dose.

Consequences of possible genetic polymorphism

BOC is a P-gp substrate but likely not a substrate of UGT. Hence polymorphisms of the latter will not affect BOC levels.

Dose proportionality and time dependency

The median T_{max} value for BOC was 1.50 hours following dosing of subjects in a fasted state; food delayed the median T_{max} values (2.50-3.00 hours). The mean ratio estimates for C_{max} and AUC values of BOC ranged from 121-142% and 135-142%, respectively, relative to the fasted state when BOC was administered with food immediately prior to breakfast, during breakfast, or immediately after breakfast. The mean $t_{½}$ of BOC was not affected by food administration. The PK values of the individual diastereomers changed in a similar manner. While administering BOC with food substantially increased the bioavailability relative to the fasted state, no apparent difference in mean exposure was noted with respect to meal timing.

Intra and inter individual variability

In regards to BOC exposure, the data does not suggest that inter- and intra-individual are not clinically relevant.

Pharmacokinetics in target population

Healthy and HCV infected subjects have similar PK profiles.

Special populations

Children

Not applicable; this application is for an adult population >18 years of age.

Elderly

No specific Phase I data is provided in the elderly population.

Gender

No gender differences revealed in Phase I.

Weight

No specific data in Phase I is provided, the reviewer notes the Body Mass Index (BMI) of participants in the PK studies was for the most part in the normal range.

Race

No dose adjustment for those of non Caucasian ethnicity (PO4488).

Impaired renal function

In those with ESRD (P05579), there was no meaningful difference in mean exposure to BOC, CL/F, or Vd/F compared with healthy subjects. No dose adjustment is recommended for those with renal impairment.

Impaired hepatic function

In a study with hepatically impaired subjects (P03747), there was a trend toward increased BOC exposure with increasing severity of liver impairment (maximum mean increase of AUC was 49% in subjects with severe impairment). Mean clearance of the drug from plasma after oral administration (CL/F) in moderate and severely hepatically impaired subjects were decreased. However, mean CL/F (even in severely impaired subjects) remained in the range of mean CL/F seen in healthy subjects. No dose adjustment is recommended for subjects with hepatic impairment including those with CHC, the target group for this drug.

Population PK analysis

In the Phase II PPK analysis, gender, body weight, height and BMI had no significant effect on BOC CL/F or Vd/F; however, an age effect was observed against CL/F. The estimated age effect on CL/F was -0.291 (which would be approximately an 8% decrease in CL/F as age increased from 49-65 years) suggesting minimal difference in CL/F. In the Phase III PPK analysis, no age effect was noted. However, effects of gender on clearance (ΔOFV: -13.3) and absorption rate (ΔOFV: -8.8) were noted. These effects were well within the range of estimated inter individual/intra individual variability in BOC exposure as well as within clinical bounds of comparability and therefore not considered clinically relevant.

Drug Interactions

During clinical development, drug-drug (D-D) interaction studies were conducted in healthy subjects with BOC and ketoconazole (CYP3A4 and P-gp efflux inhibitor), ritonavir (RTV) (potent CYP3A4 inhibitor; effect on P-gp not clear), efavirenz (EFV) (CYP3A4 inducer), diflunisal (AKR inhibitor), TDF, PEG and OCP.

In vitro pharmacokinetic interactions

BOC is a strong, reversible inhibitor of CYP3A4/5 and a moderate inhibitor of the P-gp transporter.

In vivo pharmacokinetic interactions

In general, there is little evidence to support clinically relevant changes in BOC exposure due to D-D interactions, in particular, none with BOC and PEG (P03527). In clinical trials co-administration of diflunisal or ibuprofen did not increase exposure to BOC (P03533). This finding was likely the consequence of a lack of saturation of the ubiquitous presence of AKR isoforms in multiple tissues. Although co administration with ketoconazole, increased exposure of BOC (2.3 fold), co administration of BOC with other strong CYP3A4/5 inhibitors and P-gp inhibitors, RTV and clarithromycin, did not notably change the exposure of BOC (P04624 and P05880). EFV had a notable effect only on mean trough concentration, decreasing it by ~45%. These data suggest a pathway other than P-gp or CYP3A4/5 may be affected.

BOC is a strong, reversible inhibitor of CYP3A4/5 as exemplified by the D-D interaction study with MDZ (P05880). BOC co administered with the OCP, increased the exposure to drospirenone by 100% without notably affecting ethinyl estradiol; this should not affect contraceptive efficacy, however, in patients with conditions predisposing them to hyperkalaemia or patients taking potassium-sparing diuretics, alternative contraceptives should be considered. For drugs metabolised primarily by CYP3A4/5 especially those with a narrow therapeutic window (for example, ergot alkaloid, terfenadine), co administration with BOC is contra indicated. It is noteworthy when considering the use of BOC in HIV-HCV co infected patients, no clinically notable PK interaction between BOC and tenofovir was identified (P05880).

While, interaction of BOC and PR was not directly studied in a Phase I study; all pivotal Phase II and III trials were conducted in combination with PR (and PEG) without any apparent effect on BOC or PR PK.

Overall, the clinical evaluator recommends that drugs metabolised through the CYP3A4 with a narrow therapeutic index must not be co administered with BOC.

Pharmacodynamics

Introduction

BOC is a NS3/4A serine protease inhibitor of HCV. BOC has demonstrated antiviral activity in HCV replicon *in vitro* model, as monotherapy in Phase I, and as part of triple therapy (with PEG-INF plus PR) in the Phase II and III development program.

Mechanism of action

The amino terminal third of NS3 is a serine protease responsible for the *cis* processing of the HCV polyprotein at the NS3-NS4A junction. Following NS3-4A junction cleavage, NS3 associates non covalently with NS4A to form the mature NS3/4A protease, which is responsible for the further processing of the non structural proteins at the NS4A-NS4B,

NS4B-NS5A and NS5A-NS5B junctions.[13] The NS3 protease is essential for viral replication. BOC inhibits the NS3 protease activity by forming a stable reversible covalent bond between the ketoamide of BOC and the NS3 protease active site serine.

Primary pharmacology

BOC exists as an approximately equal mixture of two diastereomers (SCH 534128 & SCH 534129), the former is ~41-130 fold more potent as an inhibitor of HCV protease NS3 than SCH 534129.

Secondary pharmacology

BOC is extensively metabolised through both oxidative and reductive (AKR) pathways**.** The main metabolite SCH 629144 has no therapeutic HCV activity.

Relationship between plasma concentration and effect

In order to make an estimation of the target plasma concentration and therapeutic dose of BOC, the compound was tested in a genotype 1b replicon system. The results indicated that the estimated plasma IC_{90} value for BOC is ~200 ng/mL. Therefore, assuming that the replicon system accurately predicts the IC_{90} of the compound for the virus, a target plasma concentration of approximately 200ng/mL was used for early dose decisions. While the plasma compartment is not the target compartment of interest (this is the liver), nonclinical studies demonstrated good distribution to the liver in rats and monkeys.

In order to determine which plasma PK parameter was most closely associated with a change in plasma HCV-RNA concentrations, a concentration response analysis was performed using data from a Phase I study (P03516). The results indicated that maximal decrease in HCV-RNA concentrations correlated best with C_{min} concentrations of BOC (R=0.653); with a less robust relationships for the AUC (R=0.511) and C_{max} (R=0.466), suggesting plasma C_{min} may be the PK parameter of interest for HCV response.

Pharmacodynamic interactions with other medicinal products or substances

BOC has always been planned as a third agent in combination with ribavirin (PR) for CHC treatment. Hence the Phase II and III program specifically explored the PD interaction of triple therapy. PO4487 followed by the long term follow up Study P04531 provided the first data on the combination of BOC plus PEG. P04487 was an open label rising multi dose Phase I study of BOC plus PEG in HCV genotype-1 PEG non responders. BOC 400mg TID with PEG produced greater reductions in HCV-RNA than PEG alone or BOC alone; moreover, 400mg TID was superior to 200mg TID with PEG in terms of PD response. BOC PK parameters were not influenced by co administration with PEG. However, there was no Sustained Virologic Response (SVR) in any patient at 24 weeks, although 16 subjects had undetectable HCV viral load at some point.

The two Phase II studies, P03659 and P03523 were the key studies that supported the key Phase III studies. Protocol P03659 was a Phase II, dose finding study and was conducted in subjects with CHC genotype 1, who failed previous PR treatment. This study was amended early after Data and Safety Monitoring Board (DSMB) review, because two factors became clear. First, that the lower (100 mg and 200 mg TID) doses of BOC were inferior to the higher doses in terms of HCV response; second, PR was an essential component. Moreover, higher doses of BOC were safe and the triple therapy was well tolerated. In the second Phase II study (P03523), conducted in subjects with treatment naïve CHC genotype 1,

[13] Reed KE, Rice CM. Overview of hepatitis C virus genome structure, polyprotein processing, and protein properties, in Hagedorn CH and Rice CM (eds.), *Current Topics in Microbiology and Immunology: The Hepatitis C Viruses* Vol. 242. Springer, Heidelberg, pp. 55-84, 2000.

BOC/PR triple therapy yielded significant increase in SVR and lower relapse rates versus the PR control arm. Consequently, for the Phase III program the triple combination chosen consisted of BOC 800 mg TID with PR and PEG; in the naive setting a four week lead in with PR was used prior to triple therapy.

Efficacy

Introduction

Several terms describing overall virologic response in the setting of HCV treatment have now become standardised,[14] some of these terms are listed in Table 9 as they are relevant to the clinical efficacy data presented in this section.

Table 9: Standardised terms relevant to clinical efficacy in the setting of HCV treatment.

Term	meaning
End of Treatment (EOT) Response	HCV-RNA at the end of the therapy independent of the assigned length of therapy
Sustained Virologic Response (SVR)	SVR is undetectable virus 24 weeks after completion or discontinuation of therapy
Relapse	Viral relapse is detectable HCV-RNA in the follow up period (typically FW 24) when EOT HCVRNA was undetectable
Viral Breakthrough (BT)	detectable HCV-RNA (>1,000 IU/mL) after achieving undetectable HCV-RNA during the treatment period;
Incomplete Virologic Response and Rebound (IVR)	a drop in VL but not reaching undetectable levels) followed by a rise of 1 log or more with levels to >1,000 IU/mL
Nonresponder (NR)	never achieves an undetectable HCV-RNA during therapy
Relapser (R)	EOT undetectable HCV-RNA but detectable HCV-RNA post therapy
Treatment Failure (TF)	includes non responder and relapsers
"Null" Responder	a sub group of non responders
Partial Responder	some degree of PEG responsiveness, that is, 2 log decrease in VL at Treatment Week (TW) 12
Early responders	Subjects who became HCV-RNA undetectable by TW8
Late responders	Subjects who became HCV-RNA undetectable later than TW8

Dose response studies and main clinical studies

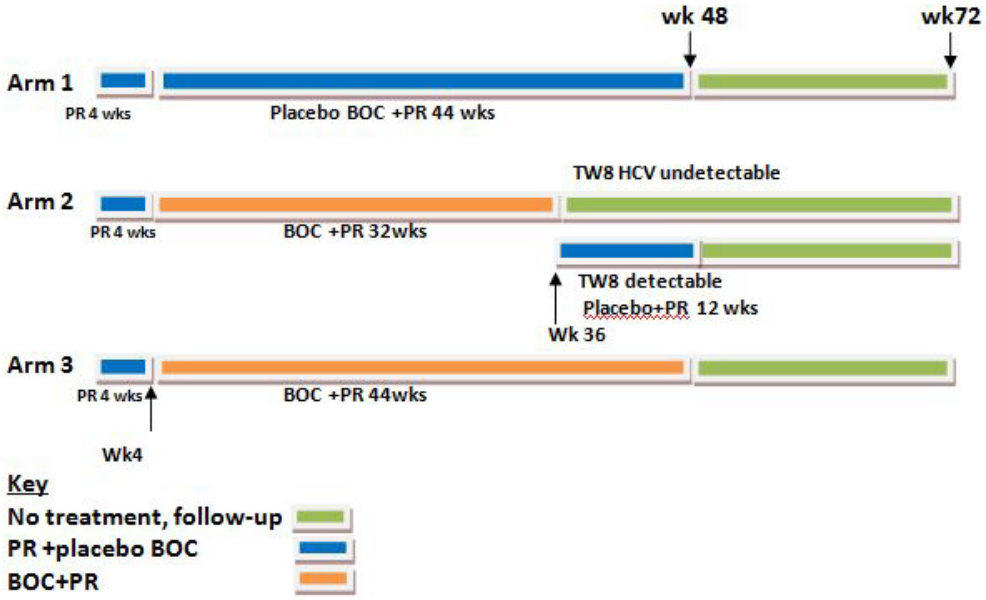
Aside from the Phase II studies described in the 'Pharmacodynamics' section of this AusPAR that informed on the dose of BOC and PR to be used as part of triple therapy for CHC genotype 1, the two key Phase III studies which informed on dose response in terms of duration of therapy in the treatment experienced and treatment naive setting respectively are PO5101 (RESPOND-2) and PO5216 (SPRINT-2).

[14] European Medicines Agency <www.ema.europa.eu>.

P05101 (RESPOND-2) study

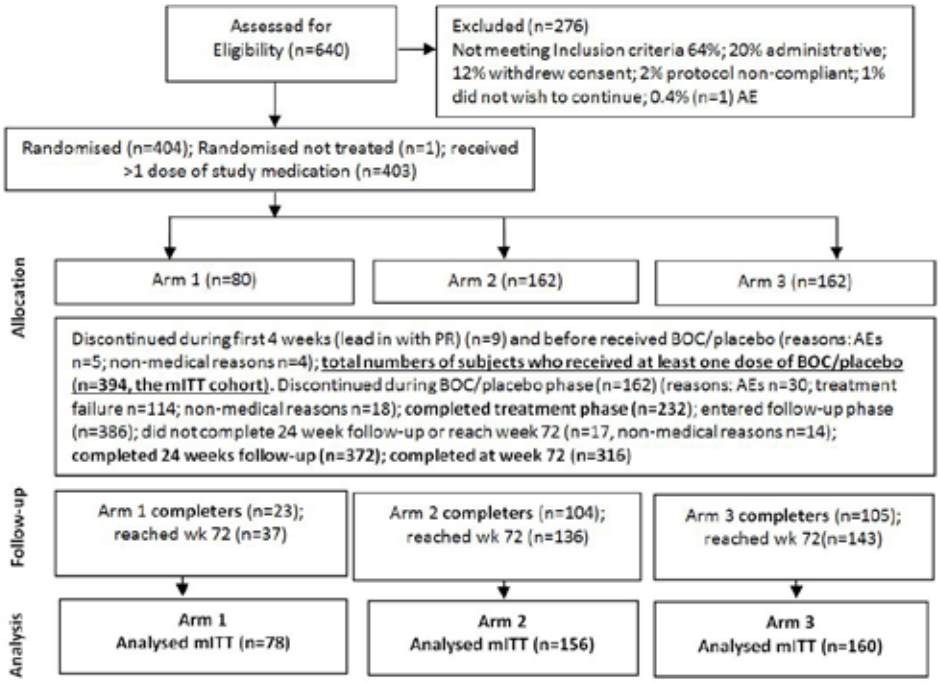
Pivotal Phase III, randomised, multi centre, double blind study conducted in patients with CHC genotype 1 who previously demonstrated PEG responsiveness but failed to achieve SVR on prior treatment with PR. The study[15] was conducted as per Good Clinical Practice (GCP) and is detailed in Figure 2.

Figure 2: P05101 (RESPOND-2) study design.



Participant flow for the RESPOND-2 study is shown in Figure 3.

Figure 3: Participant flow for the P05101 (RESPOND-2) study.



[15] Bacon BR, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. *N. Engl. J. Med.* 2011; 364:1207-17.

The modified Intention to Treat (mITT) analysis totalled 394 subjects, of whom 78, 156, and 160 were in Arm 1 (control), Arm 2, and Arm 3, respectively.

Completed:

Arm 1: 29% completed; 71% discontinued; 61% of discontinuations due to treatment failure;

Arm 2: 64% completed; 36% discontinued; 56/58 discontinuations occurred before wk 36, of these, 60%, 21% 17% were due to treatment failure, AEs and for non medical reasons respectively;

Arm 3: 65% completed; 35% discontinued; 52%, 36%, 13% were due to treatment failure, AEs and for non medical reasons respectively.

Summary baseline demographics of all randomised subjects:

Sixty-seven per cent (269/404) were male; 88% (355/404) were non Black; mean age was 52.7 years (range, 26-74 years); mean weight 85 kg. All subjects had genotype 1 (47% [189/403] subtype 1a, 44% [178/403] subtype 1b by TRUGENE™ assay); 88% (353/403) had high viral load (>800,000 IU/mL), mean $\log_{10}$ baseline HCV viral load of 6.63.

In summary:

- Primary analysis in the mITT group (derived as shown in Figure 3): SVR rates in subjects who received BOC were 61% and 67% in the Response Guided Therapy (RGT) and BOC/PR48 arms, respectively, versus 22% in the control arm; the 95% CI for the delta SVR was 27.2, 51.0 ($p<0.0001$) and 33.4, 56.8 ($p<0.0001$), respectively, versus control;
- Subjects with <1.0 $\log_{10}$ decrease in HCV-RNA at Treatment Week 4 (TW4), that is, poorly IFN responsive, who comprised approximately one third of the study population had SVR rates of 33-34% in those receiving triple therapy versus 0% in the control arm;
- IFN-responsive subjects achieved SVR rates of 73-79% with triple therapy;
- The addition of BOC to PR reduced relapse rates, that is, 15% and 12% in the RGT and BOC/PR48 arms, respectively, versus 32% in the control arm;
- In early responders, that is those with undetectable HCV-RNA by TW8, relapse rates remained low (approximately 10%) after 36 weeks of BOC/PR therapy (lead in of PR followed by 24 weeks of triple therapy);
- The SVR in BOC/PR48 arm versus the RGT arm was not statistically significantly different;
- An unexplained finding was that a higher proportion of BOC/PR48 subjects versusversus RGT subjects achieved undetectable HCV-RNA at some point during the first 36 weeks despite each of these arms receiving identical therapy for the first 36 weeks. Looking at this in a different way, 27% of RGT subjects versus 17% of BOC/PR48 subjects never achieved undetectable HCV-RNA;
- SVR rates in the RGT arm, when analysed by per protocol assignment or based on TW8 results, were high and similar to a matched group of subjects in the BOC/PR48 arm:
  - In those with undetectable HCVRNA at TW8 who were assigned 36 weeks of therapy had SVR rates of 89% and 97% in the RGT and BOC/PR48 arms, respectively;

- subjects with detectable HCV-RNA at TW8 who were assigned 48 weeks of therapy had SVR rates of 80% and 73%, RGT and BOC/PR48, respectively;
- SVR rates based on TW8 results were: 86% and 88% in subjects with undetectable HCV-RNA, and 40% and 43% in subjects with detectable HCV-RNA, RGT and BOC/PR48, respectively;

· These data show that when triple therapy was used, based on per-protocol assignment or TW8 response, early responders could be successfully treated for 36 weeks; late responders require 48 weeks of PR therapy in their regimen;

· For late responders (post TW8), triple therapy for 32 weeks (following the 4 week PR lead in) was equivalent for SVR to 48week course of triple therapy (4 week PR lead in followed by 44 weeks of triple therapy).

Predictors of SVR in RESPOND-2

In a multivariate stepwise logistic regression model for SVR by Baseline Factors[16] and TW4 response, for all treatment arms, the predictors are outlined in Table 10.

Table 10: Predictors of Sustained Virologic Response for the P05101 (RESPOND-2) study.

Covariate	**Odds Ratio (95% CI)**	***p* value**
BOC/PR48 versus Control	12.3 (6.0, 24.9)	<0.0001
RGT versus Control	9.8 (4.9, 19.7)	<0.0001
TW4 Response: ≥1.0 $\log_{10}$ versus <1.0 $\log_{10}$ decrease in HCVRNA from baseline	5.2 (3.0, 9.2)	<0.0001
Previous Treatment Response Relapser versus NR	2.3 (1.4, 3.8)	0.0015

Full Analysis Set (FAS) = all randomised subjects who received at least one dose of any study medication (PEG2b, PR, or BOC).

BT occurred in 1% (2/162) of RGT subjects and 2% (3/161) of BOC/PR48 subjects versusversus none in control arm; IVR occurred in 1% (1/80) of control arm subjects, 4% (7/162) of RGT subjects, and 3% (4/161) of BOC/PR48 subjects. IVR appeared to be associated with poor IFN responsiveness.

Conclusion

BOC as part of triple therapy introduced after a four week lead in with PR, for CHC genotype 1 substantially improves the response rate for previous PR failures independent of many of the demographic and baseline predictors of PR response. HCV RNA levels should be assessed at Weeks 8 and 12 in order to guide duration of triple therapy. Patients with undetectable HCV-RNA at TW8 and TW12 should complete treatment at TW36, while those with detectable HCV-RNA at TW8 and undetectable HCV-RNA at TW12 should be treated for 48 weeks; BOC is not required beyond 36 weeks, with last 12 weeks treatment consisting of PR alone. Subjects with detectable HCV-RNA at TW12 should be discontinued for futility.

[16] Other covariates included: genotype (1 versus 1b, 1a versus 1b), race (Blacks versus non Blacks), gender (female versus male), age (≤40 versus >40 years), weight (40-65 versus 105-125 kg; 65-80 versus 105-125 kg, 80-105 versus 105-125 kg), BMI (25-30 versus >30, 20-25 versus >30), platelets (150,000-200,000 versus >200,000, ≤150,000 versus >200,000), fibrosis score (0/1/2 versus 3/4), steatosis (0 versus >0), previous treatment (PEG2a versus PEG2b), alanine transaminase (ALT; elevated versus normal), statin use (no versus yes), and region of enrolment (North America versus Europe/Latin America).

Ancillary analyses: BOC dosing interval and SVR

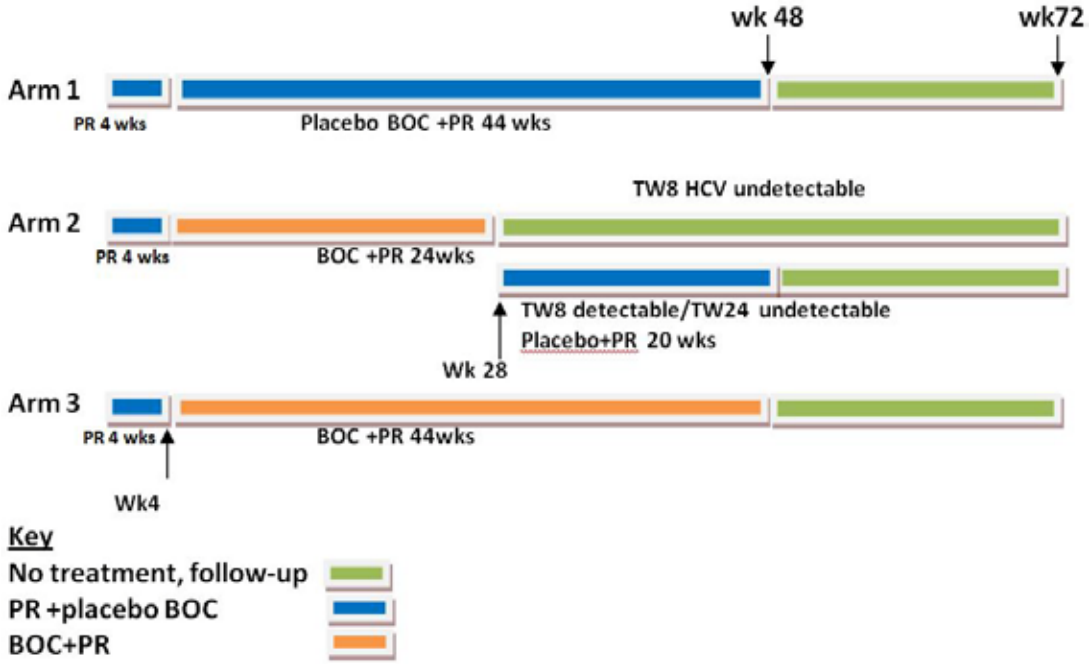
Maximal decrease in HCV-RNA concentrations correlates best with C_{min} concentrations and serum C_{min} at 8 hours was achieved with BOC TID dosing. In this study BOC was to be taken every 7 to 9 hours. The effect of adherence to the BOC dosing interval in subjects with adherence of ≥80% to triple therapy on SVR was evaluated. Adherence to the BOC dosing interval was defined as the number of BOC dosing intervals within 7 to 9 hours divided by the total number of BOC dosing intervals.

Results: >80% adherent to dosing of all three study medications had minimal impact on SVR; High SVR rates (66-70%) were observed in subjects who were >60% adherent to the BOC dosing interval; If <60% adherence, SVR rates dropped to 50%.

P05216 (SPRINT-2) study

Pivotal Phase III, randomised, multi centre, double blind study conducted in CHC genotype 1 treatment naïve patients. The study compared PR 48 weeks to two treatment paradigms containing a four week PR lead in followed by BOC plus PR for a total duration of 28 or 48 weeks. The study[17] was conducted in accordance with GCP and is detailed in Figure 4.

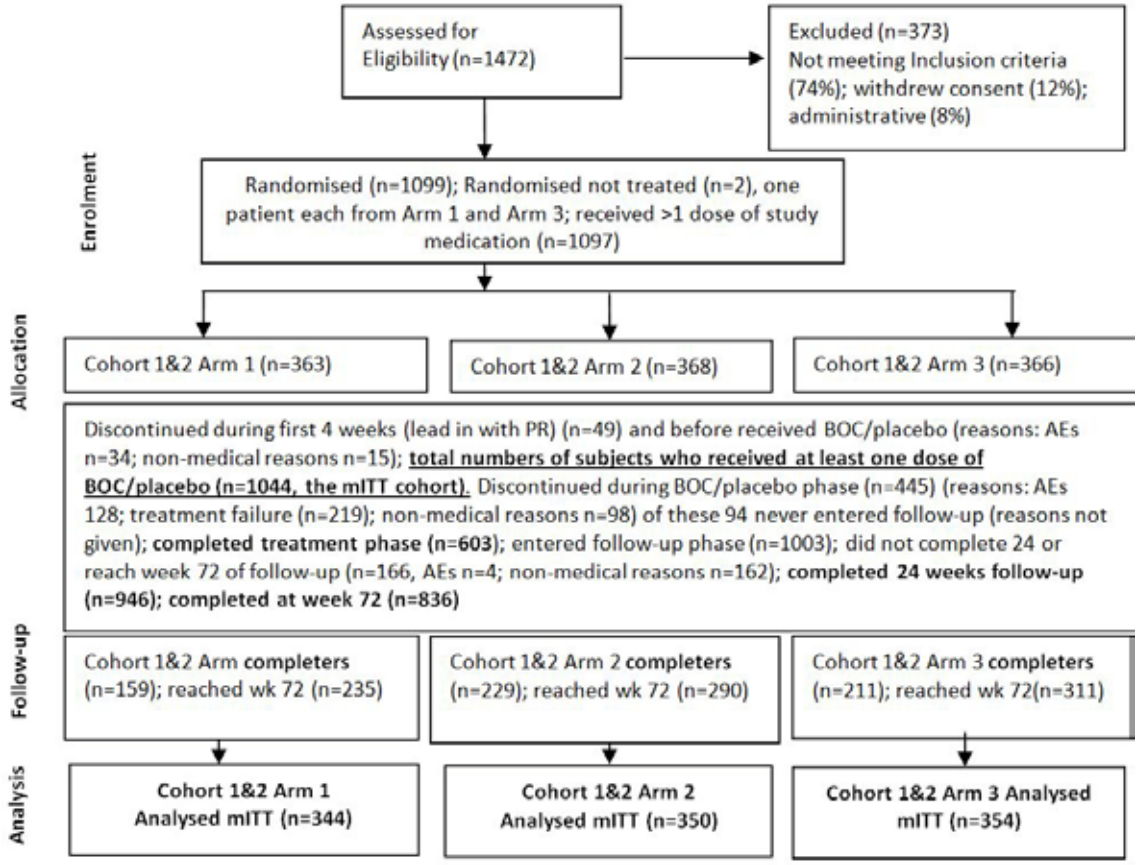
Figure 4: P05216 (SPRINT-2) study design.



Participant flow for the SPRINT-2 study is shown in Figure 5.

[17] Poordad F, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *N. Engl. J. Med.* 2011; 364:1195-1206.

Figure 5: Participant flow for the PO5216 (SPRINT-2) study.



Numbers analysed in the mITT totalled 1044 subjects, of whom 344, 350 and 354 were in Arm 1 (control), Arm 2, and Arm 3 respectively.

Completed:

Cohort 1: 58% completed the treatment phase;

Cohort 2: 38% completed the treatment phase.

Control (Arm 1 PR48): 311 subjects were treated; of these, 148 (48%) completed treatment.

Experimental (Arm 2 RGT and Arm 3 BOC/PR48): 316 and 311 subjects were treated in the RGT and BOC/PR48 arms respectively; of these, 205 (65%) and 190 (61%), respectively, completed treatment. A total of 147 subjects in the RGT arm were assigned to shorter treatment duration by Initial Virologic Response (IVR) based on virologic response and completed treatment at TW28.

Summary baseline demographics of all randomised subjects by Cohort:

Cohort 1: 95% White; 5% other ethnicities (non Black); median age 50 years; 60% male; 47% HCV genotype 1a;

Cohort 2: 100% Black; median age 52 years; 61% male; 64% HCV genotype 1a.

In summary:

- Primary analysis in the mITT group (derived as shown in Figure 5): SVR rates in subjects who received triple therapy were 67% and 68% in RGT and BOC/PR48 arms,

respectively, versus 40% in the control arm; the 95% CI for the delta SVR was 19.6, 33.9 (p<0.0001) and 21.4, 35.6 (p<0.0001) respectively versus control;

- SVR rates were 67% and 68% (for each BOC-containing Arm) in White subjects (Cohort 1) receiving triple therapy versus 40% in controls; SVR rates were numerically lower in Blacks (Cohort 2) than White (42% and 53% for each BOC containing Arm) versus the SVR rate of 23% in Black subjects in the PR48 arm (p=0.0440, p=0.0035);
- High SVR rates were primarily driven by higher End-of-Treatment (EOT) responses, that is, 71% and 76% in RGT and BOC/PR48 arms, respectively, versus 53% in control;
- Relapse rates were lower in the BOC-containing arms (9% versus 22%) and in subjects who completed assigned treatment duration (28 or 48 weeks) (5% versus 21%);
- Triple therapy resulted in higher SVR rates in subjects who demonstrate some interferon responsiveness (≥1.0$\log_{10}$ viral load decline at TW4), that is, SVR rates were 79-81%; SVR rates in subjects with <1.0$\log_{10}$ decline at TW4 were lower, that is, 28-38%, but still significantly better than the PR48 control arm (4%); in Cohort 1 and 2 respectively, BOC containing arms versus PR48 control arm had SVR of 29% to 39% versus 5% and 25% to 31% versus 0%;
- Analyses comparing matching subgroups in RGT and BOC/PR48 arms also showed similar SVR rates in both BOC arms in the early and later responders whether using either the per-protocol (TW8 through TW24) or response only at TW8 analysis, that is:
  - SVR rates in subjects with undetectable HCV-RNA at TW8 through TW 24 were 96% in RGT and BOC/PR48 arms, and 72% and 75% in subjects with detectable HCV-RNA at TW8 or any subsequent visit in RGT and BOC/PR48 arms, respectively;
  - SVR rates per TW8 response were 88% and 90% in subjects with undetectable HCV-RNA, and 36% and 40% in subjects with detectable HCV-RNA, in the RGT and BOC/PR48 arms, respectively.
- When comparing the two BOC regimens, whether based on per-protocol (TW8 through TW24) assignment or TW8 response, the data suggest early responders can be successfully treated with the 28 week regimen; late responders require 48 weeks of PR therapy in their regimen. Approximately 60% of HCV genotype-1 infected subjects would be eligible to complete treatment at TW28 (had undetectable HCV-RNA at TW8); ~20% of subjects would benefit from longer treatment duration with PR alone for the last 20 weeks of therapy (up to 48 weeks of total duration);
- Data from the RGT arm does not support the need for frequent HCV-RNA assessment between TW8 and TW24 for making a treatment duration decision. In total, only 2 subjects with undetectable HCV-RNA at TW8 had viral breakthrough between TW8 and TW24. Both subjects were discontinued from treatment after TW24.

Predictors of SVR in SPRINT-2

In a multivariate stepwise logistic regression model for SVR by Baseline Factors[18] and TW4 response, for all treatment arms, the predictors are outlined in Table 11.

[18] Covariates included treatment group, genotype, race, baseline HCV-RNA, gender, age, baseline weight, BMI, baseline platelets, baseline fibrosis score, baseline steatosis, baseline ALT, statin use prior to treatment, region of enrollment, TW4 response.

Table 11: Predictors of Sustained Virologic Response for the PO5216 (SPRINT-2) study.

Covariate	Odds Ratio (95% CI)	*p* value
Treatment: Arm 3 versus Arm 1	5.392 (3.693, 7.872)	<.0001
Treatment: Arm 2 versus Arm 1	5.021 (3.436, 7.338)	<.0001
<1.0-log_{10} Decline versus ≥1.0-log_{10} Decline in Viral Load at TW4	9.592 (6.676, 13.783)	<.0001
Genotype: Other versus 1b	2.526 (1.000, 6.383)	0.0501
Genotype: 1a versus 1b	0.677 (0.491, 0.934)	0.0174
Baseline HCV-RNA: <=400,000 versus >400,000	4.209 (2.026, 8.744)	0.0001
Age: <=40 versus >40 Years	1.606 (1.054, 2.447)	0.0274
BMI: 25-30 versus >30	1.881 (1.292, 2.739)	0.0010
BMI: 20-25 versus >30	1.945 (1.307, 2.894)	0.0010
Fibrosis: 0/1/2 versus 3/4	1.791 (1.096, 2.927)	0.0201

Full Analysis Set (FAS) = all randomised subjects who received at least one dose of any study medication (PEG2b, PR, or BOC).

In the model without TW4 response, Black race was a predictor of lower SVR; when TW4 response was included in the model, the impact of ethnicity on response was negated. Region of enrolment was not a predictor of response in this model and this contrasts with previous historical data from PR studies in which SVR rates were always higher in the European Union than North America.

As revealed in multivariate analysis, a number of baseline factors predicted poorer SVR in the BOC-RGT and BOC-PR48 containing arms versus PR, baseline HCV-RNA >400,000 IU/mL (62 and 65% versus 34%); F3/4 liver fibrosis score (41 and 52% versus 38%); genotype 1a (59 and 62% versus 34%); genotype 1b (71 and 73% versus 40%) as well as older age (>40 years of age) and higher BMI.

Viral breakthrough (BT)/incomplete virologic response (IVR) events were infrequent: BT 2%, 4%, and 2%; and IVR 6%, 7%, and 7% in PR48, RGT and BOC/PR48, respectively. BT/IVR occurred more frequently in subjects with poor IFN response (up to 24% versus 2% in IFN responsive subjects) and was more frequent in Black subjects, as this population has poorer IFN response.

Population sequence data were compared for 102 Black and 602 non Black subjects with postbaseline sequence data available for 46/102 and 151/602 Black and non Black subjects, respectively. Overall, 26% versus 12% Black versus Non Black subjects had postbaseline RAVs detected. Moreover, 68% of poor IFN responders and samples sequenced had detectable RAVs, compared to 23% of IFN responders. The higher number of RAVs detected in poor IFN responders likely reflects the poorer antiviral activity of PR in these subjects.

Conclusion

BOC as part of triple therapy introduced after a four week lead in with PR for CHC genotype 1 substantially improved the SVR for treatment naive patients regardless of demographics or baseline disease characteristics. RGT with triple therapy demonstrated an advantage versus fixed duration BOC/PR48 by substantially shortening treatment duration without compromising efficacy.

Ancillary analyses: BOC dosing interval and SVR

Previous clinical studies demonstrated that maximal decrease in HCV-RNA concentrations correlated best with C_{min} concentrations and serum C_{min} at 8 hours was achieved with BOC TID dosing. In this study, BOC was to be taken every 7 to 9 hours. Findings were similar.

Clinical studies in special populations

PO5411 is a Phase IIb study being conducted in HIC/HIV co infected patients. PO5216 is a completed study which enrolled two Cohorts; Cohort 1 enrolled patients of White ethnicity and Cohort 2 enrolled patients of Black ethnicity. The rationale behind this was to increase the understanding of BOC use in Black subjects who are underrepresented in the Phase II and III program in general. P05411 remains blinded and is not fully enrolled. Data for Cohort 2 of PO5216 is presented above.

Analysis performed across trials (pooled analyses and meta analysis)

Pooled resistance analyses performed using samples from P05101 and P05216

From these studies, there were 295 (86%) subjects with a post baseline sample sequenced; 48 (14%) missing. Reasons for the latter were samples with HCV-RNA <1,000mL/IU, failed sequencing with no subsequent sample or subjects discontinued therapy within 1-4 days of BOC initiation and there were no suitable samples for analysis.

In summary:

- BOC RAVs were relatively infrequent (7%) prior to treatment, moreover, there was no association between baseline BOC RAVs and treatment response;
- As a result of the high SVR rate among all BOC treated subjects, RAVs occurred infrequently (15%). However, of the non SVR BOC treated subjects for whom samples were analysed, 155/295 (53%) had post baseline RAVs detected. RAVs were detected in the majority of subjects with virologic breakthrough (75%) and incomplete virologic response (93%). The most commonly detected RAVs were the following amino acid substitutions R155K (52%); V36M (46%); T54S (23%) and T54A (15%);
- PEG responsiveness plays a role in the detection of BOC RAVs in those receiving triple therapy; 41% versus 6% of poor PEG responders versus PEG responders respectively. Among subjects with samples analysed, 68% of poorly PEG responsive subjects had RAVs compared to 31% of those with better PEG response;
- Black subjects had a higher percentage of RAVs detected post baseline compared to non-Black subjects. Detection of RAVs after initiation of treatment was similar for both BOC/PR treatment strategies (RGT versus 48 Weeks);

Pooled resistance analyses performed using samples from P03523 and P05216 (naive studies) for SVR

The multivariate logistic regression analysis using stepwise selection yielded the following factors as influencing CHC genotype 1 SVR:

- HCV 1 genotype: Other versus 1b (OR 4.158, 95% CI 1.574, 10.983, p=0.004)
- Race: Black versus non Black (OR 0.478, 95% CI 0.317, 0.720, p=0.0004)
- Baseline HCV-RNA: ≤400,000 versus >400,000 IU/mL (OR 6.352, 95% CI 3.024, 13.344, p<.0001)
- Age: ≤40 versus >40 Years, (OR 1.610, 95% CI 1.091, 2.375) 0.0163

- Baseline platelet count: <150,000 versus >200,000/μL (OR 0.487, 95% CI 0.296, 0.802, p= 0.0047)
- Treatment: BOC/PR48 versus PR48 (OR 4.149, 95% CI 3.111, 5.534, p=<0.0001)

When multivariate logistic regression analysis including TW4 response as a factor and using the stepwise selection method on this pooled data, TW4 response was also significant as a predictor of SVR, as well as the above covariates.

The IL28B genotype is important in predicting response to PR

In a pooled pharmacogenomic analysis from PO5216 and PO5101, 62% and 66% respectively of patient samples were genotyped for IL28B. Overall prevalence of the polymorphic site rs12979860 was 28.4% CC (favourable), 17.8% TT, 53.8% CT. The pooled analysis confirmed the findings of the IDEAL study, that is, that IL28B genotype is a strong predictor of PR responsiveness. Black subjects treated with PR were less likely to have the favourable CC genotype and hence had less SVR. Although the influence of IL28B genotype on response to triple therapy was not as profound as its effect on PR responsiveness, it did influence SVR rates, that is, SVR was 7-26% higher in IL28B CC versus CT or TT; in the pooled PR (control) arms SVR were 41-46% higher in the IL28B CC than those with CT or TT.

Supportive studies

There are two ongoing blinded Phase III studies (P05685 and PO6086) and one open label study (PO5514) in CHC genotype 1. No efficacy data is provided for these three studies. These studies have been included in this application to appraise the clinical reviewers of the breadth of the BOC development program which is aimed at expanding the efficacy and safety data of triple therapy in two groups, that is, those previously treated with PR but without SVR (P05685 and PO5514) and second, treatment naive CHC patients (PO6086). In this study, all subjects receive open label triple therapy but are randomised to one of two strategies, EPO use or PR dose reduction, for anaemia, which occurs in ~60% of patients receiving PR or triple therapy.

Product Information (PI) with respect to efficacy

The PI contains the pivotal clinical trials RESPOND-2 and SPRINT-2. There is also some general guidance on the use of EPO within these trials. There is no mention of the ongoing randomised clinical trial of triple therapy in HCV genotype 1 treatment naive patients who will be randomised to EPO use versus PR dose reduction for the management of anaemia. There is a summary of the use of BOC as part of triple therapy in treatment naive and treatment experienced patients based on the findings of the two pivotal Phase III studies. There are tables that summarise the treatment schedule depending on HCV PCR levels at TW8 and subsequently at TW24.

Safety

Introduction

The clinical evaluator did consider the nonclinical safety profile of BOC in this clinical evaluation report. The specific findings from the nonclinical studies that might be relevant in the human studies are:

- Human fertility studies: Inhibin B (a surrogate marker of testicular function) was measured in P04487, P03523 & P03659. One thousand and six hundred inhibin B samples collected from 355 males treated with BOC 800 mg TID and PR in Study P03523 for a mean duration of 32 weeks showed no shift to low inhibin B values

compared with those receiving PR. Semen analysis (sperm count and motility) in P03516 and PO4487 revealed no pattern or dose relationship to BOC receipt.

- Activated partial thromboplastin time (APTT): No clinically significant increases in APTT were observed in the clinical studies.
- ECG: PO4489, explored QT/QTc changes when BOC was given at therapeutic and supra therapeutic dose; there were no ECG changes seen.

Patient exposure

Phase I studies (n=20)

Of the twenty Phase I studies, 13 were conducted in healthy subjects, 5 studies were conducted in CHC subjects and 2 studies were in special populations (renal and hepatic impairment). Studies in healthy subjects and subjects with renal or hepatic impairment were conducted to investigate safety and tolerability and PK of BOC at doses up to 3600 mg. Studies in CHC subjects (HCV genotype 1 & genotype 2/3) were conducted as early investigations of the PK, PD and safety/tolerability of BOC. Dose levels ranged from 100 mg BID to a maximal dose of 400 mg TID of BOC when given alone or 600 mg QID with PEG.

Phase II and III studies

In the first Phase II study (P03659), 354/357 subjects received any dose (100, 200, 400, 800 mg TID) of BOC and PEG-2b (the 400 mg BOC dose was +/- PR); 143 of these subjects eventually received BOC 800 mg PO TID in combination with PEG-2b and PR. Another Phase II study and two Phase III studies were conducted in subjects with CHC (HCV genotype 1) who either were treatment naïve (P03523, P05216) or previous treatment failures (P05101). In these 3 key studies, 547 subjects in the PR arms and 1548 subjects in the BOC/PR arms received at least one dose of any study medication (BOC/PR total excludes 36 PR subjects in Study P03523 who were allowed to crossover to BOC/PR because of treatment failure). As of the data cut-off dates for the ongoing studies, an additional 717 subjects have been enrolled in Studies P05685, P05514 and P06086, and 28 subjects have been enrolled in P05411. Based on randomisation in these studies (two are blinded) it is estimated that about 670 subjects in these studies have been exposed to BOC. No new safety signals have been identified from the ongoing studies to date.

Summary

During the course of clinical development of BOC ~2827 subjects have been exposed to any dose of BOC in 28 clinical trials. Most (~2171/2827, 77%) of the subjects received BOC 800 mg TID, the proposed dose of BOC for therapeutic use. In the 1897 subjects with CHC treated with BOC 800 mg TID in combination with PR in unblinded/open label Phase II/III studies, total exposure to BOC was 960.5 person years. In the Phase II/III studies demographic and baseline disease characteristics were representative of subjects with CHC genotype 1, that is, 2/3 were male and >80% self reported their race as White. The Phase II/III studies included 48 older subjects (≥65 years) and 123 subjects with cirrhosis. Also included in the studies were 282 Black subjects, 31 Asian subjects and 1753 White subjects.

Adverse events

Phase I program

Clinical

There were no serious adverse events (SAEs) considered possibly related to BOC. Dysgeusia (altered sense of taste) was reported repeatedly.

Laboratory values and vital signs

Decreases in haemoglobin (Hb) and neutrophils counts (PMN) when BOC was co administered with PEG in CHC subjects (P04487 and P03527). Since administration of therapeutic doses of BOC for 57 days to healthy subjects (P05351) did not adversely affect red blood cell survival or volume, or numerous markers of anaemia, the observation in PO4487 and PO3527 suggested an effect of PEG which is well described.[19]

Phase II and III program

In the Phase II study, P03659 and the three key Phase III studies (P03523, P05216, PO5101) BOC was most commonly associated with an incremental decrease in serum Hb beyond that seen with PR SOC therapy and an increased incidence of dysgeusia. More details of these AEs are summarised for the pivotal studies P03523, P05216, PO5101 in Tables 12-16 below.

[19] US Food and Drug Administration <www.fda.gov/Drugs/default.htm>.

Table 12: Summary of clinical safety for the pivotal treatment experienced study (PO51010: RESPOND-2).

	P05101 (RESPOND-2) treatment experienced study	
	Control (ribavirin, PR)	**BOC/PR**
Median treatment duration in days	**104**	**253**
Treatment phase		
Treated, n	**n=80**	**n=323**
Discontinued treatment phase, n (%)	**57**(71)	114 (35
AE	2 (3)	33 (10)
Treatment failure	49 (61)	65 (20)
Non-medical reasons	6 (8)	16 (5)
Completed treatment phase	23 (29)	209 (65)
Never Entered Follow up	3	14
Follow up phase		
Entered Follow up, n	77	309
Discontinued Follow up, n (%)	2 (3)	12 (4)
Adverse Event	0	0
Non-medical reasons	2 (3)	12 (4)
Completed Follow up, n (%)	75 (97)	297 (96)

Table 13: Summary of clinical safety for the naive studies (PO3523: SPRINT; PO5216: SPRINT-2).

	PO3523 (SPRINT) & PO5216 (SPRINT-2) treatment naive studies	
	Control (ribavirin, PR)	**BOC/PR**
Median treatment duration in days	**216**	**197**
Treatment phase		
Treated, n	**n=467**	**n=1225**
Discontinued treatment phase, n (%)	256 (55)	453 (37)
AE	65 (14)	172 (14)
Treatment failure	153 (33)	150 (12)
Non medical reasons	38 (8)	131 (11)
Completed treatment phase	211 (45)	772 (63)
Never Entered Follow up	48	95
Follow up phase		
Entered Follow up, n	419	1130
Discontinued Follow up, n (%)	47 (11)	58 (5)
Adverse Event	2 (<1)	1 (<1)
Non medical reasons	45 (11)	57 (5)
Completed Follow up, n (%)	372 (89)	1072 (95)

Table 14: AE, deaths, study discontinuation & dose modifications in PO5101 (RESPOND-2) (pooled data for the naive studies).

	P05101 (RESPOND-2) treatment experienced study	
	Control (ribavirin, PR)	**BOC/PR**
Treated, n	**n=80**	**n=323**
	n (%)	**n (%)**
Treatment emergent AE	77(96)	321(99)
Treatment related treatment emergent AE	77(96)	320(99)
Serious AE	4(5)	39(12)
Death	0	1 (<1)
Life threatening	0	9(3)
Study drug discontinuation due to AE	2 (3)	33(10)
Dose modification due to AE**	11(14)	100(31)

Note: subjects may have had more than one event; death are included in the SAE count
* Excludes events for 36 subjects in Study P03523 after they crossed over from Arm 1 (PR) to BOC/PR for treatment-emergent AEs;
** Excludes subjects who discontinued due to adverse events.

Table 15: AE, deaths, study discontinuation & dose modifications in PO3523 (SPRINT) and PO5216 (SPRINT-2) (pooled data for the naive studies).

	PO3523 (SPRINT) & PO5216 (SPRINT-2) treatment naive studies	
	Control (ribavirin, PR)	**BOC/PR**
Treated, n	**n=467***	**n=1225**
	n (%)	**n (%)**
Treatment emergent AE	460 (99)	1217(99)
Treatment related treatment emergent AE	456(98)	1212(99)
Serious AE	39(8)	125(10)
Death	4(1)	3 (<1)
Life threatening	7(1)	13(1)
Study drug discontinuation due to AE	65(14)	172(14)
Dose modification due to AE**	121(26)	505(41)

Note: subjects may have had more than one event; death are included in the SAE count
* Excludes events for 36 subjects in Study P03523 after they crossed over from Arm 1 (PR) to BOC/PR for treatment-emergent AEs;
** Excludes subjects who discontinued due to adverse events.

Table 16: Treatment related, treatment emergent AEs with incidence ≥10% in pooled data for all three studies [PO5101 (RESPOND-2), PO3523 (SPRINT) and PO5216 (SPRINT-2)].

		All subjects	
		Control (PR) N=547	**BOC/PR N=1548**
Median treatment duration in days		**198**	**201**
Any AE, n (%)		533(97)	1532(99)
Blood & Lymphatic System	Anaemia	158 (29)	755(49)
	Neutropaenia	96(18)	350(23)
Gastrointestinal	Diarrhoea	100(18)	353(23)
	Dry Mouth	51(9)	174(11)
	Dysgeusia	82(15)	568(37)
	Nausea	217(40)	690(45)
	Vomiting	60(11)	271(18)
General & Admin. Site	Asthenia	97 (18)	247 (16)
	Chills	161 (29)	515 (33)
	Fatigue	312 (57)	889 (57)
	Influenza Like Illness	135 (25)	339 (22)
	Injection Site Erythema	66 (12)	167 (11)
	Injection Site Reaction	57 (10)	166 (11)
	Irritability	118 (22)	333 (22)
	Pain	42 (8)	148 (10)
	Pyrexia	168 (31)	485 (31)
	Weight Decreased	62 (11)	170 (11)
Metabolism/Nutrition -	Decreased Appetite	125 (23)	386 (25)
Musculoskeletal/Connective Tissue	Arthralgia	90 (16)	282 (18)
	Myalgia	129 (24)	354 (23)
Nervous System	Dizziness	75 (14)	269 (17)
	Headache	234 (43)	683 (44)
Psychiatric	Anxiety	60 (11)	190 (12)
	Depression	108 (20)	302 (20)
	Insomnia	170 (31)	498 (32)
Respiratory, Thoracic and Mediastinal	Cough	100 (18)	257 (17)
	Dyspnoea	86 (16)	296 (19)
	Dyspnoea - exertional	40 (7)	136 (9)
Skin and Subcutaneous Tissue	Alopecia	139 (25)	404 (26)
	Dry Skin	88 (16)	284 (18)

Table 16: continued		All subjects	
		Control (PR) N=547	BOC/PR N=1548
Skin and Subcutaneous Tissue	Pruritus	125 (23)	326 (21)
	Rash	91 (17)	249 (16)

Note: subjects may have had more than one event
* Excludes events for 36 subjects in Study P03523 after they crossed over from Arm 1 (PR) to BOC/PR for treatment-emergent AEs.

Anaemia

Anaemia is a well recognised side effect of PR therapy. BOC alone has not been shown to cause anaemia; the addition of BOC to PR is associated with an increase in the frequency of anaemia and an additional decrement in serum Hb versus PR alone, as was demonstrated in the Phase II study P03659. Both PMN and platelet counts are also further decreased when BOC is added to PR. Anaemia during triple therapy was effectively managed with PR dose reduction and/or EPO use; moreover, there is an ongoing randomised study (PO6086) which aims to better define which strategy is better.

Overall, ~25% of anaemic subjects required dose modification and of these, >85% of subjects required a PR dose modification; 2% required transfusion; 1% reported anaemia as an SAE; 1% required discontinuation. In Study P05101, fewer subjects in the RGT arm than in the BOC/PR48 arm required transfusions . Of the 39 BOC/PR treated subjects who received blood transfusion, 67% (26/39) subjects achieved SVR, despite only 19/39 (49%) subjects completing the treatment phase. A minority of subjects (7/39; 18%) had cirrhosis. More than half (21/39) were female.

In PO5216, subjects in the RGT arms were administered less EPO than those in the BOC/PR48 arms; mean exposure was 94 and 156 days, respectively. In RESPOND-2, the mean exposure to EPO was longer at 135 and 130 daysfor the RGT and BOC/PR48 arms, respectively. The difference in treatment length (12 weeks versus 20 weeks in the treatment failure and treatment-naïve trials, respectively) may not have been sufficient to demonstrate decreased exposure to EPO in the former study.

Almost all of the 798 subjects who received EPO were anaemic (73% with Hb ≤10 g/dL) and 70% completed the treatment phase. The majority of subjects who received EPO responded well and were able to stay on triple therapy longer. Paradoxically therefore, anaemia was consistently associated with higher SVR and EOT response rates, with the majority of the subjects having received EPO to manage their anaemia.

EPO itself use was not associated with a significant increase in AEs if used per protocol. There was no increased incidence in thromboembolic, elevated blood pressure or cancer events in subjects receiving EPO, although the maximum study duration of ~72 weeks limits the ability to detect new or unusual progression of the latter. In P05216, one case of pure red cell aplasia (PRCA), a rare EPO side effect, was reported during follow up. However, unusually high doses of EPO plus continued use beyond the time when the target haemoglobin had been achieved may have contributed to this AE.

Dysgeusia

This AE has been reported in previous studies of PR but occurred with greater frequency in the BOC/PR arms (43-45% versus 11% control). Severe dysgeusia was rare (1%), as were dose modifications (<1%) and discontinuations due to dysgeusia (n=1). While there was a small increase in nausea and vomiting, symptoms potentially associated with dysgeusia, in the BOC arms, most cases were mild to moderate; only 2% of subjects

reported severe nausea and 1% reported severe vomiting. Nine subjects (1%) discontinued due to nausea or vomiting, and few required dose modification.

Vital Signs

When BOC was added to PR there were no significant effects of BOC on vital signs. The most common AE related to vital signs were weight loss and pyrexia, both previously reported with PR and neither appeared to have been exacerbated by BOC with incidence lower in the BOC arms than control (PR) arm.

Cardiac/vascular

BOC plus PR was not associated with increased frequency of cardiac/vascular events with similar proportions of subjects reported cardiac/vascular AEs in triple therapy and PR arms. In the key studies, 25 SAEs occurred in the BOC arms compared to two in the control arm. Eighteen subjects experienced 20 SAEs when excluding events that occurred during the 4 week PR lead in or after 30 days of follow up. These events represented comparable proportions of rhythm disturbances, ischaemic, thromboembolic and coronary artery events, myopericarditis (n=2). A further exploration of whether the increase in anaemia with triple therapy had contributed to the ischaemic events did not suggest that anaemia had contributed and for the most part the Hb decline had been well managed. In summary:

Ischaemic cardiac/vascular events (n=9 subjects):

- 2 myocardial infarction (MI) (1 PR control, 1 BOC/PR48);
- 3 MI (1 PR control, 2 RGT);
- three events of chest pain or angina (1 RGT, 2 BOC/PR);
- 3 cases of coronary artery disease (2 RGT, 1 BOC/PR48);
- 1 cerebral ischaemia event (considered thromboembolic rather than ischaemic).

Discontinuations due to cardiac/vascular AEs were uncommon (1%) in the BOC arms.

Psychiatric

In the key studies, the proportion of subjects reporting psychiatric SAEs (2% versus 1% control) and discontinuations (3% versus 3% control) due to psychiatric events was similar in the BOC arms versus control. There were three deaths due to completed suicide during the studies; 1/547 in the PR arm and 2/1548 in the BOC/PR arms. Subjects with a history of psychiatric disorders reported more psychiatric AEs in the BOC/PR arms than did subjects with no psychiatric history, but a similar difference between the two groups also existed in the PR control group. Overall, the psychiatric AEs occurring in these studies were events previously reported with PR; no new psychiatric AEs were reported nor was there an increase compared to PR therapy.

Rash

Treatment related rash/skin eruption AEs occurred in similar proportions of subjects in the BOC-containing (30%) and PR control arms (27%). There was no evidence of Stevens-Johnson syndrome/toxic epidermal necrolysis. One subject had an SAE of erythematous rash with associated conjunctivitis. The subject was not hospitalised or dose reduced; the rash resolved on continued BOC/PR with the use of oral corticosteroids.

Response guided therapy (RGT)

RGT as a strategy offers decreased overall drug exposure to all three agents and the potential to decrease AEs as a consequence. In P05101, there were fewer SAEs (10%) and

study drug discontinuations due to AE (8%) in the RGT arm compared with the 48 week triple therapy arm (14% and 12%, respectively), but in both cases, more frequently in the BOC containing arms than in the PR control arm (in controls, 5% SAEs and 3% discontinuations). In P05216, the proportion of study drug discontinuations due to AE was less in the RGT arm (12%) compared with the BOC/PR 48 week arm (16%); SAEs were reported by a similar proportion of subjects in the RGT and BOC/PR 48 week arms (11% and 12%, respectively).

There were similar proportions of subjects with treatment emergent AEs, treatment related, treatment emergent AEs and dose modifications due to AE in the RGT arms compared with the BOC/PR 48 week arms in both studies. Dose modifications due to AE occurred with greater frequency in both BOC-containing arms compared to the PR control arm in both studies. In P05101, fewer of the subjects in the RGT arm (3/162, 2%) required a blood transfusion compared to subjects in the BOC/PR arm (14/161, 9%). In P05216, the mean duration of EPO use was almost halved in the RGT arm compared to the BOC/PR48 arm (94 versus 156 days) and shorter than that in the PR48 control arm (121 days). Within the RGT arm, those subjects who were early responders and required shorter treatment also required a shorter duration of EPO use (mean 92 days versus 141 days for RGT [28 weeks] and RGT [48 weeks], respectively. Subjects in the shorter RGT arms of both studies also experienced fewer SAEs and discontinuations due to AE than subjects randomised to the longer RGT arms.

Advanced Fibrosis/Cirrhosis

BOC was well tolerated in cirrhotic subjects treated for up to 48 weeks, although there were relatively few cirrhotics enrolled in these studies. As expected, cirrhotic subjects treated with BOC had higher rates of SAEs than non cirrhotics (16% versus 10%, respectively); in comparison, 10% of cirrhotic control subjects experienced SAEs versus 8% of non cirrhotic control subjects. There did not appear to be any BOC defining toxicity leading to treatment discontinuation in cirrhotic subjects.

Serious adverse events (SAEs)

Deaths

Of 2095 treated subjects, eight died during the course of the key studies. Four deaths (4/547, 1%) occurred in the PR control arms and four deaths (4/1548, <1%) occurred in the BOC/PR arms. Of the AEs that resulted in death, 6 were considered by the investigators to be unlikely to be related to the study drugs and two were possibly related to the study drug (one suicide each in the PR and RGT arms of P05216).

Serious Adverse Events

SAEs were reported in 8% of subjects in the PR control arms and 11% of subjects in the BOC/PR arms. Most of the SAEs were reported in only one subject; SAEs reported in 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 BOC containing arms (Haematologic: 19/1548 (1%) versus 2/547 (<1%); Gastrointestinal: 29/1548 (2%) versus 6/547 (1%); Psychiatric AEs: 24/1548 (2%) versus 5/547 (1%)).

Summary

Dysgeusia and anaemia (and to a lesser extent neutropaenia and thrombocytopenia) are increased with BOC treatment. The addition of BOC to PR did not increase the frequency of deaths, life threatening AE or AE related drug discontinuation.

Laboratory findings

Clinical Laboratory Evaluations

Of the laboratory parameters examined, only the incremental decrease in Hb required frequent clinical intervention and was considered clinically relevant.

Haemoglobin

BOC was associated with an incremental decrease in haemoglobin of ~1 g/dL below that observed with PR SOC. Subjects receiving BOC had higher incidences of WHO Grade 3 anaemia[20] and were more likely to meet dose reduction and dose discontinuation criteria. Hb concentrations returned to baseline within ~12 weeks after study medication discontinuation. Anaemia was managed using EPO or PR dose reduction or dose reduction of both. Some 2% of patients required blood transfusion.

Neutrophils

Subjects receiving BOC in combination with PR had lower PMN counts and were more likely to experience WHO Grade 3 and 4 neutropenia[21] compared with those receiving PR SOC. Forty two subjects reported infections temporally related to neutropaenia in the key studies. Of these, 34 subjects were in the BOC/PR arm and of these, 3 subjects experienced severe infections (epiglottitis, upper respiratory infection, salmonella gastroenteritis/diarrhoea) that occurred within two weeks of the Grades 3/4 neutropaenia. Neutropaenia was managed primarily with dose reduction of PEG; 9% of study subjects received G-CSF. In addition, two cases of life threatening neutropaenia/decreased PMN count were reported, both in BOC/PR subjects. One subject developed sepsis related multi organ system failure; the other experienced a Grade 4 fever of >40C; the specific infectious agent was not identified in either case.

Platelets

Platelet counts were decreased for subjects receiving BOC/PR versus PR control with more subjects experiencing WHO grade 3/4 thrombocytopenia[22] in the BOC/PR arm. However, despite declines, mean platelet counts remained above 100 x 10^9/L; there was one case of significant bleeding (haematemesis) in a subject with Grade 3 thrombocytopaenia and a history of pre-existing portal hypertension and varices.

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[20] WHO Grading of anaemia

- Grade 1 (Mild Anaemia): 10g/dL - cutoff point for ages
- Grade 2 (Moderate Anaemia): 7-10g/dL
- Grade 3 (Severe Anaemia): below 7g/dL

[21] WHO Grading of neutropenia:

- Grade 0 Mild: >2.0x10^9/L
- Grade 1 Mild: 1.5-1.9 x10^9/L
- Grade 2 Mild: 1.0-1.4 x10^9/L
- Grade 3 Moderate: 0.5-0.9 x10^9/L
- Grade 4: Severe: <0.5 x10^9/L

[22] WHO Grading of thrombocytopenia:

- Grade 1: platelet counts of 75,000 to 150,000/㎖
- Grade 2: platelet counts of 50,000 to <75,000/㎖
- Grade 3: platelet counts of 25,000 to <50,000/㎖
- Grade 4: platelet counts of <25,000/㎖

Safety in special populations

Intrinsic factors

Intrinsic factors including gender, race, age, and BMI were evaluated for any impact on clinical AE and laboratory parameters.

Anaemia in population at greater risk (female/elderly)

Females

While females are numerically somewhat underrepresented in the key trials, women tended to have a higher incidence of anaemia than males, but most anaemia cases were of moderate severity. There was no gender bias in regard to severe anaemia (Hb <8g/dL).

Elderly

In the small group (n=38) of elderly subjects (≥65 years of age), BOC/PR appeared to increase the reported incidence of anaemia; 31/38 (82%) of elderly subjects receiving BOC/PR reported anaemia versus 55% in those between 55-64 years of age. The elderly also tended to have more moderate anaemia than younger subjects. Three of the four Grade 4 anaemia cases (Hb <6.5 g/dL) occurred in subjects 50-64 years of age, while one subject over 65 years of age experienced Grade 4 anaemia.

Race and AE

Subjects of Black ethnicity are somewhat underrepresented in the key studies. However, race did not appear to affect the incidence of AE reporting but the types of reported events differed somewhat. For example, Black subjects receiving BOC/PR were more likely to have SAEs of chest pain than White subjects; White subjects who received BOC/PR had more SAEs and discontinuations of therapy due to psychiatric disease compared to Black subjects but no one event predominated. This trend was not observed in the PR control arm.

BMI and AE

There was no association with AE and BMI.

Co-morbid conditions

The safety profile of BOC/PR was evaluated in the co-morbid conditions of diabetes mellitus, psychiatric disorders, drug abuse, with no safety signal seen. However, the safety profile appeared somewhat different for hypertensive subjects receiving BOC/PR as they were more likely to experience exertional dyspnoea. In cirrhotics, thrombocytopenia and anaemia were more common and BOC did not exacerbate this difference.

Immunological events

PEG represents an immunotherapy for HCV which is adjuncted by PR. The exact mechanism is not fully understood. The Phase II and Phase III revealed that a lead in of 4 weeks of PR before BOC introduction was efficacious in terms of SVR. Liver function laboratory parameters were similar between subjects receiving standard-of-care PR versus BOC/PR. There is no evidence of enhanced “flare” of liver function tests during receipt of triple therapy compared to SOC. The safety and efficacy of triple therapy is being explored in PO5411 (HIV/HCV co infected population), in which monitoring of the T-cell subsets is mandatory.

Safety related to drug-drug interactions and other interactions

Statins

Rash was seen more commonly in the BOC/PR treated subjects who were taking statins (CYP3A4/5 substrates). In the PR arm, subjects not taking statins reported more rash than subjects on statins. The number of subjects using statins in the key studies was limited (n=48).

Calcium channel blockers

A higher incidence of dyspnoea was reported in BOC/PR treated subjects receiving calcium channel blockers (CYP3A4/5 substrates). In the PR arm, a similar number of dyspnoea cases were reported in subjects who were receiving calcium channel blockers and those who were not.

Azole antifungals

Paresthaesias, described post marketing with fluconazole, were more common in subjects receiving azole antifungals (CYP3A4/5 inhibitors). In the PR arm, no subject who was taking an azole antifungal reported paresthaesia versus a small number of subjects reporting paresthaesias who were not taking azoles.

Methadone

In the limited number of subjects receiving methadone (n=24), a drug that is metabolised by CYP3A4/5 (CYP3A4/5 substrate), no treatment emergent AE were observed.

HIV protease inhibitors (PI)

PI are both CYP3A4/5 inhibitors and substrates. The study in HIV/HCV co infected subjects remains blinded (PO5411); as of March 2010 only 30 patients have been enrolled; given these limitations there are no safety alerts to date.

Discontinuation due to Adverse Events

In the pooled key studies, no difference was seen in study drug discontinuations for AEs between the PR control (12%) and BOC/PR (13%) arms. Events leading to discontinuation were similar to those seen in previous PR studies which included, anaemia, asthenia, fatigue, nausea, depression, suicidal ideation. Only anaemia and fatigue were reported as events that led to discontinuation in >1% of subjects in any arm.

Dose Modification Because of Adverse Events

AEs led to dose modifications in 39% and 24% in the BOC/PR arms versus PR control arms of the key studies respectively; 1% of subjects had modifications solely of BOC or placebo due to AEs. In most, dose modifications were made for PEG and PR. In Studies P05216 and P05101, the proportion of subjects with PEG dose modifications was similar in the PR and BOC/PR arms; however, as expected due to the increased incidence of anaemia, the BOC-containing arms had a greater proportion of subjects with PR dose reduction (29%) than the PR control arm (16%). Subjects with anaemia (Hb <10 g/dL), were managed by PR 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 PR dose reduction and EPO use in 32% and 46% of subjects, respectively.

Post marketing experience

Not applicable as this drug has notbeen marketed. This drug is under review by two overseas regulatory agencies, that is, the US Food and Drug Administration (FDA) and

European Medicines Agency (EMA), both submitted in November 2010, given priority and/or accelerated review status with responses expected in the second quarter of 2011.

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of Questions to the sponsor is generated.

Pharmacokinetics

1. As demonstrated in the Phase I PK program, BOC should be taken with food. What is the sponsor's advice when subjects are fasted for any length of time?
2. Can you explain the *planned* pharmacokinetics in the ongoing Phase II study of BOC/PR in HIV-HCV genotype 1 co infected subjects (PO5411)? There is a paucity of data on the clinical effect of reductions in BOC levels in people on efavirenz containing combination antiretroviral therapy.
3. You do not provide data on interactions between the following:
   - herbal supplements including St. John's Wort (an inducer of the CYP3A4);
   - inducers of CYP3A4 and 2D6 inducer such as rifampicin;
   - illicit substances such as "Ecstasy".

Pharmacodynamics

1. Does BOC have any effect on the protease of HIV? If BOC does have anti-HIV activity, the use of BOC as part of HCV treatment would represent monotherapy for HIV and could lead to a more resistant HIV virus for those treated for HCV before receiving treatment for HIV.
2. Is there cross resistance between telaprevir (FDA approved 29 April 2011) and BOC?

Efficacy

1. The number of subjects in RESPOND-2 who were previous PEG non responders and randomised into Arm 2 (RGT) is very small. What is the real statistical power in this setting to say anything meaningful about RGT as strategy in PEG non responders using triple therapy?
2. Does the sponsor have any data to explain why in the RESPOND-2 study a higher proportion of BOC/PR48 subjects versus RGT subjects achieved undetectable HCV-RNA at some point during the first 36 weeks despite each of these arms receiving identical therapy for the first 36 weeks? Was there a difference in IL28B status that by chance alone influenced this outcome? Does the sponsor have any other insights?

Safety

1. What effect, if any, does BOC have on host proteases? There are some problems faced in the HIV arena in regards to HIV protease inhibitors and their association, at least in part, with the HIV metabolic syndrome.

Clinical Summary and Conclusions

Clinical aspects

Pharmacokinetics

Absorption

Oral absorption with median T_{max} of two hours; food increases BOC exposure by 40-60% when dosed at 800mg TID, the dose shown to have pharmacodynamic activity. Food increased exposure regardless of type of food or exact timing of food in relation to BOC dosing. Steady state AUC, C_{max} and C_{min} increased at a less-than-dose proportional manner especially at doses >800mg TID; the overlap in PK parameters between the 800mg and 1200 mg doses suggests decreased absorption at the higher dose. AUC (T), C_{max}, C_{min} were 6,147ng.hr/ml, 1,913 ng/ml and 90mg/ml respectively in healthy subjects receiving 800 mg TID; PK data in HCV co infected individuals was similar.

Distribution

The two diastereomers SCH 534128 (active) and SCH 534129 (inactive) exist in plasma in a ratio of approximately 2:1 and this ratio is not altered by food, concomitant medications, or in special populations. Vd/F is ~772 L at steady state; PPB of 75%.

Metabolism

BOC accumulation (mean accumulation (R) values range: 0.773-1.45) is minimal and steady state reached after ~1 day of TID dosing. SCH 534128 and SCH 534129 have similar mean $t_{½}$ and a similar R value. BOC is extensively metabolised through both oxidative and reductive (AKR) pathways. Reduction of the diastereomers occurs at the ketone adjacent to the ketoamide. Three (of the possible four) reduced ketone stereoisomers were identified as major circulating metabolites; steady state metabolite-to-parent AUC ratios were 4:1 in humans.

Elimination

The PK data support the primarily hepatic mediated clearance of BOC. Mean plasma $t_{1/2}$ was 3.4 hrs and , mean total body clearance ~161 L/hr.

Special Populations

No dose reductions in those with hepatic or renal impairment; contraindicated (in combination with PEG-PR) in cirrhotics with Child-Pugh score of >6. No gender or race related PK differences observed. There is a paucity of data in the elderly, although population PK did not suggest an aged related impact on exposure. There is no paediatric data.

Drug-drug interactions

There is a potential for significant elevations of drugs metabolised through CYP3A4 which have a narrow therapeutic index because BOC is a potent inhibitor of this oxidation pathway. Hence such co administration must be avoided. Drugs that inhibit AKR do not result in clinically meaningful elevations in BOC. The clinical relevance of inducers of CYP3A4 such as efavirenz in terms of reducing BOC levels is unknown.

Pharmacodynamics

BOC is an orally administered NS3/4A serine protease inhibitor of HCV with an IC_{50} and IC_{90} in an HCV replicon system of 200nM and 400nM, respectively. The replicon system does appear to accurately predict the IC_{90} of the compound for HCV; the target plasma concentration of ~200ng/mL was used for early dose decisions and this was subsequently supported by the PD data derived from the Phase II and III program. Maximal decrease in

HCV-RNA concentrations correlates best with C_{min} concentrations of BOC (R=0.653); with a less robust relationships for the AUC (R=0.511) and C_{max} (R=0.466). The effects of using BOC and PEG are additive without synergy or antagonism. The RAVs V36M, T54A, R155K and V170A are associated with a 2-10 fold reduction in BOC potency; A156T and A156V substitutions were associated with >50 fold loss of BOC activity. PEG responsiveness (as defined by the TW4 reduction in HCV viral load) significantly impacted on SVR with triple therapy that included BOC. In the pooled resistance analysis, 53% of subjects without SVR had RAVs detected, that is, R155K (52%) > V36M (in 46%) >> T54S (23%) >>>> T54A (in 15%). In long term follow up of those not attaining SVR, there is reversion of RAVs to wild type with T54A and V36M reverting most quickly. The presence of baseline RAVs did not impact negatively on response to triple therapy.

Dose response studies and main clinical studies

The pivotal studies, RESPOND-2 and SPRINT-2 provide convincing data that the use of BOC with PEG and PR substantially increases SVR for adults with HCV genotype 1 who are treatment experienced (PEG/PR non responders or poor responders) or treatment naive. Both studies had arms exploring response guided therapy. In treatment naives, TW8 HCV PCR was the key time point for subsequent duration of therapy. Early responders requiring a total duration of therapy of 28 weeks only (4 weeks PR then 24 weeks of triple therapy) provided HCV PCR was undetectable at TW24. In late responders (detectable HCV PCR at TW8), but undetectable HCV PCR at TW24, triple therapy ceased at TW28, and PR continued for a further 20 weeks making a total of 48 weeks of treatment (PR induction 4 weeks; triple therapy weeks 24 weeks; PR 20 weeks). In treatment-experienced patients, TW8 and 12 were key time points in terms of RGT. In those with HCV PCR undetectable at both these time points, total treatment was 36 weeks (PR induction 4 weeks, triple therapy for 32 weeks). In those with detectable HCV PCR at TW8 but undetectable at TW12 (slow responders), patients continued triple therapy until week 36 and then continued PR for a further 12 weeks to Week 48. In other words, in this setting, BOC use beyond Week 36 did not increase SVR for slow responders. The key time point for futility was TW24 in which, in either setting (treatment experienced or treatment naive), if HCV PCR was detectable, treatment should cease.

Overall, SVR rates for triple therapy in treatment experienced and treatment-naive patients were 61% to 67% versus 22% (control arm PR48 weeks) and were 67% to 68% versus 40% (control arm PR48 weeks) respectively; these results are highly statistically significant in both settings. Baseline and on study predictors of SVR in treatment experienced patients included the following covariates: BOC/PR48 versus control (PR); RGT versus PR, TW4 HCV viral load response >1 log_{10}; previous response to PEG (response relapser) versus non responder. A number of baseline factors predicted poorer responses in naive subjects, in comparing SVR in the BOC-RGT and BOC-PR48 containing arms versus PR, baseline HCV-RNA >400,000 IU/mL (62 and 65% versus 34%); F3/4 liver fibrosis score (41 and 52% versus 38%); genotype 1a (59 and 62% versus 34%); genotype 1b (71 and 73% versus 40%) as well as older age (>40 years of age) and higher BMI.

The Phase III study in naive patients (SPRINT-2) also deliberately enrolled patients of Black race, the rationale being this is a group who are often underrepresented in HCV trials and often have substantially lower SVR. For those receiving triple therapy, SVR rates were numerically lower in Black than White subjects.

Ancillary analyses

BOC dosing interval and SVR

Maximal decrease in HCV-RNA concentrations correlates best with C_{min}; serum C_{min} at 8 hours was achieved with BOC TID dosing. In assessing the "forgiveness" of BOC dosing

interval substudy was conducted in RESPOND-2 and SPRINT-2. Overall, >80% adherent to dosing of all three study medications had minimal impact on SVR; high SVR rates (66-70%) were observed in subjects who were at least 60% adherent to the desired BOC dosing interval but if <60% adherence, SVR rates dropped to 50%. This means there is some flexibility in terms of dosing adherence, with only very poor adherence resulting in a negative impact on SVR. This is important as duration of triple therapy for success (in slow responders) can be as long as 32 weeks.

Clinical studies in special populations

Ongoing studies are being conducted in HIC/HIV co infected patients (Phase IIb); this study remains blinded and is not fully enrolled. This is an important cohort as the response to PR is less that an HCV mono infected population and HCV is thought to have a negative impact on HIV outcomes and vice versa.[23]

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

In an endeavour to understanding the impact of baseline and emergent BOC RAVs on SVR, a pooled resistance analyses was performed using SPRINT-2 and RESPOND-2 samples (n=295). Baseline RAVs were found in 7% and surprisingly did not appear to impact treatment response. Of those BOC treated subjects who did not achieve SVR, 155/295 (53%) had on study RAVs detected. RAVs were detected in the majority of subjects with virologic breakthrough (75%) and incomplete virologic response (93%). The most commonly detected RAVs were the following amino acid substitutions R155K (52%), V36M(46%), T54S(23%) and T54A(15%). Moreover, PEG responsiveness impacted on the emergence of BOC RAVs, that is, 41% of all poor PEG responders versus 6% of all PEG responders had RAVs. Among subjects with samples analysed, 68% of poorly PEG responsive subjects had RAVs compared to 31% of those with better PEG response.

Further analysis by race demonstrated that Black subjects had a higher percentage of RAVs detected post baseline compared to non Black subjects. Detection of RAVs after initiation of treatment was similar for both BOC/PR treatment strategies (RGT versus 48 Weeks). Some of the explanation for PEG responsiveness lies in the IL28B genotype, recognised as important in predicting response to PR. In a pooled pharmacogenomic analysis from PO5216 and PO5101, 62% and 66%, respectively, of patient samples were genotyped for IL28B. Overall, prevalence of the polymorphic site rs12979860 was 28.4% CC (favourable), 17.8% TT and 53.8% CT. Black subjects treated with PR were less likely to have CC genotype and hence had less SVR. Although the influence of IL28B genotype on response to triple therapy was not as profound as its effect on PR responsiveness, nevertheless it did influence SVR rates, that is, SVR was 7-26% higher in IL28B CC versus CT or TT; in the pooled PR (control) arms SVR were 41-46% higher in the IL28B CC than those with CT or TT.

In a multivariate logistic regression analysis stepwise selection using pooled data from P03523 + P05216 (naive studies), the following factors influenced SVR:

- Baseline factors: HCV 1 genotype: Other versus 1b (OR 4.158, 95% CI 1.574, 10.983, p=0.004);
- Race: Black versus non Black (OR 0.478, 95% CI 0.317, 0.720, p=0.0004;
- Baseline HCV-RNA: ≤400,000 versus >400,000 IU/mL (OR 6.352, 95% CI 3.024, 13.344, p<.0001);

[23] Soriano V, et al. Update on the treatment of chronic hepatitis C in HIV-infected patients. *AIDS Rev.* 2007; 9:99-113.

- Age: ≤40 versus >40 Years, (OR 1.610, 95%CI 1.091, 2.375) 0.0163;
- Platelet count (as surrogate for more advanced liver disease): <150,000 versus >200,000/μL (OR 0.487, 95% CI 0.296, 0.802, p= 0.0047)
- On-study treatment: BOC/PR48 versus PR48 (OR 4.149, 95% CI 3.111, 5.534, p=<0.0001);

When multivariate logistic regression analysis including TW4 response as a factor; TW4 response was also significant as a predictor of SVR.

Supportive studies

There are two ongoing blinded studies of? CHC genotype 1, that is, P05685 & PO6086 (Phase III) and one open label study (PO5514). The first group is those previously treated with PR but without SVR (P05685 & PO5514). The second group are treatment naive CHC patients (PO6086) who receive open label triple therapy but are randomised to one of two strategies, EPO use or PR dose reduction, for the management of anaemia, which occurs in ~60% of patients receiving PR or triple therapy and can limit treatment exposure and hence SVR outcomes.

Clinical safety

Patient exposure

During the course of BOC clinical development ~2827 subjects have been exposed to any dose of BOC in 28 clinical trials; 77% received BOC 800 mg TID, the proposed dose for therapeutic use. In the 1897 subjects with CHC treated with BOC 800 mg TID in combination with PR in unblinded/open label Phase II/III studies, total exposure to BOC was 960.5 person years. In the Phase II/III studies demographic and baseline disease characteristics were representative of subjects with CHC genotype 1, that is, 2/3 were male and >80% were White. There were very few subjects ≥65 years (n=48 subjects) and only 123 subjects with cirrhosis. In terms of ethnicities represented, those of Black (N=282) and Asian race (N=31) are underrepresented.

Adverse events

BOC as part of triple therapy versus PR is well tolerated with a predictable AE profile, that is, anaemia (49% versus 29%) >>> neutropenia (7% versus 4%)) >>> thromobocytopenia (3% versus 1%). However, this AE profile is familiar and manageable by clinicians used to treating HCV with PR. In the pooled key studies, no difference was seen in study drug discontinuations for AEs between the PR control (12%) and BOC/PR (13%) arms and events leading to discontinuation were similar to those seen in previous PR studies, that is, anaemia, asthenia, fatigue, nausea, depression and suicidal ideation. Moreover, RGT using key time points shortens exposure to treatment for many subjects thereby reducing the risk of AE. Aside from increasing the haematological side effects of PR, BOC as part of triple therapy did not appear to have any signature AE of its own.

Dose modification because of adverse events

AEs led to dose modifications in 39% and 24% in the BOC/PR arms versus PR control arms of the key studies respectively; 1% of subjects had modifications solely of BOC/placebo due to AEs. In most, dose modifications were made for PEG and PR. In Studies SPRINT-2 and RESPOND-2, the proportion of subjects with PEG dose modifications was similar in the PR and BOC/PR arms; however, as expected due to the increased incidence of anaemia, the BOC containing arms had a greater proportion of subjects with PR dose reduction (29%) than the PR control arm (16%). The management strategy for anaemia (Hb <10 g/dL), was similar between the PR and BOC/PR arms respectively, that

is, PR dose reduction alone in10% and 7% of subjects; EPO use alone in 37% and 33% of subjects; PR dose reduction plus EPO in 32% and 46% of subjects.

Serious adverse events and deaths

SAEs were reported in 8% versus 11% in PR control versus BOC/PR arms. Most of the SAEs were reported in only one subject; SAEs reported in more than one subject were events reported with long term PR therapy but those reported with higher frequency in the BOC-containing arms were:

- Haematologic: 1% versus <1%;
- Gastrointestinal: 2% versus 1%;
- Psychiatric: 2% versus 1%;
- Deaths: Of 2095 treated subjects, eight died during the course of the key studies; no excess deaths were seen in those receiving BOC <1% versus 1%.

In summary, dysgeusia, anaemia, neutropaenia and thrombocytopenia are increased with BOC treatment. The addition of BOC to PR did not increase the frequency of deaths, life threatening AE, or AE related drug discontinuation.

Laboratory findings

BOC as part of triple therapy appeared to exacerbate declines in haematological parameters compared to PR alone. Only the incremental decrease in Hb (~1g/dL below that observed with PR) required frequent clinical intervention.

- Neutrophils: Subjects receiving BOC in combination with PR had lower PMN counts and were more likely to experience WHO Grade 3 and 4 neutropaenia compared with those receiving PR. Thirty-two of 44 subjects (73%) in the BOC/PR arm reported infections temporally related to neutropaenia in the key studies, of these, 3 subjects experienced severe infections. Neutropaenia was managed primarily with dose reduction of PEG; 9% received G-CSF.
- Platelets: More patients receiving BOC experienced WHO grade 3/4 thrombocytopenia. However, mean platelet counts remained >100 x 10^9/L.

Safety in special populations

Intrinsic factors including gender, race, age, and BMI were evaluated for any impact on clinical AE and laboratory parameters and none were noted although in women and the elderly, who tend to have lower haemoglobin, BOC/PR did impact to a greater extent. The numbers of elderly patients enrolled in the BOC studies was very small, but anaemia was worse in those receiving triple therapy; more data is required to evaluate the risk in this population. Co-morbid conditions: The safety profile of BOC/PR was evaluated in the co-morbid conditions of diabetes mellitus, psychiatric disorders, drug abuse, with no safety signal seen. However, hypertensive subjects receiving BOC/PR were more likely to experience exertional dyspnoea. In cirrhotics, thrombocytopenia and anaemia were more common, but BOC did not exacerbate these parameters more than PR.

Immunological events

None reported.

Safety related to drug-drug interactions and other interactions

The Phase I program confirmed that BOC is a strong, time-dependent, reversible inhibitor of CYP3A4 and drugs with a narrow therapeutic window must not be co-administered.

BOC is also metabolised via AKR but drugs inhibiting this pathway did not result in clinically meaningful changes in BOC levels. The Combined Oral Contraceptive Pill (COCP) can be administered with BOC without dose adjustment but levels of drospirenone (a synthetic progestin which is an analogue of spironolactone) are increased substantially, this might only matter in patients also taking drugs that lead to potassium retention. In terms of the Phase II and III program, rash was seen more commonly in the BOC/PR treated subjects who were taking statins (CYP3A4/5 substrates) but overall, numbers of statin users was small (n=48). No cases of myopthy or rhabdomyolysis were seen. A higher incidence of dyspnoea was reported in BOC/PR treated subjects receiving calcium channel blockers (CYP3A4/5 substrates). In the PR arm, a similar number of dyspnoea cases were reported in subjects who were receiving calcium channel blockers and those who were not. Paresthaesias were more common in subjects receiving azole antifungals (CYP3A4/5 inhibitors). In the PR arm, no subject who was taking an azole antifungal reported paresthaesia. A small number of subjects who were not taking azoles reported paresthaesias. In the limited number of subjects receiving methadone (n=24) (metabolized by CYP3A4/5 and a CYP3A4/5 substrate), no treatment-emergent AE were observed. HIV protease inhibitors are both CYP3A4/5 inhibitors and substrates; data from the Phase I PK program does not suggest any clinically meaningful interaction.

Discontinuation due to adverse events

In the pooled key studies, no difference was seen in study drug discontinuations for AEs between the PR control (12%) and BOC/PR (13%) arms. Events leading to discontinuation were similar to those seen in previous PR studies, that is, anaemia, asthenia, fatigue, nausea, depression, suicidal ideation. Only anaemia and fatigue were reported as events that led to discontinuation in >1% of subjects in any arm.

Benefit risk assessment

The key body of clinical data in support of this application consists of 20 Phase I studies, 3 Phase II studies (2 completed; 1 ongoing); 5 Phase III studies (2 completed; 3 ongoing) and 1 long-term safety study.

Benefits

The pivotal Phase III studies demonstrate a substantial increase in SVR in both settings compared to SOC with PEG-INF and ribavarin for HCV genotype 1. The data from the RGT arms for both studies also provides data in support of reduced treatment duration in those with rapid responses, that is, at Treatment Week 8.

Risks

Haematological adverse events in particular anaemia are exacerbated in those receiving BOC as part of the triple therapy compared to PR alone. No signature adverse event attributable to BOC has been revealed in these pivotal studies, although person-years of follow up are relatively small to date.

Safety Specification

The safety specification must state that the groups in which this drug has been trialled in the pivotal Phase III studies are treatment experienced or treatment naive participants CHC genotype 1 adults without liver decompensation and that there is a paucity of data in the elderly ≥65 years of age and none in HIV-HCV co infected participants (Phase IIb trial ongoing). The most common side-effect of triple therapy that included BOC was anaemia which was managed with the usual strategies applied to the treatment of anaemia with SOC PR. The other main side effects appeared to be gastrointestinal, particularly dysgeusia. There was no signature adverse event identified during the BOC development

program that was identified, all the AE's seen were reported in the PR group. However, BOC did amplify the haematological disturbance (haemoglobin >>> neutrophils >> platelets) with clinical consequences. The safety of BOC cannot be separated from that of PEG-INF and ribavarin as the drugs are dosed together as part of triple therapy, the safety information must state this.

Balance

The substantial increase in sustained viral response of triple therapy, which includes BOC, in the treatment of non decompensated CHC genotype 1 in the treatment experienced and treatment naive settings outweigh the adverse events associated with the use of the drug. The adverse event profile revealed in the pivotal studies has been predictable and manageable.

Conclusions

Triple therapy with BOC represents a major advance in the treatment of CHC genotype 1, the most difficult genotype to achieve SVR with. This is true in both settings, those who are treatment naive and those who are treatment experienced. The greatest response in terms of SVR was in those who were treatment naive, as one might expect. The drug is well tolerated with a predictable side effect profile predominant anaemia which can be managed successfully using the usual algorithm utilised in those who develop anaemia with PEG and PR, that is, PR dose reduction, EPO use or both. Further data on the best approach will be forthcoming from an ongoing study in naive patients of triple therapy in which the randomisation is to either a PR reduction or EPO introduction strategy in those developing anaemia (around 60%). Boceprevir is an oral drug and adds to pill burden of patients, however, the drug has forgiveness, in so much as, less than perfect adherence with the dosing schedule (eight hourly) is not associated with a significant negative impact on SVR. Baseline BOC resistance associated mutations were rare, but somewhat surprisingly did not appear to impact negatively in response. PEG responsiveness was an important component of overall response to triple therapy but the IL28B genotype (favourable versus less so) impacted less on SVR with triple therapy compared to SVR with PEG-INF and ribavarin alone.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan (RMP) which was reviewed by the TGA's Office of Product Review (OPR).

Safety Specifications and Pharmacovigilance Plan

Proposed pharmacovigilance activities

A summary of Ongoing Safety Concerns as specified by the sponsor and planned pharmacovigilance actions is shown in Tables 17-19.

Table 17: Summary of Ongoing Safety Concerns (Important Identified Risks) for BOC and planned pharmacovigilance actions.

Safety Concern	Planned Action(s)
Important Identified Risks	
1) Anemia	1) a. Routine Pharmacovigilance b. Additional pharmacovigilance activities, including use of an anemia questionnaire to enhance collection of postmarketing reports c. Ongoing comparative trial of erythropoietin versus ribavirin dose reduction for anemia management (P06086) d. Other ongoing clinical trials (P05514 and P05411). e. Planned mechanistic study for anemia f. Postmarketing drug utilization study
2) Neutropenia	2) a. Routine Pharmacovigilance. b. Ongoing clinical trials (P06086, P05514 and P05411). c. Postmarketing drug utilization study
3) Thrombocytopenia	3) a. Routine Pharmacovigilance. b. Ongoing clinical trials (P06086, P05514 and P05411). c. Postmarketing drug utilization study
4) Drug-Drug Interaction (CYP3A4/5)	4) a. Routine Pharmacovigilance. b. Ongoing clinical trials (P06086, P05514 and P05411). c. Planned studies: • P08371, P08123, P08124, P08335, P08384, P08431 • Investigator initiated studies of omeprazole and etravirine • Evaluation of the potential for inhibition of AKR 1C2 by boceprevir

Table 18: Summary of Ongoing Safety Concerns (Important Potential Risks) for BOC and planned pharmacovigilance actions.

Safety Concern	Planned Action(s)
1) Resistance-associated amino acid variants	1) a. Routine Pharmacovigilance. b. Ongoing clinical trials (P05063, P06086, P05514 and P05411).
2) Impact of dysgeusia on quality of life or treatment discontinuation	2) a. Routine Pharmacovigilance. b. Ongoing clinical trials (P05063, P06086, P05514 and P05411).
3) Medication errors	3) a. Routine Pharmacovigilance.
4) QT interval prolongation	4) a. Routine Pharmacovigilance.
5) Thyroid neoplasm (thyroid nodule)	5) a. Routine Pharmacovigilance.

Table 19: Summary of Ongoing Safety Concerns (Important Missing Information) for BOC and planned pharmacovigilance actions.

Safety Concern	Planned Action(s)
1) Potential exposure during pregnancy	1) a. Routine Pharmacovigilance. b. Participation in the Ribavirin Pregnancy Registry.
2) Exposure during lactation	2) a. Routine Pharmacovigilance.
3) HIV/HCV coinfection	3) a. Routine Pharmacovigilance. b. Ongoing clinical trial P05411. c. The MAH has committed to discussions with the AIDS Clinical Trial Group (ACTG) to explore establishing studies in the HIV/HCV coinfected population. d. 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.
4) HBV/HCV coinfection	4) a. Routine Pharmacovigilance.
5) HCV genotype 2/3/4	5) a. Routine Pharmacovigilance. b. For HCV genotype 2/3, results from clinical trial P03648 c. Pilot studies under Merck investigator initiated study program are going to be conducted.
6) Patients with previous tritherapy boceprevir - PR treatment failure	6) a. Routine Pharmacovigilance.
7) Exposure in patients with severe cirrhosis (Child-Pugh > 6, Class B&C)	7) a. Routine Pharmacovigilance.

Table 19: Summary of Ongoing Safety Concerns (Important Missing Information) for BOC and planned pharmacovigilance actions (continued).

Safety Concern	Planned Action(s)
8) Exposure in organ transplant patients	8) a. Routine Pharmacovigilance. b. Additional investigations: - 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, protocol has been developed.
9) Exposure in the pediatric population	9) a. Routine Pharmacovigilance. b. 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 following the determination of dose(s) from study P07614.
10) Exposure in elderly patients	10) a. Routine Pharmacovigilance. b. Ongoing clinical trials (P06086, P05514 and P05063).
11) Exposure in patient s with hemoglobin < 13g/dL (male) or < 12 g/dL (female)	11) a. Routine Pharmacovigilance. b. Ongoing clinical trials (P06086, P05514 and P05063).
12) Exposure in patients with psychiatric disorders	12) a. Routine Pharmacovigilance.
13) Long term therapy	13) a. Routine Pharmacovigilance.

Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;

Submission of Periodic Safety Update Report (PSURs):

- Meeting other local regulatory agency requirements.

OPR reviewer comment with respect to Safety Specifications:

It is noted that post licensure BOC (Victrelis) is only indicated for use with the PEG/PR combination in adults. A detailed account of the combined safety specifications of all three products has not been provided by the sponsor, and as such has not been considered in this evaluation. Evaluation of the RMP for BOC is not complete without the current safety concerns, updated pharmacovigilance plan and risk minimisation activities of the Victrelis-PEG/PR as a whole being considered in a RMP. Comments that appear throughout this evaluation report pertain to the BOC component of the indication.

OPR reviewer comment with respect to Pharmacovigilance Plan:

In light of my earlier comments with regard 'Safety Specification', the pharmacovigilance plan for this indication cannot be fully evaluated.

In general there is no objection to the implementation of the pharmacovigilance plan as outlined.

It is understood that many of these proposed studies are being developed under the post-marketing plan agreed with the FDA. The sponsor is requested to provide a protocol synopsis for each of these studies, when they become available, to OPR for information. It is expected a summary of the final results of each study as they become available will be included with each next scheduled PSUR.

The proposed studies (P07614 and P08034) to further establish the safety and efficacy of BOC in a paediatric population has not been evaluated as part of this submission as its scope does not fall within the proposed indication.

Risk Minimisation Activities

Sponsor's conclusion in regard to the need for risk minimisation activities

The sponsor proposes routine risk minimisation activities[24] for all important identified risks, the important potential risk and all important missing information.

The sponsor proposes additional risk minimisation activities as outlined below for the identified potential risk 'Anaemia', 'Neutropenia', and Thrombocytopenia'. The sponsor has provided educational material addressing Anaemia.

OPR reviewer comment:

In light of the evaluator's earlier comments with regard 'Safety Specification', the risk minimisation plan for this indication cannot be fully evaluated. All comments henceforth pertain only to the submitted risk minimisation for the boceprevir component.

In the educational materials dealing with anaemia the sponsor has provided guidance for the monitoring on anaemia, and includes tables outlining dose reduction strategies for PR and PEG-INFa2a. These appear comprehensive and in a format that would be useful to a clinician. The sponsor also provides guidance for the use of EPO in the setting of anaemia. This advice is also found in the draft Product Information. The concern with this advice is that it is outside the indications for use for EPO in Australia and as such constitutes off label use. It is unclear to the evaluator if sufficient evidence has been provided by the sponsor regarding the safety of EPO in this setting. Educational materials have not been provided for the risks 'Neutropenia' and 'Thrombocytopenia' and should be provided for review before supply.

Additional risk minimisation activities are required for the Important Identified Risk of CYP3A4/5 Inhibition.

Potential for medication errors, drug overdose

The sponsor notes that to lower the potential medication error, BOC is packaged in blisters containing the daily dose, and that there will be seven blister packs in each folding carton which will represent each week's dose. One month's supply will be provided in a separate box.

[24] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

The sponsor notes in the two known cases of overdose no adverse events for the patients were noted.

OPR reviewer comment:

The sponsor's argument that the potential for medication error (for BOC alone) is reduced with this strategy appears adequate.

The experience in overdose is limited to accident additional dosing in the clinical trial situation. The potential for serious drug-drug interaction in overdose with other drugs metabolised via the CYP3A4/5 pathway or with p-glycoprotein interactions is not considered. Depression occurring while taking this medication is an identified adverse event with the combination medication (Victrelis-PEG/PR), raising the potential for intentional overdose. The implication for this in terms of safety is not primarily with BOC but with its many drug-drug interactions and its potential to cause long QTc which may be additive. It is recommended the overdose section reiterate briefly the main concerns with interacting drugs that could be life threatening in overdose such as drugs metabolised by CYP3A4, possible prolongation of QTc and p-glycoprotein interactions.

The RMP outlines a strategy for the management of overdose that includes the induction of vomiting and gastric lavage. These decontamination strategies do not form part of current practice in Australia in the acute management of overdose. The RMP should be updated to reflect current practice. It is noted that this advice does not appear in Overdose section of the PI.

Summary of Recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of RMP Version 1.4 dated 18 May 2011 imposed as a condition of registration when so qualified:

General Comment

The indication for BOC (Victrelis) is for the treatment of HCV genotype 1 infection, in a combination regimen with PEG-INFa and PR, in adult patients (18 years and older) with compensated liver disease who are previously untreated or who have failed previous therapy. Evaluation of the RMP for BOC is not complete without the current safety concerns, updated pharmacovigilance plan and risk minimisation activities of the Victrelis-PEG/PR as a whole being considered in a RMP. Comments that appear throughout this evaluation report pertain to the BOC component of the indication as does this summary of recommendations. A RMP that addresses the safety specifications, pharmacovigilance plans and risk minimisation activities, including the interaction between the three drug components identified in the indication for boceprevir must be submitted for this evaluation to be considered complete.

The RMP outlines a strategy for the management of overdose that includes the induction of vomiting and gastric lavage. These decontamination strategies do not form part of current practice in Australia in the acute management of overdose. The RMP should be updated to reflect current practice. It is noted that this advice does not appear in 'Overdose' section of the PI.

Pharmacovigilance Plan

It is understood that many of these proposed studies are being developed under the post-marketing plan agreed with the FDA. The sponsor is requested to provide a protocol synopsis for each of these studies, when they become available, to OPR for information. It is expected a summary of the final results of each study as they become available will be included with each next scheduled PSUR.

Risk Minimisation Plan

The sponsor has provided educational materials for Anaemia. The sponsor is also requested to provide educational materials for the Important Identified risks 'Neutropenia' and 'Thrombocytopenia' before supply.

Both the proposed PI and the educational materials give guidance for the use of EPO as a management option for anaemia. The current Australian PIs for EPO do not include drug induced anaemia as an indication, thus this represents off-label use. It is suggested the Delegate give consideration to the above before the guidelines are approved.

It is recommended the education program be extended to include drug-drug interactions and contraindicated drugs because of drug-drug interactions precautions when prescribing concomitant medications. It is recommended this component of the program be made available to the Royal Australian College of General Practitioners, the Royal Australian and New Zealand College of Psychiatrists, the Australian and New Zealand College of Anaesthetists, and the Australasian College for Emergency Medicine.

In addition the education program should incorporate safety concerns with BOC used in combination with PEG and PR.

The experience in overdose is limited to accident additional dosing in the clinical trial situation. The potential for serious drug-drug interaction in overdose with other drugs metabolised via the CYP3A4/5 pathway or with p-glycoprotein interactions is not considered. Depression occurring while taking this medication is an identified adverse event with the combination medication (Victrelis-PEG/PR), raising the potential for intentional overdose. The implication for this terms of safety is not primarily with boceprevir but with its many drug-drug interactions its potential to increase the C_{max} of drugs which cause a long QTc. It is recommended the overdose section reiterate briefly the main concerns with interacting drugs that could be life threatening in overdose – drugs metabolised by CYP3A4, possible prolongation of QTc and p-glycoprotein interactions.

There are a number of illicit substances known to be metabolised by CYP3A4, including cannabinoids, opioids, and cocaine. There is no mention of these substances interacting with boceprevir in the PI or CMI. BOC will be prescribed in a population at risk of use of illicit substances. It is recommended that patients be warned of potential interactions and prolonged effects. It is recommended that clinicians are urged via the educational material to discuss these possible interactions with their patients and material outlining potential illicit drug-drug interactions be presented in educational material provided to clinicians.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

This application proposes registration of a new chemical entity, boceprevir (BOC; Victrelis), in a 200mg capsule presentation. BOC is a HCV protease inhibitor which inhibits HCV replication by binding the NS3 protease active serine site and preventing cleavage of the viral polyprotein into functional units. The proposed indications are:

> "Victrelis (boceprevir) is indicated for the treatment of Chronic Hepatitis C (CHC) genotype 1 infection, in a combination regimen with peginterferon alfa and ribavirin, in adult patients (18 years and older) with compensated liver disease who are previously untreated or who have failed previous therapy."

The safety, efficacy and pharmacokinetic profile of Victrelis in patients below 18 years of age have not yet been established. Victrelis must be administered in combination with peginterferon alfa and ribavirin. The recommended dose of Victrelis is 800 mg administered three times daily with food. Response guided treatment recommendations are provided for patients who are previously untreated and patients who have failed previous treatment. Dose reduction or dose modification of Victrelis is not recommended.

Nonclinical

Nonclinical data were extensive and generally compliant with all relevant nonclinical guidelines.

Nonclinical studies provided adequate evidence that BOC effectively inhibits HCV replication *in vitro* at concentrations readily exceeded in the liver *in vivo* (IC_{50} and IC_{90} values were 200 nM and 400 nM, respectively). Numerous resistance variants to boceprevir emerge with time and increasing drug concentration. Of the RAVs identified to date, greatest reductions in BOC potency were observed with A156T/S/V, T54C and R155I/G/T substitutions. RAVs remained sensitive to interferon-α and were cross resistant to another ketoamide protease inhibitor, telaprevir. BOC is not indicated as monotherapy due to the propensity for resistance. BOC showed no significant activity against the HIV protease *in vitro*.

In vitro secondary pharmacology screens with boceprevir showed no evidence for interactions with a wide range of enzyme, non HCV protease, and neurotransmitter receptor systems, indicating selective activity.

The nonclinical toxicity studies were generally of adequate duration and did not identify any effects which would preclude registration. Deficiencies in animal exposure to the components of BOC, relative to expected human exposure, limit the value of the nonclinical program for predicting potential toxicities of potential human relevance. The limitations of the nonclinical testing include once daily dosing in all toxicity studies compared to three times daily dosing recommended for humans, and substantial quantitative differences in metabolites and the active diastereomer between species. No toxicity studies were performed where exposure to individual diastereomers and metabolites matched or exceed the exposure to these components expected in humans. Toxicity of BOC in combination with PR and PEG-INF was investigated in a single toxicity study in monkeys but this study was limited to one month duration due to formation of antibodies.

The nonclinical evaluation concludes the nonclinical program has not sufficiently defined the potential toxicity profile of BOC.

Clinical

The clinical data in this application consists of twenty Phase I studies, two Phase II studies (two completed; one ongoing); five phase III studies (two completed; three ongoing) and one long term safety study.

Pharmacokinetics

Pharmacokinetics were assessed in 13 studies in healthy subjects, five studies in subjects with CHC, and two special population studies, in hepatically impaired and renally impaired subjects. A total of 377 healthy subjects were included in these studies. In CHC patients, sparse sampling data in the phase III studies were used for population pharmacokinetic analyses.

Median T_{max} was approximately two hours after oral administration. Food increased BOC exposure by 40-60% when dosed at 800mg TID, the dose shown to have

pharmacodynamic activity. Steady state AUC, C_{max} and C_{min} increased at a less-than-dose proportional manner especially at doses >800mg TID.

The two diastereomers SCH 534128 (active) and SCH 534129 (inactive) exist in plasma in a ratio of approximately 2:1. BOC undergoes extensive metabolism, through the aldoketoreductase pathway and to a lesser extent by CYP3A4/5 metabolism. In pooled studies the mean steady state half life was 3.4 hrs. Mean total body clearance was ~ 16 L/hr. In a study with [^{14}C]BOC 9.3% and 78.9% of the dose were excreted in urine and faeces, respectively.

PK profile was similar in healthy and HCV infected subjects. In subjects with end stage renal disease exposure was comparable to healthy subjects. In subjects with impaired hepatic function there was a trend to increased BOC exposure with increasing severity of liver impairment. Mean increase in AUC was 49% in subjects with severe hepatic impairment.

Drug-drug interactions assessed *in vivo* in clinical studies concluded that BOC and PEG co administered was no associated with clinically relevant changes in BOC exposure (P03527). Co administration of diflunisal or ibuprofen did not increase exposure to BOC (P03533). This finding was likely the consequence of a lack of saturation of the ubiquitous presence of AKR isoforms in multiple tissues. While co administration with ketoconazole increased exposure of BOC (2.3 fold), co administration of BOC with other strong CYP3A4/5 inhibitors and P-gp inhibitors (RTV and clarithromycin) did not notably change the exposure of BOC (PO4624 and PO5880). BOC is a strong, reversible inhibitor of CYP3A4/5 as exemplified by the drug-drug interaction study with midazolam (P05880). For drugs metabolised primarily by CYP3A4/5 especially those with a narrow therapeutic window (for example, ergot alkaloid, terfenadine) co administration with BOC is contraindicated.

Pharmacodynamics

Two Phase IIb studies, P03659 and P03523 were the key studies of dose-response of BOC in combination with PEG2b +/- ribavirin in HCV genotype 1 patients. Protocol P03659 was a Phase II, dose-finding study and was conducted in subjects with CHC genotype 1 who had failed previous PR treatment. This study was amended early after DSMB review, because two factors became clear. First, that the lower (100mg and 200mg TID) doses of BOC were inferior to the higher doses in terms of HCV response. Second, PR was an essential component. Moreover, higher doses of BOC were safe and the triple therapy was well tolerated. In the second Phase II study (P03523), conducted in subjects with treatment naïve CHC genotype 1, BOC/PR triple therapy yielded significant increase in SVR and lower relapse rates versus the PR control arm. For the Phase III program, the triple combination chosen consisted of BOC 800 mg TID with PR and PEG; in the naive setting a 4 week lead in with PR was used prior to triple therapy.

Clinical Efficacy

Two pivotal Phase III studies, one in pretreated patients (P05101/RESPOND 2) and one in treatment naïve patients (P05216/SPRINT 2), have been completed.

P05101 (RESPOND 2) is a Phase III, randomised, multi centre, double blind study conducted in patients with CHC genotype 1 who previously demonstrated PEG responsiveness but failed to achieve SVR on prior treatment with PR.

Treatment arms were as described in Table 20. A 12 week futility rule was used for all arms, whereby therapy was discontinued for all subjects with detectable HCV-RNA at TW12.

Table 20: Treatment arms in Study P05101 (RESPOND 2).

Arm 1 (PR Control)	PEG2b 1.5 µg/kg QW+ PR 600 to 1400 mg/day (WBD) for 4 weeks followed by placebo + PEG2b 1.5 µg/kg + PR (WBD) for 44 weeks, with 24 weeks post-treatment follow-up.
Arm 2 (Response-guided therapy)	PEG2b 1.5 µg/kg QW+ PR (WBD) for 4 weeks followed by BOC 800mg TID + PR for 32 weeks in either a 36-week (a, below) or 48-week (b, below) course of therapy based on HCV-RNA status at TW8. a. 36 week regimen in subjects with undetectable HCV-RNA at TW8. 36 weeks post-treatment follow-up. b. 48 week regimen in subjects with detectable HCV-RNA at TW8. Subjects were assigned to additional 12 weeks of placebo + PEG2b/PR followed by 24 weeks post-treatment follow-up.
Arm 3 BOC/PR48	PEG2b 1.5 µg/kg + PR (WBD) for 4 weeks followed by BOC 800mg TID +PR for 44 weeks, with 24 weeks post-treatment follow-up.

A total of 404 subjects were randomised and 403 received one or more doses of study therapy, of whom 80, 162 and 162 were in Arm 1, Arm 2 and Arm 3, respectively. Numbers analysed in the mITT cohort totalled 394 subjects, of whom 78, 156 and 160 were in Arm 1, Arm 2 and Arm 3 respectively.

- Arm 1**:** 29% completed treatment; 71% discontinued; 61% of discontinuations due to treatment failure;
- Arm 2: 64% completed treatment; 36% discontinued; 56/58 discontinuations occurred before Week 36, of these, 60%, 21% 17% were due to treatment failure, AEs and for non-medical reasons respectively;
- Arm 3: 65% completed treatment; 35% discontinued; 52%, 36%, 13% were due to treatment failure, AEs and non medical reasons respectively.

Baseline demographics and disease characteristics overall are as follows. 67% (269/404) male; 88% (355/404) were non Black; mean age was 52.7 years (range, 26-74 years); mean weight 85 kg. All subjects had genotype 1 (47% [189/403] subtype 1a, 44% [178/403] subtype 1b by TRUGENE™ assay); 88% (353/403) had high viral load (>800,000 IU/mL), mean $\log_{10}$ baseline HCV viral load of 6.63. Demographic and disease characteristics were reasonably balanced between treatment groups. An inclusion criteria was Previous PEG/PR responder, defined as decrease in HCV-RNA $\geq$ 2 $\log_{10}$ by Week 12 or undetectable HCV-RNA at EOT who did not achieve SVR on PR.

The primary efficacy analysis was SVR (defined as undetectable plasma HCV-RNA) rates at follow up Week 24 in the full analysis set (randomised subjects who received at least one dose of study medication). SVR rates were based on LOCF approach. The key secondary endpoint was SVR rates at follow up Week 24 in mITT data set.

SVR rates in subjects who received BOC were 66.5% and 58.67% in the RGT and BOC/PR48 arms, respectively, versus 21.3% in the control arm; the 95% CI for the delta SVR was 25.7, 49.1 ($p<0.0001$) and 33.7, 56.8 ($p<0.0001$) respectively versus control .

SVR rates in mITT analysis in subjects who received BOC were 61% and 67% in the RGT and BOC/PR48 arms, respectively, versus 22% in the control arm; the 95% CI for the delta SVR was 27.2, 51.0 ($p<0.0001$) and 33.4, 56.8 ($p<0.0001$) respectively versus control

The SCV rates in BOC/PR48 arm versus RGT arm were not statistically different.

SVR response based on TW4 (lead-in response) < 1.0 $\log_{10}$ decrease in HCV-RNA (that is, poorly IFN responsive) was 32-34% in those receiving triple therapy versus 0% in control

arm. In subjects with detectable HCV-RNA in TW8 results SCV rates were 40% and 43% for RGT and BOC/PR48, respectively.

Relapse rates were 15% and 12% in the RGT and BOC/PR48 arms, respectively, versus 32% in the control arm in mITT analysis.

In early responders, that is, those with undetectable HCV-RNA by TW8, relapse rates remained low (approximately 12%) after 36 weeks of BOC/PR therapy (lead in of PR followed by 32 weeks of triple therapy).

Viral breakthrough occurred in 1% (2/162) of RGT subjects and 2% (3/161) of BOC/PR48 subjects versus none in control arm; and incomplete virological response occurred in 1% (1/80) of control arm subjects, 4% (7/162) of RGT subjects and 3% (4/161) of BOC/PR48 subjects.

P05216 (SPRINT 2) is a Phase III, randomised, multi centre, double blind study conducted in CHC genotype 1 treatment naïve patients.

- Arm 1 received PR (PEG2b 1.5 µg/kg QW (once weekly) plus PR 600 to 1400 mg/day [weight based dosing; WBD]) for 48 weeks with 24 weeks post treatment follow up.
- Arm 2 (Response Guided Therapy) received a 4 week PR lead in followed by BOC/PR for 24 weeks; those with undetectable HCV-RNA at TW8 through TW 24 completed therapy at TW 28 and entered follow up. Those with detectable HCV-RNA at TW8 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 treatment duration of 48 weeks.
- Arm 3 (BOC/PR48) received a 4 week PR lead in followed by 44 weeks of BOC/PR. The BOC dose was 800 mg TID. A 24 week futility rule was followed for all arms, whereby therapy was discontinued for subjects with detectable HCV-RNA at TW 24.

A total of 1099 subjects were randomised and 1097 received one or more doses of study therapy, of whom 363, 368 and 366 were in Arm 1, Arm 2 and Arm 3, respectively. Numbers analysed in the mITT cohort totalled 1044 subjects, of whom 344, 350 and 354 were in Arm 1, Arm 2 and Arm 3 respectively.

- Arm 1**:** 48% completed treatment;
- Arm 2: 65% completed treatment;
- Arm 3: 61% completed treatment.

The study included two separate cohorts (Cohort 1 [White subjects] and Cohort 2 [Black subjects]), with 52, 52, and 55 subjects in Cohort 2 for Arms 1, 2 and 3, respectively. For treatment groups, combined characteristics were:

- *Cohort 1*: 95% White; 5% other ethnicities (non Black); median age 50 years; 60% male; 47% HCV genotype 1a;
- *Cohort 2*: 100% Black; median age 52 years; 61% male; 64% HCV genotype 1a.

The primary endpoint is SVR, defined as undetectable HCV-RNA, at follow up Week 24. The primary efficacy endpoint was analysed in the Full Analysis Set (FAS), which included all randomised subjects who received at least one dose of any study medication. The key secondary endpoint was SVR at follow up week 24 in the mITT data set.

SVR rates in subjects who received triple therapy were 63% and 66% in RGT and BOC/PR48 arms, respectively, versus 38% in the control arm; the 95% CI for the delta SVR was 18.6, 32.6 ($p<0.0001$) and 21.4, 35.3 ($p<0.0001$) respectively versus control.

SVR rates were 67% and 68% (for each BOC containing Arm) in White subjects (Cohort 1) receiving triple therapy versus 40% in controls; SVR rates were 42% and 53% for each BOC containing Arm in Black subjects (Cohort 2) versus 23% in controls.

In the mITT analysis, SVR rates were 67% and 68% in RGT and BOC/PR48 arms, respectively, versus 40% in the control arm; the 95% CI for the delta SVR was 19.6, 33.9 ($p<0.0001$) and 21.4, 35.6 ($p<0.0001$), respectively, versus control.

High SVR rates were primarily driven by higher End-of-Treatment (EOT) responses, that is, 71% and 76% in RGT and BOC/PR48 arms, respectively, versus 53% in control. Relapse rates were lower in the BOC-containing arms (9% versus 22%), and in subjects who completed assigned treatment duration (28 or 48 weeks) (5% versus 21%).

SVR response based on TW4 (lead in response) < 1.0 $\log_{10}$ decrease in HCV-RNA (that is, poorly IFN responsive) was 28% and 38% in RGT and BOC/PR48 arms, respectively, versus 4%.

In early responders, that is, those with undetectable HCV-RNA by TW8, relapse rates remained low (approximately 12%) after 28 weeks of BOC/PR therapy (lead in of PR followed by 24 weeks of triple therapy).

Analyses comparing matching subgroups in RGT and BOC/PR48 arms also showed similar SVR rates in both BOC arms in the early and later responders whether using either the per protocol (TW8 through TW24) or response only at TW8 analysis.

Viral breakthrough events occurred in 4% of RGT subjects and 2% of BOC/PR48 subjects and 2% in control arm; and incomplete virological response occurred in 6% of control arm subjects, 7% of RGT subjects, and 7% of BOC/PR48 subjects.

In a regression model of predictors of SVR, a number of baseline factors predicted poorer SVR in the BOC-RGT and BOC-PR48 containing arms versus PR. These were baseline HCV-RNA >400,000 IU/mL (62 and 65% versus 34%); F3/4 liver fibrosis score (41 and 52% versus 38%); genotype 1a (59 and 62% versus 34%); genotype 1b (71 and 73% versus 40%) as well as older age (>40 years of age) and higher BMI. Black race was a predictor of lower SVR, although when TW4 response was included this was negated.

A pooled resistance analyses using samples from PO5101 and PO5216 reported that for non SVR BOC treated subjects 155/295 had post baseline resistance associated variations reported. RAV were reported in 75% of subjects with virological breakthrough and 93% of subjects with incomplete virological response. The most common RAVs were R155K, V36M, T54S and T54A.

In a pooled pharmacogenomic analysis from PO5101 and PO5216, 62% and 66% of patient samples were genotyped for IL28B. The IL28B genome was a predictor of response to triple therapy. SVR rates were 7-26% higher for IL28B CC genotype versus CT or TT.

Clinical Safety

During the course of clinical development of BOC, approximately 2827 subjects have been exposed to any dose of BOC in 28 clinical trials. Most (~2171/2827, 77%) of the subjects received BOC 800 mg TID, the proposed dose of BOC for therapeutic use. In the Phase II/III studies, demographic and baseline disease characteristics were representative of subjects with CHC genotype 1, that is, 2/3 were male and >80% self reported their race as White. The Phase II/III studies included 48 older subjects (≥ 65 years) and 123 subjects with cirrhosis.

In Phase I studies, no SAE were considered possibly related to BOC. A dose dependent increase in dysgeusia was seen. Decreases in haemoglobin and neutrophils were seen when BOC was co administered with PEG in CHC subjects.

An integrated safety assessment has been undertaken for the Phase II/III randomised blinded studies PO3523, PO5216 and PO5101 with 800 mg TID BOC dose. A total of 547 subjects were in the PR arms with median treatment duration of 198 days and 1548 subjects were in the BOC/PR arms with median treatment duration of 201 days. SAEs were reported in 8% of subjects in the PR control arms and 11% of subjects in the BOC/PR arms. Death was reported in 4/547 (1%) subjects in the PR arm and in 4/1548 (<1%) in BOC/PR arms. Three deaths due to completed suicide were reported, 1/547 in the PR arm and 2/1548 in the BOC/PR arm.

In the treatment experienced study (PO5101), drug discontinuation due to AE was reported in 3% in the PR arm and 10% of the BOC/PR arm. In treatment naive studies, drug discontinuation due to AE was reported in 14% in both arms. Dose modification due to AE was more frequent in BOC/PR arm than the? PR arm in both the treatment experienced study (31% versus 14%) and the pooled naïve studies (41% versus 26%).

Addition of BOC to PR is associated with an increase in the frequency of anaemia (49% versus 29% control in the pooled Phase II/III analysis) and additional decrease in serum haemoglobin versus PR alone. Both neutrophil (PMN) and platelet counts are also further decreased when BOC is added to PR. Anaemia during BOC/PR therapy was managed by PR dose reduction and/or EPO use. With the addition of BOC at TW4 after PR lead in, Hb concentrations continued to decline up to TW6 to TW8. In these studies, the change in Hb over time beyond TW8 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. Overall, around 25% of anaemia subjects required dose modification. In Study P05101, fewer subjects in the RGT arm required transfusions compared with the BOC/PR48 arm. In PO5216**,** subjects in the RGT arms were administered less EPO than those in the BOC/PR48 arms; mean exposure was 94 and 156 days, respectively. In P05101**,** the mean exposure to EPO was longer at 135 and 130 days, for the RGT and BOC/PR48 arms, respectively. Medically important AEs potentially attributable to the use of EPO, 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).

Neutropenia is a side effect of PEG and subjects receiving BOC/PR had a higher frequency of neutropenia (18% of all subjects PR arm and 23% of subjects in the BOC/PR arms of the Phase II/III pooled analysis). Subjects receiving BOC/PR were more likely to experience WHO Grade 3 and 4 neutropenia compared with those receiving PR SOC. Forty two subjects reported infections temporally related to neutropenia in the key studies. Of these, 34 subjects were in the BOC/PR arm; of these, three subjects experienced severe infections (epiglottitis, upper respiratory infection, salmonella gastroenteritis/diarrhoea) that occurred within two weeks of the Grades 3/4 neutropenia.

Dysgeusia was reported with higher frequency in BOC/PR arms than PR arms (43-45% versus 11% control). Severe dysgeusia was reported in 1% of subjects and dose modification in <1% of subjects.

The proportion of subjects reporting psychiatric SAE (2% versus 1% control) and discontinuation due to psychiatric events (3% versus 3% control) was similar in the BOC/PR and PR arms. Overall, the psychiatric AEs in these studies were events previously reported and frequency was similar in the BOC/PR and PR arms.

Clinical Conclusions

The pivotal Phase III studies demonstrate a substantial increase in SVR in both treatment naïve patients and in previous PEG/PR experienced patients. Haematological adverse events, in particular anaemia, are exacerbated in those receiving BOC as part of the triple therapy compared to PR alone. Anaemia was manageable PR dose reduction and/or EPO. A clinical study is ongoing to inform the best strategy for management of anaemia with BOC/PR therapy. The clinical evaluator supported registration of BOC as a component of combination therapy with PEG and PR.

Risk Management Plan

The RMP evaluation has commented that a RMP for boceprevir (BOC; Victrelis) is not complete and a RMP for Victrelis-PEG/PR as a whole should be submitted. The sponsor has enhanced pharmacovigilance and additional risk minimisation activities around the important identified risk 'anaemia'. The proposed PI and educational materials give guidance on use of EPO as a management option. This represents an off label use as the current Australian PIs for EPO do not include drug induced anaemia as an indication. Neutropenia and thrombocytopenia have been added as important identified risks in the current version RMP and in the product information for boceprevir. The risk minimisation activities undertaken to minimize the risk of these events from will be extended to neutropenia. The RMP evaluation recommends the educational program be extended to include drug-drug interactions.

The RMP evaluation includes numbers of recommendations for product information amendment and an amendment to consumer medicines information.

Risk-Benefit Analysis

Delegate Considerations

The Delegate concurred with the conclusion in the clinical evaluator that pivotal studies PO5101 and PO5216 provide convincing data that the use of BOC with PEG and PR substantially increases SVR in the study populations.

Haematological adverse events, in particular anaemia, are exacerbated in those receiving BOC with PEG and PR. Anaemia appeared to be manageable in the clinical studies using an algorithm involving PR dose-reduction and/or use of EPO. The clinical evaluator also noted that a randomised clinical study is ongoing to compare management of BOC with PEG and PR by either PR reduction or EPO introduction.

The sponsor in Australia has a current application for PEG alfa-2b and PR which provides for PR weight based dose amendments and increased steps in management of dose reduction of PR and PEG-2b because of haematological adverse reactions. PR oral solution is not registered in Australia for dosage adjustments less than 200 mg.

The study population in PO5051 was patients with CHC genotype 1 who previously demonstrated PEG responsiveness but failed to achieve SVR on prior treatment with PEG with PR. There is currently no clinical study assessment of BOC with PEG and PR in patients documented to be historical null responders (less than a 2-$\log_{10}$ HCV-RNA decline by TW12) during prior therapy with PEG and PR. A statement relevant to null responders should be added to the PI.

In treatment experienced early responders in PO5101 that were randomised to the RGT arm and thus received 4 weeks of lead in followed by 32 weeks of triple therapy, SVR rates were lower (79% versus 73%) than in corresponding patients randomised to 44 weeks of triple therapy. This reflects an uncertainty whether the 36 and a 48 week total duration of therapy in treatment experienced patients can be regarded as equivalent in efficacy.

In regards to IL28b, this genotype has recently been shown to be important in predicting response to PEG with PR. A retrospective analysis was conducted based on PO5216 and PO5101 patient samples. The influence of IL28b on response to BOC with PEG and PR was not as profound as for PEG/PR. A prospective study is appropriate to allow conclusions on influence of IL28b on response to BOC with PEG and PR.

The Delegate agreed with the clinical evaluator that the benefit risk balance for triple therapy which includes BOC is favourable and the Delegate proposed to support registration of BOC for indications proposed by the sponsor. Clinical data are considered adequate to support registration despite the conclusion of insufficient definition of potential toxicity in the nonclinical evaluation.

The Delegate also supported the comments on the draft PI that were provided in the various evaluation reports.

Delegate's Proposed Action

The Delegate proposed to register boceprevir (Victrelis) 200mg capsules. Boceprevir is indicated for the treatment of Chronic Hepatitis C (CHC) genotype 1 infection, in a combination regimen with peginterferon alfa and ribavirin, in adult patients (18 years and older) with compensated liver disease who are previously untreated or who have failed previous therapy. The recommended dose is 800 mg administered three times daily with food.

The advice of ACPM is requested.

The ACPM consideration and comment is requested specifically on the following aspects:

- The weight of clinical support for registration balanced against a conclusion of insufficient definition of potential toxicity in the nonclinical evaluation.
- Whether the sponsor's algorithm involving RBV dose reduction and/or use of erythropoietin is anticipated to achieve comparable results in Australia clinical practice compared to clinical studies.
- The lack of data on historical null responders (less than a 2-$\log_{10}$ HCV-RNA decline by treatment week 12) during prior therapy with PEG and RBV and appropriate statements in product information.
- In treatment experienced early responders whether the 36 and a 48 week total duration of therapy in treatment experienced patients can be regarded providing equivalent efficacy.

Response from Sponsor

The sponsor agrees with the Delegate's proposed action to recommend the approval of Victrelis (boceprevir) for the following indication:

> *Victrelis is indicated for the treatment of Chronic Hepatitis C (CHC) genotype 1 infection, in a combination regimen with peginterferon alfa and ribavirin, in adult patients (18 years and older) with compensated liver disease who are previously untreated or who have failed previous therapy.*

The Delegate has agreed with the clinical evaluator that treatment with Victrelis in combination with peginterferon alfa and ribavirin (PR) increases SVR rates in the study population and the main safety concerns are manageable. However, the Delegate has suggested whether certain limitations with the nonclinical safety/toxicity evaluation of Victrelis with regard to drug exposure data and potential toxicity are acceptable when balanced against the clinical data. The sponsor has responded to questions raised in the

evaluation and contends that the nonclinical program was sufficient to support the progression of the clinical studies, which the nonclinical evaluator has acknowledged in the evaluation report. The proposed limitations of the nonclinical data must be considered in the context of the overall experience of the compound during clinical development for the treatment of chronic HCV and whether safety findings during human exposure warrant any further consideration of the antecedent preclinical studies.

The high rates of SVR in both treatment naïve patients and those patients who have failed prior PR treatment, including sub groups who are usually poor responders, were clinically and statistically significant and there were no sub-groups of patients for whom PR was more efficacious than therapy that included Victrelis. Data from an ongoing long term follow up study indicate that virologic responses obtained with Victrelis are durable.

The safety profile of Victrelis is characterised in more than 2000 subjects, including over 1500 patients who received Victrelis at the proposed clinical dose in combination with PR in the pivotal studies. Administration for up to 44 weeks was generally well tolerated, and side effects were primarily those previously described in patients treated with PR alone. The most common adverse events observed were flu like symptoms typically reported with PR therapy. The safety evaluation has demonstrated that anemia is a principal risk associated with Victrelis treatment and occurs more frequently in subjects receiving Victrelis in combination PR compared with PR alone. Anemia has long been recognized as a complication of treatment of HCV patients with interferon and ribavirin and can be managed with the use of ribavirin dose reduction. Based on these options, discontinuation of therapy due to anaemia associated with Victrelis should be infrequent. Neutropenia, and to a lesser extent thrombocytopenia, have also been reported more frequently with Victrelis therapy, but do not commonly require intervention. The dysgeusia that occurs with Victrelis is not a severe or treatment limiting side effect.

The clinical studies have demonstrated that the benefit/risk for Victrelis in combination with PR is positive and the safety profile is in line with the current stand of care. The increased numbers of patients experiencing anaemia are manageable, as confirmed by the Delegate. Thus the safety has been demonstrated up to the maximum treatment period of 44 weeks, although shorter treatment duration is preferred where possible. This weight of clinical evidence should be considered to be of greater value in evaluating the benefit/risk of a treatment in HCV than what can be gathered from the nonclinical program.

The Delegate has raised a concern over the potential impact of EPO use as an anaemia management strategy with Victrelis + PR therapy compared with ribavirin dose reduction, which is the current practice in Australia. Clinical studies of Victrelis incorporated guidelines for use of EPO. Given this concern, the issue to be addressed is to what extent the anaemia associated with Victrelis + PR therapy can be managed without resorting to the use of EPO and whether this had an impact on the SVR rates achieved in the pivotal clinical trials.

EPO treatment was permitted in the Phase III studies based not only on its accepted role in the management of anaemia during treatment of HCV and the increased rates of anaemia observed with the addition of the first generation HCV protease inhibitors but also because data from earlier clinical studies (for example, SPRINT-1), suggested that subjects treated with Victrelis + PR who developed anaemia and received EPO achieved a substantial increase in SVR. Anaemia management decisions in the clinical trials, including whether to use EPO, were left to the discretion of the investigators and were the same for anaemia associated with either Victrelis and PR therapy or PR therapy alone.

To understand whether the different anaemia management strategies affected SVR rates, an exploratory analysis was conducted on data from the pivotal studies. Across all Victrelis

and PR control arms in both treatment-naïve and previous treatment-failure study populations, anaemia was consistently associated with higher rates of SVR. For the Response Guided Therapy (RGT), Victrelis/PR 48 week and PR control arms in SPRINT-2, rates of SVR were 69%, 76%, and 56% among patients whose nadir hemoglobin level was <10 g/dL during the treatment period, compared with 60%, 56%, and 31% among patients whose haemoglobin level was 10 g/dL or greater. For the corresponding arms in RESPOND-2, rates of SVR were 76%, 76%, and 25%, compared with 57%, 43%, and 20%, respectively.

Among patients in these studies whose nadir haemoglobin value was <10 g/dL, anaemia was managed by ribavirin dose reduction alone in 7% of patients in a Victrelis-containing treatment arm and 10% of patients in a PR control arm, respectively; EPO alone was used in 33% and 37% of Victrelis + PR and PR subjects, and both ribavirin dose reduction and EPO use was used in 46% and 32% of subjects patients, respectively.

In SPRINT-2, among Victrelis + PR treated subjects (pooled for the RGT and Victrelis + PR 48 week treatment arms) whose nadir haemoglobin level was <10 g/dL, rates of SVR were 78%, 74%, 71% for ribavirin dose reduction alone, EPO alone, or ribavirin dose reduction and EPO, respectively. In RESPOND-2, the corresponding rates of SVR were 83%, 80%, and 72%, respectively, for these respective categories.

It is important to acknowledge that the efficacy results with and without EPO can only be reliably interpreted in the context of randomisation according to EPO use or not. The sponsor was, t the time of this AusPAR, performing PN06086, a Phase III trial to compare EPO use versus ribavirin dose reduction in treatment-naïve GT1 infected subjects with serum haemoglobin nadirs of ≤10 g/dL during therapy with Victrelis + PR. The primary objective is to compare SVR between the two groups.

However, the sponsor recommended ribavirin dose reduction as the management strategy for anaemia associated with Victrelis + PR therapy, as the available data suggest that this will not compromise treatment results. The current Product Information for Victrelis is consistent with this position, as it refers to the Pegatron Product Insert for dose-reduction guidelines. These guidelines remain the same for subjects who are treated with either PR or Victrelis + PR, and should be appropriate for clinical practice in Australia. The sponsor proposed to maintain a statement in the "Clinical Trials" section to adequately inform doctors about the use of EPO in the clinical studies.

The sponsor acknowledged the Delegate's comments about the lack of data on historically defined null responders in the Phase III study of treatment experienced subjects (RESPOND-2) and proposed the following statement for the Victrelis Product Information for patients with prior null response:

> *"Response-Guided Therapy was not studied in patients who had less than a 2-log_{10} HCVRNA decline by treatment week 12 during prior therapy with peginterferon alpha and ribavirin (null responders). If considered for treatment, these subjects should receive 4 weeks of peginterferon alpha and ribavirin followed by 44 weeks of Victrelis 800 mg orally three times daily in combination with peginterferon alpha and ribavirin. Discontinuation of therapy is recommended in patients with prior null response with detectable HCV-RNA at TW12".*

Null responders had not been included in the RESPOND-2 study based on an agreement between the sponsor and the FDA to first see results from Phase III trials evaluating patients who had relapsed or who were partial responders. A Phase II trial had enrolled previous treatment failure subjects, including null responders and partial responders, and established that these subjects could be treated. However, changes to the design of that study, including the dose, precluded a formal assessment of efficacy in the null population.

The sponsor's rationale for the proposed statement in the Product Information for treatment of historical null responders is based on several considerations as follows:

1. A correlation between IFN responsiveness and the historical definition of "null response" is established on the basis of the IDEAL study, which enrolled 3070 treatment naïve patients with chronic HCV GT 1 infection, randomised to one of three arms: peginterferon alfa-2b 1.5 µg/kg/wk or peginterferon alfa-2b 1.0 µg/kg/wk, both with weight-based dosing of ribavirin, or peginterferon alfa-2a 180 µg/wk plus ribavirin. A total of 2098 patients had ≥2.0-$\log_{10}$ decline in HCV-RNA from baseline or undetectable HCV-RNA at TW12, and 679 patients had detectable HCV-RNA with <2.0-$\log_{10}$ decline from baseline at TW12. The overall concordance of a <1.0-log10 decline in HCV-RNA at TW4 with a <2.0-$\log_{10}$ decline in HCV-RNA at TW12 was 89%. Only 4% of patients who had a <1.0-$\log_{10}$ decline in HCV-RNA at TW4 were able to achieve SVR. The conclusion is that virologic response at either timepoint (Week 4 or 12) predicts which subjects are unlikely to achieve SVR, and that a <1 $\log_{10}$ HCV RNA TW4 response to PR therapy is an excellent indicator of poor interferon (IFN) responsiveness in this context, and a useful alternative to the conventional definition of null response to prior PR therapy (defined as < 2 $\log_{10}$ HCV RNA decline at TW12).

2. Post hoc analyses of the Phase III studies were performed to evaluate the correlation between virologic response at TW4 and TW12 as established by the IDEAL study. For SPRINT-2, 20% of patients in the PR control arm met the TW12 definition of "null response". The concordance between a <1.0-log10 decline in HCV-RNA at TW4 and a <2.0-$\log_{10}$ decline in HCV-RNA at TW12 in the PR control was high (89%). For RESPOND-2 a very similar correlation was observed: 19% in the PR control arm met the TW12 definition of "null response", and the concordance between a <1.0-$\log_{10}$ decline in HCV-RNA at TW4 and a <2.0-$\log_{10}$ decline in HCV-RNA at TW12 in the PR control was very high (91%). Because of randomisation, it is likely that a similar distribution of subjects was present in the PR control arms and the arms treated with Victrelis. Overall this analysis also supports the conclusion that poor interferon responsiveness as defined at TW4 is a valid alternative to the definition of TW12 null response.

3. The inclusion of a four week PR lead in period in the Phase III studies allowed a real-time assessment of interferon responsiveness, and thus application of the TW4 and TW12 correlation to assess efficacy of Victrelis in poor interferon responders. A poor response to PR at 4 weeks (< 1 $\log_{10}$ HCV RNA decline) as observed during lead-in is a surrogate for null response. Approximately 25% of patients in the Phase III studies were poorly interferon responsive (<1-$\log_{10}$ decline in HCV-RNA at TW4). SVR rates in SPRINT-2 for such subjects receiving Victrelis + PR were substantially increased (28% for RGT, 38% for Victrelis + PR for 48 weeks) compared to PR treatment alone (4%). SVR rates in RESPOND-2 for such subjects receiving Victrelis + PR were also substantially increased (33% for RGT; 34% for Victrelis + PR for 48 weeks), compared to 0% for PR. The differences for Victrelis remained consistent across a range of interferon responsiveness, including very poorly responsive subjects likely to be true null responders. Using a lower cut-off at TW4 (≤ 0.5 $\log_{10}$ decline in HCV RNA) revealed that 88% of such subjects were also null responders to PR (< 2 $\log_{10}$ decline at TW12) and the SVR was 0%, whereas for Victrelis, SVR was 30% for RGT, and 28% for Victrelis/PR48. These results emphasise the value of the on treatment response to PR at TW4, compared to prior treatment history, in predicting response to therapy.

4. Finally, results from the PROVIDE "roll over" study allow direct assessment of the efficacy of Victrelis + PR in historically defined null responders. Patients in the PR control arms of SPRINT-2 and RESPOND-2 who met futility rules for stopping therapy were eligible to receive treatment with Victrelis + PR in the PROVIDE study. Forty-eight such

prior null responders enrolled in the PROVIDE study. A total of 45/48 subjects initiated Victrelis treatment, 42 completed follow up, two are still on treatment and one is in early follow up. Following a null response to prior PR therapy, 38% achieved SVR with Victrelis + PR. Furthermore, the magnitude of HCV RNA decline after 4 weeks of PR lead-in was positively related to SVR (50% SVR rate in those with a >1 log_{10} HCV RNA decline, and 34% SVR rate in those with a <1 log_{10} decline). These results are highly consistent with the results observed for poorly interferon-responsive subjects in the Phase III studies, where SVR rates of approximately 35% were achieved when those patients were treated with Victrelis + PR.

In summary, data across three large studies (IDEAL, SPRINT-2, RESPOND-2), demonstrate a strong and consistent correlation between poor interferon responsiveness at TW4 and "null response" at TW12. In the Phase III studies and the PROVIDE study, Victrelis + PR yielded substantial improvements in SVR compared to PR alone in poorly-interferon responsive patients. The optimal duration of therapy in this group is not known; however, it is prudent to adhere to a regimen of 48 weeks in subjects who are responding to therapy.

The sponsor acknowledges the Delegate's observation regarding a difference in SVR rates among early responders in the treatment-experienced Phase III study RESPOND-2. Additional analyses have been conducted to understand the basis for the difference and the data used to propose an acceptable dosing recommendation for treatment-experienced subjects.

RESPOND-2 enrolled chronic HCV GT1 subjects who were non-responders, generally classified as previous partial responders (≥ 2 log10 decline in viral RNA at Week 12 but never achieving undetectable HCV RNA); and subjects who had relapsed (undetectable HCV RNA at the end of therapy but detectable HCV RNA during follow up). As noted earlier, prior null responders (< 2 log10 decline in HCV RNA at TW12 of prior therapy) were excluded from the trial. Subjects were randomised to one of 3 treatment arms:

- Arm 1: pegylated interferon alfa-2b (PegIntron®) plus ribavirin (Rebetol®) alone (PR48)
- Arm 2: Victrelis plus PR response-guided therapy (RGT)
- Arm 3: Victrelis plus PR for 48 weeks

All subjects received a four week lead in treatment phase with PR alone. In the RGT arm, subjects with an undetectable HCV RNA at Week 8 completed all therapy at Week 36 (early responders); while those with detectable HCV RNA at Week 8 but undetectable HCV RNA at TW12 (late responders) received triple therapy through TW 36 followed by an additional 12 weeks of PR alone (total of 48 weeks therapy). In all treatment arms, subjects with detectable HCV RNA at Week 12 discontinued all therapy for treatment futility and were considered treatment failures.

The sponsor's analysis of the primary efficacy endpoint, SVR, defined as HCV RNA of < 25 IU/mL at Week 24 after the end of treatment, revealed that SVR was higher and relapse rates were lower in both Victrelis arms than in the PR control arm in this treatment experienced population. However, as the Delegate has noted, the SVR was numerically (7%) higher in Arm 3 than in the RGT arm in this population, even though this difference was not statistically significant in a post hoc comparison. Additional analyses suggested that the difference is largely related to a difference in SVR among patients with cirrhosis in the two subgroups, as explained below.

The majority of the patients in the study, approximately 85 percent, did not have cirrhosis, and the SVR rates for such subjects were also analysed separately. SVR rates are nearly identical for subjects in the Victrelis + PR response-guided therapy arm and the Victrelis + PR 48-week arm (64% and 66%, respectively), and are substantially higher than the 24% observed in the PR control arm. For the approximately 15 percent of patients with cirrhosis, the SVR rate for the Victrelis + PR 48-week arm was higher than that for the Victrelis + PR RGT arm (77% versus 35%, respectively), and both were substantially higher than the 0% SVR rate in the PR control arm.

Analysis was further conducted on the approximately 85% of patients without cirrhosis, to better compare SVR rates in the Victrelis + PR RGT and Victrelis + PR 48 week groups. Comparison on the basis of historic response to PR revealed similar rates: 47% and 51% for the Victrelis + PR RGT subjects and Victrelis + PR 48 weeks subjects, respectively, among prior non responders; and 74% and 75 percent in the Victrelis + PR RGT subjects and Victrelis + PR 48-weeks subjects, respectively, among prior subjects who had relapsed. Both of the Victrelis + PR arms exhibited multiple-fold increases in SVR compared to the PR control arm. Similar response rates for Victrelis + PR RGT and Victrelis + PR 48 weeks were also observed with late responders (80% of subjects in the RGT arm and 73% of patients in the Victrelis + PR 48 weeks). When subjects with no cirrhosis are considered for the late responder group, the response rates for the two Victrelis regimens are again similar (85% and 78% percent for Victrelis + PR RGT and Victrelis + PR 48 weeks, respectively).

Taken together, these data demonstrate that Victrelis + PR response guided therapy and Victrelis + PR 48 week therapy are equally effective in treatment experienced subjects who do not have cirrhosis. The difference in the SVR rates based on cirrhosis remains unexplained. The data nonetheless indicate that Victrelis improves efficacy in these difficult to treat patients. Given the uncertainty regarding equivalence of the two Victrelis regimens in cirrhotic subjects, these patients may require a longer duration of therapy. This recommendation is made in the proposed Product Information as follows:

"Patients with compensated cirrhosis should receive 4 weeks peginterferon alpha and ribavirin followed by 44 weeks Victrelis 800 mg orally three times daily in combination with peginterferon alpha and ribavirin. Discontinuation of therapy is recommended in previously untreated patients with detectable HCV-RNA at TW24 and in patients who failed therapy with detectable HCV-RNA at TW12".

In conclusion, the sponsor agreed with the Delegate's proposed action to recommend the approval of Victrelis (boceprevir) for the indication:

"Victrelis is indicated for the treatment of Chronic Hepatitis C (CHC) genotype 1 infection, in a combination regimen with peginterferon alfa and ribavirin, in adult patients (18 years and older) with compensated liver disease who are previously untreated or who have failed previous therapy".

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

Efficacy

The ACPM agreed with the delegate that while there was limited clinical data to confirm full efficacy, in treatment naive and HCV treatment experienced individuals, the data was reassuring and that longer term data will continue to provide evidence of efficacy. The sponsor's algorithm involving PR dose-reduction and/or use of EPO may achieve

comparable results in Australian clinical practice in the hospital setting compared to clinical studies, but it is unlikely to do so in a community setting. The ACPM expressed concern about the impact of variable access to EPO in all care setting.

Safety

The ACPM agreed with the Delegate that there were no new safety signals identified in the studies; however it was noted that there was insufficient definition of potential toxicity in the nonclinical data.

Indication

The ACPM considered this product to have a positive benefit-risk profile for the indication of:

> *For the treatment of Chronic Hepatitis C (CHC) genotype 1 infection, in a combination regimen with peginterferon alfa and ribavirin, in adult patients (18 years and older) with compensated liver disease who are previously untreated or who have failed previous therapy.*

The recommended dose is 800 mg administered three times daily with food.

PI/ CMI

The ACPM advised that in addition to the changes proposed by the Delegate that Product Information (PI) and Consumer Medicines Information (CMI) amendments should include:

- A statement in the Clinical Trials section citing the data on historical non-responders.
- A statement to the effect that a review of treatment should occur at 12 and 24 weeks to determine efficacy, given the differences in response between the 'rapid', 'early' and 'non-responder' populations.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided for Victrelis capsules, 200 mg, would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Victrelis (boceprevir) 200 mg capsule blister packs indicated for:

> *Victrelis (boceprevir) is indicated for the treatment of Chronic Hepatitis C (HCV) genotype 1 infection, in combination regimen 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 following Specific Conditions apply to this therapeutic good:

> *The implementation in Australia of the Boceprevir Risk Management Plan (RMP), Version 4.4 dated 18 May 2011, and any subsequent revisions, as agreed with the TGA and its Office of Product Review.*

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

Therapeutic Goods Administration

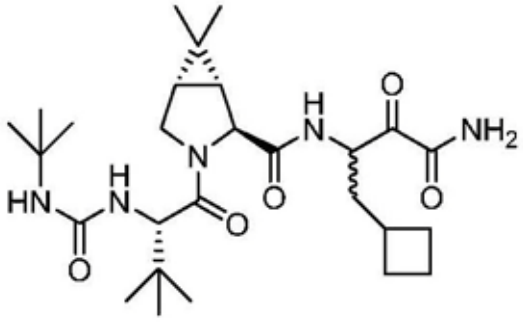
PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au
Reference/Publication #

PRODUCT INFORMATION
VICTRELIS® (Boceprevir) Capsules

NAME OF THE MEDICINE

VICTRELIS

Boceprevir has the following structural formula:



CAS registry number: 394730-60-0

Boceprevir has the following chemical name: (1R,5S)-N-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(S)-[[[(1,1-dimethylethyl)amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2(S)-carboxamide.

The molecular formula is $C_{27}H_{45}N_5O_5$ and its molecular weight is 519.7.

DESCRIPTION

VICTRELIS (boceprevir) is an inhibitor of the Hepatitis C virus (HCV) non-structural protein 3 (NS3) serine protease. Boceprevir is manufactured as an approximately equal mixture of two diastereomers.

Boceprevir is a white to off-white amorphous powder. It is freely soluble in methanol, ethanol and isopropanol and slightly soluble in water with a partition coefficient ($logP_{octanol/water}$) of 3.0.

VICTRELIS 200 mg capsules are available as hard gelatin capsules for oral administration. Each capsule contains 200 mg of boceprevir and the following inactive ingredients: sodium lauryl sulfate, microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, pre-gelatinized starch, and magnesium stearate.

The yellowish-brown opaque cap consists of gelatin, E172 Red Iron Oxide, E172 Yellow Iron Oxide and titanium dioxide. The off-white opaque body contains gelatin, titanium dioxide and E172 Yellow Iron Oxide.

The capsule is printed in red ink (Red SB-1100). The red ink contains Shellac, Ph.Eur., Ethanol anhydrous, Ph.Eur., Isopropyl alcohol

PHARMACOLOGY

Pharmacodynamic Properties

A direct-acting antiviral for treatment of Chronic Hepatitis C.

Mechanism of action

VICTRELIS is an inhibitor of the HCV NS3 protease. VICTRELIS covalently, yet reversibly, binds to the NS3 protease active site serine (Ser139) through a (alpha)-ketoamide functional group to inhibit viral replication in HCV-infected host cells.

Antiviral activity in cell culture

The antiviral activity of boceprevir was evaluated in a biochemical assay for slow binding inhibitors of NS3 protease and in the HCV replicon system. The IC_{50} and IC_{90} values for boceprevir were approximately 200 nM and 400 nM, respectively, in a 72-hour cell culture assay. Loss of replicon RNA appears to be first-order with respect to time of treatment. Treatment at IC_{90} for 72 hours resulted in a 1-log drop in replicon RNA. Prolonged exposure resulted in a 2-log decrease in RNA levels by Day 15.

Evaluation of varying combinations of boceprevir and interferon alfa-2b that produced 90% suppression of replicon RNA showed additivity of effect; no evidence of synergy or antagonism was detected.

Resistance

In Cell Culture

Resistance to boceprevir was characterized in biochemical and HCV genotype 1b replicon assays. The activity of boceprevir against the HCV NS3/4A protease or genotype 1b replicon was reduced (2- to 10- fold) by the following amino acid substitutions in the NS3 protease domain: V36A/I/M, Q41R, F43C/S, T54A/S, V55A/I, R155K/M/Q, V158I, V170A/T and M175L. A greater than 15-fold reduction in boceprevir anti-HCV activity was conferred by the substitutions T54C, R155G/I/T and A156S/T/V. The fold decrease in boceprevir anti-HCV activity conferred by double resistance-associated substitutions was approximately equal to the product of that for the individual substitutions. In cell-based protease assays, an NS3 Q80K substitution did not reduce HCV sensitivity to boceprevir. In addition, the decreased sensitivity to boceprevir observed with R155K was not further decreased when combined with either Q80K or Q80R. A loss of potency (> 50 fold) was observed with resistant-associated amino acid variant: A156T. Of note, replicons carrying the A156T variant are less fit than replicons carrying other RAVs.

In Clinical Studies

An as-treated, pooled genotypic resistance analysis was conducted for subjects who received four weeks of PegIntron/REBETOL followed by VICTRELIS 800 mg three times daily in combination with PegIntron/REBETOL in two Phase 3 studies, SPRINT-2 and RESPOND-2. Among VICTRELIS-treated subjects who did not achieve a sustained virologic response, and for whom samples were analyzed, 53% had one or more specific post-baseline, treatment-emergent NS3 protease domain amino acid substitutions detected by a population-based sequencing assay (Table 1). Nearly all of these substitutions have been shown to reduce boceprevir anti-HCV activity in cell culture or biochemical assays. Among VICTRELIS-treated subjects who did not achieve SVR and for whom post-baseline samples were analyzed, 31% of PegIntron/REBETOL-responsive subjects, as defined by greater than or equal to 1-$\log_{10}$ decline in viral load at Treatment Week 4 (end of 4-week PegIntron/REBETOL lead-in period), had detectable treatment-emergent substitutions, compared to 69% of subjects with less than 1-$\log_{10}$ decline in viral load at Treatment Week 4. Clear patterns of boceprevir treatment-emergent substitutions in the NS3 helicase domain or NS4A coding regions of the HCV genome were not observed.

Table 1 **Pooled Analysis of Treatment-Emergent NS3 Protease Domain Amino Acid Substitutions Detected Among VICTRELIS-Treated Subjects in SPRINT-2 and RESPOND-2 Who Did Not Achieve a Sustained Virologic Response (SVR)**

	Subjects Infected with HCV Genotype 1a	**Subjects Infected with HCV Genotype 1b**
>10% of VICTRELIS treated subjects who did not achieve SVR	V36M, T54S, R155K	T54A, T54S, V55A, A156S, I/V170A
<1% to 10% of VICTRELIS treated subjects who did not achieve SVR	V36A, T54A, V55A, V55I, V107I, R155T, A156S, A156T, V158I, D168N, I/V170T, I/V170F	V36A, V36M, T54C, T54G, V107I, R155K, A156T, A156V, V158I, I/V170T, M175L

Persistence of Resistance-Associated Substitutions

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

Effect of Baseline HCV Polymorphisms on Treatment Response

A pooled analysis was conducted to explore the association between the detection of baseline NS3/4A amino acid polymorphisms and treatment outcome in the two Phase 3 studies, SPRINT-2 and RESPOND-2.

Baseline resistance associated polymorphisms were detected in 7% of subjects by a population-based sequencing method. Overall, the presence of these polymorphisms alone did not impact SVR rates in subjects treated with VICTRELIS. However, among subjects with a relatively poor response to PegIntron/REBETOL during the 4-week lead-in period, the efficacy of VICTRELIS appeared to be reduced for those who had V36M, T54A, T54S, V55A or R155K detected at baseline. Subjects with these baseline polymorphisms and reduced response to PegIntron/REBETOL represented approximately 1% of the total number of subjects treated with VICTRELIS.

Cross-Resistance

Many of the treatment-emergent NS3 amino acid substitutions detected in VICTRELIS-treated subjects who did not achieve SVR in the Phase 3 clinical trials have been demonstrated to reduce the anti-HCV activity of other HCV NS3/4A protease inhibitors. The impact of prior exposure to VICTRELIS or treatment failure on the efficacy of other HCV NS3/4A protease inhibitors has not been studied. The efficacy of VICTRELIS has not been established for patients with a history of exposure to other NS3/4A protease inhibitors. Cross-resistance is not expected between VICTRELIS and interferons, or VICTRELIS and ribavirin.

Pharmacokinetics

VICTRELIS capsules contain a 1:1 mixture of two diastereomers, SCH534128 and SCH534129. In plasma the diastereomer ratio changes to 2:1, favouring the active diastereomer, SCH534128. Plasma concentrations of boceprevir described below consist of both diastereomers SCH534128 and SCH534129, unless otherwise specified.

Absorption

Boceprevir was absorbed following oral administration with a median T_{max} of 2 hours. Steady state AUC, C_{max} and C_{min} increased in a less-than dose-proportional manner and individual exposures overlapped substantially at 800 mg and 1,200 mg, suggesting diminished absorption at higher doses. Accumulation is minimal and pharmacokinetic steady state is achieved after approximately 1 day of three times daily dosing.

In healthy subjects who received 800 mg three times daily alone, boceprevir medicine exposure was characterized by AUC(τ) of 6,147 ng.hr/ml, C_{max} of 1,913 ng/ml, and C_{min} of 90 ng/ml. Pharmacokinetic results were similar between healthy subjects and HCV-infected subjects. The absolute bioavailability of boceprevir has not been studied.

Effect of Food on Oral Absorption

VICTRELIS should be administered with food. Food enhanced the exposure of boceprevir by up to 60% at the 800 mg three times daily dose when administered with a meal relative to the fasting state. The bioavailability of boceprevir was similar regardless of meal type (e.g., high-fat vs. low-fat) or whether taken 5 minutes prior to eating, during a meal, or immediately following completion of the meal. Therefore, VICTRELIS may be taken without regard to either meal type or timing of the meal.

Distribution

Boceprevir has a mean apparent volume of distribution (Vd/F) of approximately 772 l at steady state. Human plasma protein binding is approximately 75% following a single dose of VICTRELIS 800 mg. Boceprevir is administered as an approximately equal mixture of two diastereomers which rapidly interconvert in plasma. The predominant diastereomer is pharmacologically active and the other diastereomer is inactive.

Metabolism

Studies *in vitro* indicate that boceprevir primarily undergoes metabolism through the aldo-ketoreductase (AKR)-mediated pathway to ketone-reduced metabolites that are inactive against HCV. After a single 800-mg oral dose of ^{14}C-boceprevir, the most abundant circulating metabolites were a diasteriomeric mixture of ketone-reduced metabolites with a mean exposure approximately 4–fold greater than that of boceprevir. Boceprevir also undergoes, to a lesser extent, oxidative metabolism mediated by CYP3A4/5.

Elimination

Boceprevir is eliminated with a mean plasma half-life (t½) of approximately 3.4 hours. The two diastereomers, SCH534128 and SCH534129, had similar mean plasma half-life. Boceprevir has a mean total body clearance (CL/F) of approximately 161 l/hr. Following a single 800 mg oral dose of ^{14}C-boceprevir, approximately 79% and 9% of the dose was excreted in faeces and urine, respectively, with approximately 8% and 3% of the dosed radiocarbon eliminated as boceprevir in faeces and urine. The data indicate that boceprevir is eliminated primarily by the liver.

Special Populations

Hepatic impairment

In a study of patients with varying degrees of stable chronic liver impairment (mild, moderate and severe), no clinically significant differences in pharmacokinetic parameters were found, and no dose adjustment is recommended. VICTRELIS, in combination with peginterferon alpha and ribavirin, is contraindicated in cirrhotic patients with a Child-Pugh score > 6 (class B and C) (see CONTRAINDICATIONS).

Renal impairment

No clinically significant differences in pharmacokinetic parameters were observed between patients with end-stage renal disease (ESRD) and healthy subjects. No dose adjustment is required in these patients and in patients with any degree of renal impairment.

Gender

No gender-related pharmacokinetic differences have been observed in adult patients.

Race

Population pharmacokinetic analysis of VICTRELIS indicated that race had no apparent effect on exposure.

Age

Population pharmacokinetic analysis of VICTRELIS indicated that age had no apparent effect on exposure.

CLINICAL TRIALS

The efficacy of VICTRELIS as a treatment for Chronic Hepatitis C (genotype 1) infection was assessed in approximately 1,500 adult subjects who were previously untreated (SPRINT-2) or who had failed previous therapy (RESPOND-2) in Phase III clinical studies. In both studies, the addition of VICTRELIS to the current standard of care (peginterferon alpha and ribavirin) significantly increased sustained virologic response (SVR) rates compared to the current standard of care alone.

Patients who are previously untreated

SPRINT-2 (P05216) was a randomized, double blinded, placebo-controlled study comparing two therapeutic regimens of VICTRELIS 800 mg orally three times daily in combination with PR [peginterferon alfa-2b 1.5 µg/kg/week subcutaneously and weight-based dosing with ribavirin (600-1,400 mg/day orally divided twice daily)] to PR alone in adult subjects who had Chronic Hepatitis C (HCV genotype 1) infection with detectable levels of HCV-RNA and were not previously treated with interferon alfa therapy. Subjects (N=1099) were randomized in a 1:1:1 ratio in two cohorts (Cohort 1/non-Black and Cohort 2/Black) and stratified by HCV genotype (1a or 1b) and by HCV-RNA viral load (≤ 400,000 IU/ml vs. > 400,000 IU/ml) to one of the following three treatment arms:

- Peginterferon alfa-2b + ribavirin for 48 weeks (PR48).
- Peginterferon alfa-2b + ribavirin for 4 weeks followed by VICTRELIS 800 mg three times daily + peginterferon alfa-2b + ribavirin for 24 weeks. The subjects were then continued on different regimens based on Treatment Week (TW) 8 response-guided therapy (VICTRELIS -RGT). All patients in this treatment arm were limited to 24 weeks of therapy with VICTRELIS.

- Subjects with undetectable HCV-RNA at TW 8 (early responders) and who were also negative through TW 24 discontinued therapy and entered follow-up at the TW 28 visit.
- Subjects with detectable HCV-RNA at TW 8 or any subsequent treatment week but subsequently and negative at TW 24 (late responders) were changed in a blinded fashion to placebo at the TW 28 visit and continued therapy with peginterferon alfa-2b + ribavirin for an additional 20 weeks, for a total treatment duration of 48 weeks.

- Peginterferon alfa-2b + ribavirin for four weeks followed by VICTRELIS 800 mg three times daily + peginterferon alfa-2b + ribavirin for 44 weeks (VICTRELIS -PR48).

Mean age of subjects randomised was 49 years. The racial distribution of subjects was as follows: 82% White, 14% Black, and 4% others. The distribution of subjects by gender was 60% men and 40% women.

All subjects with detectable HCV-RNA in plasma at TW 24 were discontinued from treatment. Sustained Virologic Response (SVR) to treatment was defined as undetectable[1] plasma HCV-RNA at follow-up week 24.

The addition of VICTRELIS to peginterferon alfa-2b and ribavirin significantly increased the SVR rates compared to peginterferon alfa-2b and ribavirin alone in the combined cohort (63% to 66% VICTRELIS -containing arms vs. 38% PR48 control) for randomized subjects who received at least one dose of any study medication (Full-analysis -Set population) and decreased the length of therapy to 28 weeks for early responders (see Table 2). SVR rates for Blacks who received the combination of VICTRELIS with peginterferon alfa-2b and ribavirin were 42% to 53%; these rates are approximately two-fold higher than the SVR rate for the PR48 control (23%) (see Table 2). A secondary analysis of subjects who received at least one dose of VICTRELIS or placebo after the four-week lead-in with peginterferon alfa-2b and ribavirin (Modified-Intent-to-Treat population) demonstrated SVR rates in the combined cohort of 67% to 68% VICTRELIS-containing arms vs. 40% PR48 control.

[1] In clinical trials, HCV-RNA in plasma was measured with a Roche COBAS TaqMan® assay with a limit of detection of 9.3 IU/ml.

Table 2 **Sustained Virologic Response (SVR)[*], End of Treatment (EOT) and Relapse[†] Rates for patients who are previously untreated**

Study Cohorts	VICTRELIS-RGT	VICTRELIS-PR48	PR48
Cohort 1 Plus Cohort 2	n=368	n=366	n=363
SVR[‡] %	63	66	38
EOT(Undetectable HCV-RNA) %	71	76	53
Relapse[†] % (n/N)	9 (24/257)	9 (24/265)	22 (39/176)
Cohort 1 (non-Black)	n=316	n=311	n=311
SVR[‡] %	67	68	40
EOT(Undetectable HCV-RNA) %	74	77	57
Relapse[†] % (n/N)	9 (21/232)	8 (18/230)	23 (37/162)
Cohort 2 (Black)	n=52	n=55	n=52
SVR[‡] %	42	53	23
EOT (Undetectable HCV-RNA) %	50	65	29
Relapse[†] % (n/N)	12 (3/25)	17 (6/35)	14 (2/14)

[*] The Full Analysis Set (FAS) consisted of all randomized subjects who received at least one dose of any study medication (N=1,097) (peginterferon alfa-2b, ribavirin, or VICTRELIS).

[†] 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 End of Follow-up (EOF) data.

[‡] SVR: The last available value in the period at or after Follow-up Week (FW) 24. If there is no such value, the FW 12 value is carried forward. SVR24 rates (SVR with "missing=failure" approach) were nearly identical. Cohort 1: 39% PR48; 66% VICTRELIS -RGT, 68% VICTRELIS -PR48. Cohort 2: 21% PR48, 42% VICTRELIS -RGT, 51% VICTRELIS -PR48. Cohort 1+ Cohort 2: 37% Control; 62% VICTRELIS -RGT, 65% VICTRELIS -PR48.

Interferon-responsiveness (as defined by ≥ 1-$\log_{10}$ decline in viral load at TW 4) was predictive of SVR. VICTRELIS -treated subjects who demonstrated interferon responsiveness by TW 4 achieved SVR rates of 79-81%. In subjects with < 1-$\log_{10}$ decline in viral load at TW 4 (poor interferon-responsiveness), treatment with the combination of VICTRELIS with peginterferon alfa-2b and ribavirin resulted in SVR rates of 28–38%, respectively, compared to 4% in patients treated with standard of care.

Response-guided therapy based on TW 8 response is equally effective as adding VICTRELIS to the 48-week standard of care regimen. Fifty-seven percent (208/368) of subjects in the VICTRELIS -RGT arm had undetectable HCV-RNA at TW 8 (early responders). After accounting for treatment discontinuations, 44% (162/368) of subjects reached TW 24 and were assigned a short (28 weeks) treatment with VICTRELIS in combination with peginterferon alfa-2b and ribavirin in the VICTRELIS -RGT arm. These VICTRELIS -RGT early responders demonstrated similar SVR rates (156/162 or 96%) after 28 weeks of treatment compared with the matched population in the VICTRELIS -PR48 arm (e.g., those subjects in the Victrelis-PR48 arm who also had undetectable HCV-RNA at TW 8 through TW 24) (155/161 or 96%) (see Table 3).

Similarly, subjects in the VICTRELIS -RGT arm with detectable HCV-RNA at any assay from TW 8 up to TW 24, but achieving undetectable HCV-RNA at TW 24 (82/368, 22%), were considered late responders and received an initial 4 weeks of peginterferon alfa-2b and ribavirin, then 24 weeks of VICTRELIS with peginterferon alfa-2b and ribavirin followed by 20 weeks of peginterferon alfa-2b and ribavirin alone in the VICTRELIS -RGT arm. These VICTRELIS -RGT late responders who were assigned to the VICTRELIS -RGT arm that received 48 weeks of treatment also had SVR rates (72%, 59/82) that were similar to those in the matched subjects in the Victrelis-PR48 arm (75%, 55/73) (see Table 3). Subjects in the VICTRELIS -RGT arm received a total of 48 weeks of therapy with peginterferon alfa-2b and ribavirin, but only 24 weeks of VICTRELIS (TW 4 to TW 28). While these late responders in the VICTRELIS -RGT arm continued on peginterferon alfa-2b and ribavirin alone (plus placebo) for the last 20 weeks of therapy, subjects in the VICTRELIS -PR48 arm received VICTRELIS plus peginterferon alfa-2b and ribavirin for 44 weeks. These data support the concept that continued therapy with Victrelis in addition to peginterferon alfa-2b and ribavirin standard of care after TW 28 (as executed in the VICTRELIS -PR48 arm) does not improve SVR rates in late responders who receive a total of 48 weeks of peginterferon alfa-2b and ribavirin treatment.

Table 3 **Sustained Virologic Response (SVR), End of Treatment (EOT) and Relapse Rates in experimental arms with undetectable or detectable HCV-RNA at TW 8 through TW 24 in patients who are previously untreated in the combined cohort**

	Undetectable HCV-RNA at TW 8*		Detectable HCV-RNA at TW 8*	
	VICTRELIS-RGT†	VICTRELIS-PR48	VICTRELIS-RGT†	VICTRELIS-PR48
SVR‡ % (n/N)	96 (156/162)	96 (155/161)	72 (59/82)	75 (55/73)
EOT (Undetectable HCV-RNA), % (n/N)	100 (162/162)	99 (159/161)	80 (66/82)	90 (66/73)
Relapse‡‡ % (n/N)	3 (5/161)	1 (2/157)	11 (7/66)	14 (9/64)

* Per the study design, subjects with undetectable HCV-RNA at TW 8 and all subsequent assays through TW 24 ended treatment at TW 28 (treatment duration assigned by Interactive Voice Response System (IVRS).

† VICTRELIS -RGT – Subjects received peginterferon alfa-2b and ribavirin for 4 weeks, then VICTRELIS 800 mg three times daily + peginterferon alfa-2b and ribavirin as follows: VICTRELIS 800 mg three times daily + peginterferon alfa-2b and ribavirin for 24 weeks (subjects with undetectable HCV-RNA at TW 8 (early responders) and all subsequent assays through TW 24) or VICTRELIS 800 mg three times daily + peginterferon alfa-2b and ribavirin for 24 weeks followed by placebo + peginterferon alfa-2b and ribavirin for 20 weeks (subjects with detectable HCV-RNA at TW 8 up to TW 24; but achieving undetectable HCV-RNA at TW 24).

‡ Sustained Virologic Response (SVR): The last available value in the period at and after Follow-up Week (FW) 24. If there is no such value, the FW 12 value was carried forward.

‡‡ 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 End of Follow-up (EOF) data.

SVR rates in subjects by demographics and baseline factors in the VICTRELIS -RGT and VICTRELIS -PR48 compared to subjects receiving PR alone are presented in Table 4.

Table 4 Sustained Virologic Response (SVR)* by Demographics and Baseline Characteristics in Previously Untreated Subjects in the combined cohort

Demographics/Baseline Characteristic		VICTRELIS-RGT	VICTRELIS-PR48	PR48
Age (years)	<40,	73 (35/48)	70 (37/53)	53 (30/57)
	≥40-<65,	63 (193/308)	66 (201/306)	35 (103/291)
	≥65,	42 (5/12)	57 (4/7)	27 (4/15)
	≥75,	64 (151/237)	68 (159/235)	32 (70/217)
Body Mass Index (BMI)	≤25,	58 (59/101)	68 (83/123)	47 (60/129)
	>25-30,	75 (129/173)	65 (90/138)	33 (49/148)
	>30,% (n/N)	48 (45/94)	66 (69/105)	33 (28/86)
Baseline Viral Load: (IU/mL)	≤ 400,000, , % (n/N)	78 (25/32)	88 (22/25)	81 (21/26)
	> 400,000, % (n/N)	62 (208/336)	65 (220/341)	34 (116/337)
HCV-1 Subtype:	1a, % (n/N)	59 (139/234)	62 (147/237)	34 (78/227)
	1b, % (n/N)	71 (88/124)	73 (85/117)	39 (48/121)
Baseline Fibrosis	Metavir Fibrosis Score (F0/1/2) , % (n/N)	67 (213/319)	67 (211/313)	38 (123/328)
	Metavir Fibrosis Score (F3/4), % (n/N)	41 (14/34)	52 (22/42)	38 (9/24)
Baseline Platelet Count (10^9/L)	<150	55 (18/33)	53 (20/38)	30 (8/27)
	≥150	64 (215/335)	68 (222/328)	38 (129/336)

* The Full Analysis Set (FAS) consisted of all randomized subjects who received at least one dose of any study medication (N=1,097) (peginterferon alfa-2b, ribavirin, or VICTRELIS). Mean age of subjects randomized was 49.1 years. The race distribution of subjects was as follows: 82% White, 14% Black, 2% Asian, 1% multiracial, 1% American Indian or Alaskan Native. The distribution of subjects by gender was 60% men and 40% women.

Patients who have failed previous therapy

RESPOND-2 (P05101) was a randomized, parallel-group, double-blinded study comparing two therapeutic regimens of VICTRELIS 800 mg orally three times daily in combination with PR [peginterferon alfa-2b 1.5 µg/kg/week subcutaneously and weight-based ribavirin (600 – 1,400 mg BID) orally divided twice daily] compared to PR alone in adult subjects with Chronic Hepatitis C (HCV) genotype 1 infection with demonstrated interferon responsiveness (as defined historically by a decrease in HCV-RNA viral load ≥ 2 $\log_{10}$ by Week 12 or undetectable HCV-RNA at end of prior treatment with a subsequent detectable HCV-RNA in plasma) and who failed prior treatment with peginterferon alpha and ribavirin. Subjects (N=404) were randomized in a 1:2:2 ratio and stratified based on response to their previous qualifying regimen (relapsers vs. non-responders) and by HCV subtype (1a vs. 1b) to one of the following treatment arms:

- Peginterferon alfa-2b + ribavirin for 48 weeks (PR48).
- Peginterferon alfa-2b + ribavirin for 4 weeks followed by VICTRELIS 800 mg three times daily + peginterferon alfa-2b + ribavirin for 32 weeks. The subjects were then continued on different treatment regimens based on TW 8 response-guide therapy (VICTRELIS-RGT). All patients in this treatment arm were limited to 32 weeks of VICTRELIS.
    - Subjects with undetectable HCV-RNA at TW 8 (early responders) and TW 12 completed therapy at TW 36 visit.

- Subjects with a detectable HCV-RNA at TW 8 but subsequently undetectable at TW 12 (late responders) were changed in a blinded fashion to placebo at the TW 36 visit and continued treatment with peginterferon alfa-2b + ribavirin for an additional 12 weeks, for a total treatment duration of 48 weeks.

- Peginterferon alfa-2b + ribavirin for 4 weeks followed by VICTRELIS 800 mg three times daily + peginterferon alfa-2b + ribavirin for 44 weeks (VICTRELIS-PR48).

RESPOND-2 enrolled patients who were partial responders or relapsers on prior therapy with peginterferon alfa and ribavirin. The trial did not enrol patients who had less than a 2-$\log_{10}$ HCV-RNA decline by treatment week 12 during prior therapy with peginterferon alpha and ribavirin (null responders).

Mean age of subjects randomised was 53 years. The racial distribution of subjects was as follows: 85% White, 12% Black, and 3% others. The distribution of subjects by gender was 67% men and 33% women.

All subjects with detectable HCV-RNA in plasma at TW 12 were discontinued from treatment. Sustained Virologic Response (SVR) to treatment was defined as undetectable[2] plasma HCV-RNA at FW 24.

The addition of VICTRELIS to the peginterferon alfa-2b and ribavirin therapy significantly increased the SVR rates compared to peginterferon alfa-2b and ribavirin therapy alone (59% to 66% VICTRELIS-containing arms vs. 21% PR48 control) for randomized subjects who received at least one dose of any study medication (Full Analysis Set population) and decreased the length of therapy to 36 weeks for many previous treatment failures (see Table 5). A secondary analysis of subjects who received at least one dose of VICTRELIS or placebo after the four week lead-in with peginterferon alfa-2b and ribavirin (Modified Intent to Treat population) demonstrated SVR rates of 61% to 67% in the VICTRELIS-containing arms compared to 22% PR48 control.

Achievement of SVR was associated with the subject's response to peginterferon alfa-2b and ribavirin therapy, whether defined by classification of response to previous treatment, or by a decrease in HCV-RNA at TW 4 (see Table 5). The TW 4 response was a stronger predictor of SVR compared to response to previous treatment and allowed the determination of the subject's on-treatment interferon responsiveness.

[2] In clinical trials, HCV-RNA in plasma was measured with a Roche COBAS TaqMan® assay with a limit of detection of 9.3 IU/ml.

Table 5 **Sustained Virologic Response (SVR)[*], End of Treatment (EOT), and Relapse[**] Rates for patients who have failed previous therapy**

	Overall	Previous Treatment Response		Lead-In Response[‡] (Viral Load Reduction)	
		Previous Non-Responders[***]	Previous Relapsers[†]	< 1-log_{10} decline	≥ 1-log_{10} decline
PR48 (N=80)					
SVR[‡‡] % (n/N)	21 (17/80)	7 (2/29)	29 (15/51)	0 (0/12)	25 (17/67)
Relapse[**] % (n/N)	32 (8/25)	33 (1/3)	32 (7/22)	0 (0/0)	32 (8/25)
EOT % (n/N)	31 (25/80)	10 (3/29)	43 (22/51)	0 (0/12)	37 (25/67)
Victrelis-RGT (N=162)					
SVR[‡‡] % (n/N)	59 (95/162)	40 (23/57)	69 (72/105)	33 (15/46)	73 (80/110)
Relapse[**] % (n/N)	15 (17/111)	18 (5/28)	14 (12/83)	12 (2/17)	16 (15/94)
EOT % (n/N)	70 (114/162)	54 (31/57)	79 (83/105)	41 (19/46)	86 (95/110)
Victrelis-PR48 (N=161)					
SVR[‡‡] % (n/N)	66 (107/161)	52 (30/58)	75 (77/103)	34 (15/44)	79 (90/114)
Relapse[**] % (n/N)	12 (14/121)	14 (5/35)	10 (9/86)	25 (5/20)	9 (9/99)
EOT % (n/N)	77 (124/161)	60 (35/58)	86 (89/103)	48 (21/44)	89 (101/114)

[*] The Full Analysis Set (FAS) consisted of all randomized subjects who received at least one dose of any study medication (N=403) (peginterferon alfa-2b, ribavirin, or VICTRELIS).

[**] 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 End of Follow-up (EOF) data.

[***] Previous Non-Responder = subject who failed to achieve SVR after at least 12 weeks of previous treatment with peginterferon alfa and ribavirin, but demonstrated a ≥ 2 log_{10} reduction in HCV-RNA by Week 12.

[†] Previous Relapser = subject who failed to achieve SVR after at least 12 weeks of previous treatment with

peginterferon alfa and ribavirin, but had undetectable HCV-RNA at the end of treatment.

‡ Eleven subjects were missing TW 4 assessment (HCV-RNA) and were not included in the Lead-In response results.

‡‡ Sustained Virologic Response (SVR): The last available value in the period at and after Follow-up Week (FW) 24. If there is no such value, the FW 12 value was carried forward. SVR rates (SVR with "missing=failure" approach) 17/80 [21.3%] PR48, 94/162 [58.0] Victrelis-RGT, 106/161 [65.8%] Victrelis-PR48.

Response-guided therapy based on TW 8 response is equally effective as adding VICTRELIS to the 48-week standard of care regimen. Forty-six percent (74/162) of subjects in the VICTRELIS-RGT arm and 52% (84/161) of subjects in the VICTRELIS -PR48 arm were early responders (subjects with undetectable HCV-RNA at TW 8). Of the subjects that were early responders, 71 subjects were undetectable at TW12 in the VICTRELIS-RGT arm and 81 subjects were undetectable at TW 12 in VICTRELIS-PR48 arm. VICTRELIS-RGT early responders, who received 36 weeks of therapy (an initial 4 weeks of peginterferon alfa-2b and ribavirin followed by 32 weeks of VICTRELIS with peginterferon alfa-2b and ribavirin), had an SVR rate of 86% (64/74) compared with an SVR rate of 88% (74/84) in the matched population in the VICTRELIS-PR48 arm who received 48 weeks of therapy (an initial 4 weeks of peginterferon alfa-2b and ribavirin followed by 44 weeks of VICTRELIS with peginterferon alfa-2b and ribavirin) (see Table 6).

In subjects who were not early responders (subjects with detectable HCV-RNA at TW 8), the SVR rate in the VICTRELIS-RGT arm was 40% (29/72) compared with an SVR rate of 43% (30/70) in the matched population in the VICTRELIS-PR48 arm (see Table 6). Thirty-eight subjects in the VICTRELIS-RGT arm and 37 subjects in the VICTRELIS-PR48 arm had detectable HCV-RNA at TW 8 but were subsequently undetectable at TW 12 (late responders). VICTRELIS-RGT late responders, who received an initial 4 weeks of peginterferon alfa-2b and ribavirin then 32 weeks of VICTRELIS with peginterferon alfa-2b and ribavirin followed by 12 weeks of peginterferon alfa-2b and ribavirin alone, had an SVR rate of 76% (29/38) compared with an SVR rate of 62% (23/37) in the matched population in the VICTRELIS-PR48 arm, who received 4 weeks of peginterferon alfa-2b and ribavirin followed by 44 weeks of VICTRELIS in addition to peginterferon alfa-2b and ribavirin. These data support that, in late responders, 36 weeks of VICTRELIS with peginterferon alfa-2b and ribavirin followed by 12 weeks of peginterferon alfa-2b and ribavirin is adequate and that treatment with VICTRELIS may be shortened to 32 weeks in patients who have received previous therapy.

Table 6 **Sustained Virologic Response (SVR), End of Treatment (EOT), and Relapse Rates in the experimental arms with undetectable or detectable HCV-RNA at TW 8 in patients who have failed previous therapy**

	Undetectable HCV-RNA at TW 8		Detectable HCV-RNA at TW 8	
	VICTRELIS-RGT[†]	**VICTRELIS-PR48**	**VICTRELIS-RGT**[† and §]	**VICTRELIS-PR48**
SVR[*] %, (n/N)	86 (64/74)	88 (74/84)	40 (29/72)	43 (30/70)
EOT (Undetectable HCV-RNA) % (n/N)	97 (72/74)	95 (81/84)	56 (40/72)	57 (40/70)
Relapse[‡‡] % (n/N)	11 (8/71)	8 (6/80)	24 (9/38)	21 (8/38)

[*] Sustained Virologic Response (SVR): The last available value in the period at and after Follow-up Week (FW) 24. If there is no such value, the FW 12 value was carried forward.

[†] VICTRELIS-RGT – Subjects received peginterferon alfa-2b and ribavirin for 4 weeks, then VICTRELIS 800 mg three times daily + peginterferon alfa-2b and ribavirin as follows: VICTRELIS 800 mg three times daily + peginterferon alfa-2b and ribavirin for 32 weeks (subjects with undetectable HCV-RNA at TW 8 (early responders) and TW 12) or VICTRELIS 800 mg three times daily + peginterferon alfa-2b and ribavirin for 32 weeks followed by placebo + peginterferon alfa-2b and ribavirin for 12 weeks (subjects detectable HCV-RNA at TW 8 but subsequently negative by TW 12).

[‡‡] 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 End of Follow-up (EOF) data.

[§] Includes all subjects with detectable HCV-RNA at TW 8. Late responders represent a subset of this group, subjects with a detectable HCV-RNA at TW 8 but subsequently undetectable at TW 12. In late responders, the SVR rate was 76% (29/38) in VICTRELIS -RGT arm and 62% (23/37) in the VICTRELIS -PR48.

The difference in the number of subjects who achieved SVR between the VICTRELIS-RGT arm and the VICTRELIS-PR48 arm is explained by imbalances in treatment response observed while subjects in each arm were receiving identical therapy prior to TW 36.

SVR rates in subjects by demographics and baseline factors in the VICTRELIS -RGT and VICTRELIS -PR48 compared to subjects receiving PR alone are presented in Table 7.

Table 7 Sustained Virologic Response (SVR)* by Demographics and Baseline Characteristics in patients who have failed previous therapy

Demographics/Baseline Characteristic		VICTRELIS-RGT	VICTRELIS-PR48	PR48
Race	White/Other,	58 (84/144)	68 (97/142)	24 (16/68)
	Black,	61 (11/18)	53 (10/19)	8 (1/12)
Age (years)	<40,	60 (3/5)	71 (5/7)	0 (0/4)
	≥40-<65,	58 (84/146)	65 (95/146)	23 (16/70)
	≥65,	73 (8/11)	88 (7/8)	17 (1/6)
Body Mass Index (BMI)	≤25,	60 (21/35)	68 (30/44)	20 (4/20)
	>25-30,	60 (41/68)	67 (44/66)	26 (11/42)
	>30,% (n/N)	56 (33/59)	65 (33/51)	11 (2/18)
Baseline Viral Load: (IU/mL)	≤ 400,000, , % (n/N)	100 (7/7)	71 (5/7)	50 (3/6)
	> 400,000, % (n/N)	57 (88/155)	66 (102/154)	19 (14/74)
HCV-1 Subtype:	1a, % (n/N)	53 (50/94)	64 (61/96)	24 (11/46)
	1b, % (n/N)	67 (44/66)	71 (43/61)	18 (6/34)
Baseline Fibrosis	Metavir Fibrosis Score (F0/1/2) , % (n/N)	66 (77/117)	68 (81/119)	23 (14/61)
	Metavir Fibrosis Score (F3/4), % (n/N)	44 (14/32)	68 (21/31)	13 (2/15)
Baseline Platelet Count (10^9/L)	<150	20 (2/10)	68 (13/19)	38 (8/21)
	≥150	21 (15/70)	66 (94/142)	62 (87/141)
Previous Treatment Response	Relapser	29 (15/51)	75 (77/103)	69 (72/105)
	Nonresponder	40 (23/57)	52 (30/58)	7 (2/29)

* The Full Analysis Set (FAS) consisted of all randomized subjects (N=403) who received at least one dose of any study medication (peginterferon alfa-2b, ribavirin, or VICTRELIS). Mean age of subjects randomized was 52.7 years. The race distribution of subjects was as follows: 85% White, 12% Black, 1% Asian, < 1% multiracial, < 1% Native Hawaiian or Other Pacific Islander. The distribution of subjects by gender was 67% men and 33% women.

The use of erythropoietin was permitted with or without ribavirin dose reduction in the clinical trials in subjects who are previously untreated and subjects who have failed previous therapy as a supportive therapy for the management of anaemia (see PRECAUTIONS).

INDICATIONS

VICTRELIS (boceprevir) is indicated for the treatment of Chronic Hepatitis C (HCV) genotype 1 infection, in a combination regimen 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.

CONTRAINDICATIONS

VICTRELIS Capsules, in combination with peginterferon alpha and ribavirin, is contraindicated in:

§ Patients with previously demonstrated clinically significant hypersensitivity to the active substance or any of its excipients.

- § Patients with autoimmune hepatitis.
- § Patients with hepatic decompensation [Child-Pugh score > 6 (class B and C)] (see PHARMACOLOGY).
- § Co-administration with medicines that are highly dependent on CYP3A4/5 for clearance, and for which elevated plasma concentrations are associated with serious and/or life-threatening events such as orally administered midazolam, triazolam, amiodarone, cisapride, alfuzosin, REVATIO (sildenafil) or tadalafil when used for the treatment of pulmonary arterial hypertension, and ergot derivatives (dihydroergotamine, ergotamine) (see Drug Interaction).
- § Pregnant women and in men whose female partners are pregnant because of the risks of birth defects and foetal death with ribavirin (see Use in Pregnancy) (see PRECAUTIONS).

Refer to the corresponding Product Information for peginterferon alpha and ribavirin for additional information regarding co-administration.

PRECAUTIONS

VICTRELIS must be administered in combination with peginterferon alpha and ribavirin.

Dose reduction of VICTRELIS is not recommended.

The Product Information of peginterferon alpha and ribavirin must be consulted prior to initiation of therapy with VICTRELIS.

Anaemia: Anaemia has been reported with peginterferon alpha/ribavirin therapy. The addition of VICTRELIS to peginterferon alpha and ribavirin is associated with an additional decrease in serum haemoglobin concentrations. Complete blood counts should be obtained pretreatment, Treatment Week 4, Treatment Week 8, and thereafter, as clinically appropriate. If serum haemoglobin is < 10 g/dl, a decrease in dose or interruption of ribavirin and/or administration of erythropoietin (epoetin alfa) may be warranted.

Refer to the Product Information for ribavirin for statements regarding dose reduction and/or interruption.

Neutropenia: In Phase 2 and 3 clinical trials, seven percent of subjects receiving the combination of VICTRELIS with PegIntron/REBETOL had neutrophil counts of less than 0.5 x 109/L compared to 4% of subjects receiving PegIntron/REBETOL alone. Three subjects experienced severe or life-threatening infections associated with neutropenia, and two subjects experienced life-threatening neutropenia while receiving the combination of VICTRELIS with PegIntron/REBETOL. Complete blood count must be conducted in all patients prior to initiating VICTRELIS combination therapy. Complete blood counts should be obtained at Treatment Weeks 4, 8, and 12, and should be monitored closely at other time points, as clinically appropriate. Decreases in neutrophil counts may require dose reduction or discontinuation of peginterferon alfa and ribavirin.

Refer to the Product Information for peginterferon alpha and ribavirin for statements regarding dose reduction and/or interruption.

HCV protease monotherapy: Based on results of clinical studies, VICTRELIS must not be used alone due to the high probability of increased resistance without combination anti-HCV therapies. It is unknown what effect therapy with VICTRELIS will have on the activity of subsequently administered HCV protease inhibitors, including re-treatment with VICTRELIS.

Use in patients with rare hereditary disorders: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Potent CYP3A4 inducers: The concomitant use of Victrelis with potent CYP3A4 inducers (rifampicin, carbamazepine, phenobarbital, phenytoin) is not recommended.

Drospirenone-containing medications: Caution should be exercised in patients taking drospirenone-containing medications with conditions that predispose them to hyperkalaemia or patients taking potassium-sparing diuretics. Alternative contraceptives should be considered (see Drug Interactions).

Simvastatin: Co-administration of VICTRELIS with simvastatin may increase plasma levels of simvastatin, which could increase the risk of myopathy, including rhabdomyolysis.

Impairment on fertility

***Use with Ribavirin and Peginterferon alfa*:** Ribavirin caused reversible testicular toxicity in animals; while peginterferon alfa may impair fertility in females. Extreme care must be taken to avoid pregnancy in partners of male patients taking ribavirin or female patients of childbearing potential. Please refer to Product Information for ribavirin and peginterferon alfa for additional information.

No human data on the effect of VICTRELIS on fertility are available. Available pharmacodynamic/toxicological data in rats have shown effects of boceprevir/metabolites on fertility, which in females have been shown to be reversible.
In rats, VICTRELIS induced reversible effects on fertility and early embryonic development in female rats with a no effect level (NEL) of 75 mg/kg. At this dose, the rat-to-human exposure multiple is 1.3-fold higher than the systemic human exposure at the recommended human therapeutic dose of 800 mg three times daily. Decreased fertility was also observed in male rats, most likely as a consequence of testicular degeneration (NEL of 15 mg/kg which represents a rat-to-human exposure multiple of less than 1-fold the human exposure at the human therapeutic dose of 800 mg three times daily). Testicular degeneration has not been observed in mice or monkeys and therefore is considered species-specific to rats. Additionally, clinical monitoring of the surrogate marker inhibin B, as well as semen analysis, has revealed no evidence that this finding is clinically relevant in human subjects.

Use in Pregnancy: Category (X) - Use with Ribavirin and Peginterferon alfa Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin; and therefore ribavirin is contraindicated in women who are pregnant and in the male partners of women who are pregnant (see CONTRAINDICATIONS and ribavirin Product Information). Interferons have abortifacient effects in animals and should be assumed to have abortifacient potential in humans (see peginterferon alfa Product Information).

Extreme caution must be taken to avoid pregnancy in female patients and female partners of male patients while taking this combination. Women of childbearing potential and their male partners should not receive ribavirin unless they are using effective contraception (two reliable forms) during treatment with ribavirin and for 6 months after treatment. Systemic hormonal contraceptives may not be as effective in women while taking VICTRELIS. Therefore, two alternative effective methods of contraception, including intrauterine devices and barrier methods, should be used in women during treatment with VICTRELIS and concomitant ribavirin.

Use in Pregnancy: Boceprevir(Category B2) – VICTRELIS must not be used as monotherapy (see INDICATIONS).There are no adequate and well-controlled studies with VICTRELIS in pregnant women. Fertile women should only be treated when they are using effective contraception during the treatment period.
No effects on fetal development with VICTRELIS alone have been observed in rats and rabbits. VICTRELIS, in combination with ribavirin and peginterferon alpha, is contraindicated in women who are pregnant (see CONTRAINDICATIONS). Please refer to the Product Information for ribavirin and peginterferon alpha for additional information.

Use in Lactation *Use with ribavirin and peginterferon alfa:* It is not known whether peginterferon alfa, ribavirin or their metabolites are excreted in human milk.

Use in Lactation: VICTRELIS: Available pharmacodynamic/toxicological data in animals have shown excretion of boceprevir/metabolites in milk. Following a single, oral dose of 30 mg/kg ^{14}C-boceprevir, drug-derived radiocarbon was transferred into the milk of lactating, 12-day postpartum rats. Peak systemic concentrations of drug-derived radiocarbon in nursing pups were over 100-fold lower than in the mothers.
Exposure to drug-derived materials in nursing human infants is estimated to be less than 1% of the dose. Because of the potential for adverse reactions from the drug in nursing infants, a decision must be made whether to discontinue nursing or discontinue treatment, taking into account the importance of the therapy to the mother.

Patients under the age of 18 years: The safety, efficacy and pharmacokinetic profile of VICTRELIS in paediatric patients below 18 years of age have not yet been established.

Elderly patients ≥ 65 years of age: Clinical studies of VICTRELIS did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other clinical experience has not identified differences in responses between the elderly and younger patients.

Carcinogenesis and Mutagenesis *Use with Ribavirin and Peginterferon alfa:* Ribavirin is genotoxic in *in vitro* and in *in vivo* assays. There is no evidence for genotoxicity with interferon alfa. Ribavirin was not carcinogenic in mice and rats at doses less than the maximum recommended daily human dose. No carcinogenicity studies have been done with interferon alfa. Please refer to Product Information for ribavirin and peginterferon for additional information.

Carcinogenesis and Mutagenesis: *Use with VICTRELIS*: Two-year carcinogenicity studies in mice and rats were conducted with VICTRELIS. Mice were administered doses up to 650 mg/kg. Rats were administered doses of up to 125 mg/kg in males and 100 mg/kg in females. At the high dose of 650 mg/kg in female mice, the incidence of hepatocellular adenomas was increased at systemic exposures 5.7-fold higher than those in humans at the recommended 800 mg three times daily clinical dose; there was no increase in incidence at the next highest dose which corresponded to systemic exposure greater than the human exposure at the recommended 800 mg three times daily clinical dose. There were no increases in mortality or malignancy associated with the hepatocellular adenomas. Induction of CYP450 enzymes has been demonstrated previously in mice administered VICTRELIS, and liver tumours are a recognized sequelae with chronic exposure to an enzyme inducer. There were no increases in the incidence of tumours in male mice at any dose in the study. In rats, no adenomas or carcinomas occurred at systemic exposures higher than those in humans at the recommended 800 mg three times daily clinical dose. The clinical relevance of the hepatocellular adenomas observed in female mice, if any, is unknown.

VICTRELIS was not mutagenic or genotoxic in a battery of *in vitro* or *in vivo* assays, including bacterial mutagenicity, human peripheral blood lymphocyte and mouse micronucleus assays.

Drug Interaction

VICTRELIS is a strong inhibitor of CYP3A4/5. Medicines metabolized primarily by CYP3A4/5 may have increased exposure when administered with VICTRELIS, which could increase or prolong their therapeutic and adverse effects (see Table 8). VICTRELIS does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP2E1 *in vitro.* In addition, VICTRELIS does not induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4/5 *in vitro.*

Boceprevir is a potential inhibitor of p-glycoprotein (P-gp) based on in vitro studies. The potential for a drug interaction with sensitive substrates of p-glycoprotein (e.g., digoxin) has not been evaluated in a clinical trial.

VICTRELIS is partly metabolized by CYP3A4/5. Co-administration of VICTRELIS with medicines that induce or inhibit CYP3A4/5 could increase or decrease exposure to VICTRELIS.

VICTRELIS, in combination with peginterferon alpha and ribavirin, is contraindicated when co-administered with medicines that are highly dependent on CYP3A4/5 for clearance, and for which elevated plasma concentrations are associated with serious and/or life-threatening events such as orally administered midazolam, triazolam, amiodarone, cisapride, alfuzosin, REVATIO (sildenafil) or tadalafil when used for the treatment of pulmonary arterial hypertension, and ergot derivatives (dihydroergotamine, ergotamine) (see CONTRAINDICATIONS).

Caution should be exercised with medicines known to prolong QT interval such as amiodarone, quinidine, methadone, pentamidine and some neuroleptics.

Table 8 **Pharmacokinetic interactions data**

Medicinal products by therapeutic areas	Interaction* (postulated mechanism of action, if known)	Recommendations concerning co-administration
ANTI-INFECTIVES		
Antiviral		
Peginterferon alfa-2b (peginterferon alfa-2b 1.5 mcg/kg subcutaneous (SC) weekly + Victrelis 400 mg three times daily)	Victrelis AUC[**] ↔ Victrelis C_{max} ↔ 12% Victrelis C_{min} N/A peginterferon alfa-2b AUC ↔ 1%[† and ‡] peginterferon alfa-2b C_{max} N/A	No dose adjustment required for Victrelis or peginterferon alfa-2b.
Antibiotic		
Clarithromycin (in combination with diflunisal) (clarithromycin: 500 mg three times daily + diflunisal 500 mg two to three times daily + Victrelis 400 mg two times daily)	Victrelis AUC ↔ 21% Victrelis C_{max} ↑ 36% Victrelis C_{min} ↔ 15%	No dose adjustment is required with Victrelis in combination with clarithromycin, or Victrelis in combination with clarithromycin and diflunisal.
Antifungals		
Ketoconazole (ketoconazole 400 mg two times daily + Victrelis 400 mg single dose)	Victrelis AUC ↑ 131% Victrelis C_{max} ↑ 41% Victrelis C_{min} N/A	No dose adjustment required for Victrelis or ketoconazole.
Antiretroviral		
Nucleoside Reverse Transcriptase Inhibitor (NRTI)		
Tenofovir (tenofovir 300 mg daily + Victrelis 800 mg three times daily)	Victrelis AUC ↔ 8%[**] Victrelis C_{max} ↔ 5% Victrelis C_{min} ↔ 8% tenofovir AUC ↔ 5% tenofovir C_{max} ↑ 32%	No dose adjustment required for Victrelis or tenofovir.
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI)		
Efavirenz (efavirenz 600 mg daily + Victrelis 800 mg three times daily)	Victrelis AUC ↔ 19%[**] Victrelis C_{max} ↔ 8% Victrelis C_{min} ↓ 44% efavirenz AUC ↔ 20% efavirenz C_{max} ↔ 11%	Plasma trough concentrations of Victrelis were decreased when administered with efavirenz. The clinical outcome of this observed reduction of Victrelis trough concentrations has not been directly assessed.
HIV Protease Inhibitor (PI)		
Ritonavir (ritonavir 100 mg daily + Victrelis 400 mg three times daily)	Victrelis AUC ↔ 19% Victrelis C_{max} ↓ 27% Victrelis C_{min} ↔ 4%	No dose adjustment required for Victrelis or ritonavir.

Medicinal products by therapeutic areas	Interaction* (postulated mechanism of action, if known)	Recommendations concerning co-administration
ANALGESIC		
Non-steriodal anti-inflammatories (NSAIDs)		
Diflunisal (diflunisal 250 mg two times daily + Victrelis 800 mg two to three times daily)	Victrelis AUC ↔ 4% Victrelis C_{max} ↔ 14% Victrelis C_{min} ↑ 31%	No dose adjustment required for Victrelis or diflunisal.
Ibuprofen (ibuprofen 600 mg three times daily + Victrelis 400 mg single dose)	Victrelis AUC ↔ 4% Victrelis C_{max} ↔ 6% Victrelis C_{min} N/A	No dose adjustment required for Victrelis or ibuprofen.
ORAL CONTRACEPTIVES		
Drospirenone/Ethinyl estradiol: (drospirenone 3 mg daily + ethinyl estradiol 0.02 mg daily + Victrelis 800 mg three times daily)	drospirenone AUC ↑ 99% drospirenone C_{max} ↑ 57% ethinyl estradiol AUC ↓ 24% ethinyl estradiol C_{max} ↔ (drospirenone - CYP3A4/5 inhibition)	Caution should be exercised in patients with conditions that predispose them to hyperkalaemia or patients taking potassium-sparing diuretics. Alternative contraceptives should be considered.
SEDATIVES		
Midazolam (oral administration) (4 mg single oral dose + Victrelis 800 mg three times daily)	midazolam AUC ↑ 430% midazolam C_{max} ↑ 177% (CYP3A4/5 inhibition)	Co-administration with Victrelis is contraindicated.
Alprazolam, midazolam, triazolam (intravenous administration)	Interaction not studied (CYP3A4/5 inhibition)	Close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised during co-administration of Victrelis with intravenous benzodiazepines (alprazolam, midazolam, triazolam). Dose adjustment of the benzodiazepine should be considered.
Methadone	Not studied	Therapeutic monitoring is recommended when administering Victrelis with CYP3A4/5 substrates that have a narrow therapeutic window. Individual patients may require additional titration of their methadone dosage when Victrelis is started or stopped to ensure clinically effective blood levels.

Medicinal products by therapeutic areas	Interaction* (postulated mechanism of action, if known)	Recommendations concerning co-administration
* Interaction of VICTRELIS with other medicinal products (change in mean ratio estimate of VICTRELIS in combination with co-administered medicine/ VICTRELIS alone): ↓ equals a decrease in mean ratio estimate > 20%; ↑ equals an increase in mean ratio estimate > 25%; no effect (↔) equals a decrease in mean ratio estimate of ≤ 20% or increase in mean ratio estimate ≤ 25%. ** 0-8 hours † 0-168 hours ‡ Reported AUC is 200 mg and 400 mg cohorts combined.		

Effects on ability to drive and use machines

No studies of the effects of VICTRELIS in combination with peginterferon alpha and ribavirin on the ability to drive and use machines have been performed. However, certain side effects that have been reported may affect some patients' ability to drive or operate machinery. Individual response to VICTRELIS in combination with peginterferon alpha and ribavirin may vary. Patients should be informed that fatigue and dizziness have been reported.

Please see the Product Information for PEG-INTRON, PEGATRON Combination Therapy or REBETOL Capsules for additional PRECAUTIONS.

ADVERSE REACTIONS

The safety profile represented by approximately 1,500 patients for the combination of VICTRELIS with peginterferon alfa-2b and ribavirin was based on pooled safety data in two clinical trials in patients who were previously untreated and one clinical trial in patients who had failed prior therapy. Patients with Chronic Hepatitis C received VICTRELIS 800 mg three times daily in combination with peginterferon alfa-2b and ribavirin. SPRINT-1 (P03523) evaluated the use of VICTRELIS in combination with peginterferon alfa-2b and ribavirin with or without a four week lead-in period with peginterferon alfa-2b and ribavirin compared to peginterferon alfa-2b and ribavirin alone in subjects who were previously untreated. SPRINT-2 (P05216 – subjects who were previously untreated) and RESPOND-2 (P05101 – subjects who had failed previous therapy) evaluated the use of VICTRELIS 800 mg three times daily in combination with peginterferon alfa-2b and ribavirin with a four-week lead-in period with peginterferon alfa-2b and ribavirin compared to peginterferon alfa-2b and ribavirin alone (see CLINICAL TRIALS). The population studied had a mean age of 49 years (2% of patients were > 65 years of age), 39% were female, and were 82% white and 15% black. Subjects received VICTRELIS 800 mg three times daily in each study. Patients with Chronic Hepatitis C were randomized to receive VICTRELIS in the three studies for a median exposure of 201 days.

The most frequently reported adverse reactions were similar across all study arms. The most frequently reported adverse reactions considered by investigators to be causally related to the combination of VICTRELIS with peginterferon alfa-2b and ribavirin in adult subjects in clinical studies were: fatigue, anaemia (see PRECAUTIONS), nausea, headache, and dysgeusia.

During the four-week lead-in period with peginterferon alfa-2b and ribavirin, 28/1,263 subjects in the VICTRELIS-containing arms experienced adverse reactions leading to discontinuation of treatment. During the entire course of treatment, the proportion of subjects who discontinued treatment due to adverse reactions was 13% for subjects receiving the combination of VICTRELIS with peginterferon alfa-2b and ribavirin and 12% for subjects receiving peginterferon alfa-2b and ribavirin alone. Events resulting in discontinuation were similar to those seen in previous studies

with peginterferon alfa-2b and ribavirin. Only anaemia and fatigue were reported as events that led to discontinuation in > 1% of subjects in any arm.

Adverse reactions that led to dose modifications of any medication occurred in 39% of subjects receiving the combination of VICTRELIS with peginterferon alfa-2b and ribavirin compared to 24% of subjects receiving peginterferon alfa-2b and ribavirin alone. The most common reason for dose reduction was anaemia, which occurred more frequently in subjects receiving the combination of VICTRELIS with peginterferon alfa-2b and ribavirin than in subjects receiving peginterferon alfa-2b and ribavirin alone.

Adverse reactions considered by investigator to be causally related reported in ≥10% of subjects who received the combination of VICTRELIS with peginterferon alfa-2b and ribavirin are listed in Table 9.

Table 9 **Adverse reactions reported in ≥10% of subjects receiving the combination of VICTRELIS with peginterferon alfa-2b and ribavirin reported during clinical trials**

Adverse Reactions	Previously Untreated (SPRINT-1 & SPRINT-2)		Previous Treatment Failures (RESPOND-2)	
	Percentage of Subjects Reporting Adverse Reactions		Percentage of Subjects Reporting Adverse Reactions	
Body System Organ Class	VICTRELIS + peginterferon alfa-2b +ribavirin (n=1225)	peginterferon alfa-2b +ribavirin (n=467)	VICTRELIS + peginterferon alfa-2b +ribavirin (n=323)	peginterferon alfa-2b +ribavirin (n=80)
Median Exposure (days)	**197**	**216**	**253**	**104**
Blood and Lymphatic System Disorders				
Anemia*	50	30	45	20
Neutropenia*	25	19	14	10
Gastrointestinal Disorders				
Nausea*	45	40	41	38
Dysgeusia*	35	16	44	11
Diarrhea*	23	19	23	15
Vomiting*	19	12	15	8
Dry Mouth*	10	9	13	8
General Disorders and Administration Site Conditions				
Fatigue*	58	58	55	50
Chills	33	29	33	30
Pyrexia*	32	32	28	21
Influenza Like Illness	**22**	**25**	**23**	**25**
Irritability	22	23	21	13
Asthenia*	15	18	21	16
Pain	*10*	*8*	*7*	*4*
Investigations				
Weight decreased	11	12	11	9
Metabolism and Nutrition Disorders				
Decreased Appetite*	25	24	25	16
Musculoskeletal and Connective Tissue Disorders				
Myalgia	22	24	24	24
Arthralgia	18	17	20	14
Nervous System Disorders				
Headache*	45	42	40	48

Dizziness*	18	14	15	10
Psychiatric Disorders				
Insomnia	33	33	29	20
Depression*	21	21	15	15
Anxiety*	12	12	12	6
Respiratory, Thoracic, and Mediastinal Disorders				
Cough*	16	19	20	15
Dyspnea*	19	16	21	16
Dyspnea Exertional	*8*	*8*	*11*	*5*
Skin and Subcutaneous Tissue Disorders				
Alopecia	27	27	22	16
Pruritus	22	24	19	18
Dry Skin	17	18	22	8
Rash	16	19	15	5

* Includes adverse reactions which may be serious as assessed by the investigator in clinical trial subjects.

† Since VICTRELIS is prescribed with peginterferon alpha and ribavirin, please also refer to the respective Product Information of peginterferon alpha and ribavirin.

‡ Injection-site reactions have not been included since VICTRELIS is administered orally.

Anaemia: Anaemia was observed in 49% of subjects treated with the combination of VICTRELIS with peginterferon alfa-2b and ribavirin compared with 29% of subjects treated with peginterferon alfa-2b and ribavirin alone. VICTRELIS was associated with an additional decrease of approximately 1 g/dl in haemoglobin concentration. The mean decreases in haemoglobin values from baseline were larger in previously treated patients compared to patients who had never received prior therapy. Dose modifications due to anaemia/hemolytic anaemia occurred twice as often in patients treated with the combination of VICTRELIS with peginterferon alfa-2b and ribavirin (26%) compared to peginterferon alfa-2b and ribavirin alone (13%). In these clinical trials, proper management of anaemia was associated with continued treatment and higher sustained virologic response, with the majority of the anaemic subjects having received erythropoietin (see PRECAUTIONS). The proportion of subjects who received a transfusion for the management of anaemia was 3% of subjects in the VICTRELIS -containing arms compared to < 1% of subjects receiving peginterferon alfa-2b and ribavirin alone.

Neutrophils and Platelets: The proportion of subjects with decreased neutrophil and platelet counts was higher in the VICTRELIS-containing arms compared to subjects receiving only peginterferon alfa-2b and ribavirin. Seven percent of subjects receiving the combination of VICTRELIS with peginterferon alfa-2b and ribavirin had neutrophil counts of $< 0.5 \times 10^9$ /l compared to 4% of subjects receiving only peginterferon alfa-2b and ribavirin. Three percent of subjects receiving the combination of VICTRELIS with peginterferon alfa-2b and ribavirin had platelet counts of $< 50 \times 10^9$ /l compared to 1% of subjects receiving only peginterferon alfa-2b and ribavirin.

DOSAGE AND ADMINISTRATION

VICTRELIS must be administered in combination with peginterferon alpha and ribavirin. The Product Information of peginterferon alpha and ribavirin must be consulted prior to initiation of therapy with VICTRELIS.

Recommended Dose

The recommended dose of VICTRELIS is 800 mg administered orally three times daily (TID) (every 7-9 hours) with food (meal or light snack).

Patients without cirrhosis who are previously untreated

- Initiate therapy with peginterferon alpha and ribavirin for 4 weeks (Treatment Weeks 1 – 4).
- Add VICTRELIS 800 mg orally three times daily to peginterferon alpha and ribavirin regimen Treatment Week (TW) 5. Based on the patient's hepatitis C virus ribonucleic acid (HCV-RNA) levels at TW 8 and TW 24, use the following Response Guided Therapy (RGT) guidelines to determine duration of treatment (see Table 10).

Table 10 **Duration of therapy using Response Guided Therapy (RGT) in patients without cirrhosis who are previously untreated**

ASSESSMENT (HCV-RNA Results*)		ACTION
At Treatment Week 8	**At Treatment Week 24**	
Undetectable	Undetectable	Complete three medicines regimen at Treatment Week 28.
Detectable	Undetectable	1. Continue all three medications until Treatment Week 28, and then 2. Administer peginterferon alpha and ribavirin until Treatment Week 48.
Any Result	Detectable	Discontinue three medicines regimen.
* In clinical trials, HCV-RNA in plasma was measured with a Roche COBAS® TaqMan® assay with a limit of detection of 9.3 IU/ml.		

Patients without cirrhosis who have failed previous therapy (partial responders and relapsers)

- Initiate therapy with peginterferon alpha and ribavirin for 4 weeks (Treatment Weeks 1 – 4).
- Add VICTERLIS 800 mg orally three times daily to peginterferon alpha and ribavirin regimen at Treatment Week (TW) 5. Based on the patient's HCV-RNA levels at TW 8 and TW 12, use the following Response Guided Therapy (RGT) guidelines to determine duration of treatment (see Table 11). If patient has detectable HCV-RNA at TW 24 discontinuation of therapy is recommended.

Table 11 **Duration of therapy using Response Guided Therapy (RGT) in patients without cirrhosis who have failed previous therapy (partial responders and relapsers)***

ASSESSMENT (HCV-RNA Results†)		ACTION
At Treatment Week 8	**At Treatment Week 12**	
Undetectable	Undetectable	Continue three medicines regimen until completion through Treatment Week 36.
Detectable	Undetectable	1. Continue all three medications until Treatment Week 36, and then 2. Administer peginterferon alpha and ribavirin until Treatment Week 48.
Any Result	Detectable	Discontinue three medicines regimen.

* Previous Partial responders - Patients with a decrease in HCV-RNA viral load ≥ 2-log10 by Week 12 but never achieved SVR; Relapsers -Patients with undetectable HCV-RNA at end of prior treatment with a subsequent detectable HCV-RNA in plasma.
† In clinical trials, HCV-RNA in plasma was measured with a Roche COBAS TaqMan® assay with a limit of detection of 9.3 IU/ml.

Patients with Prior Null Response

Response-Guided Therapy was not studied in patients who had less than a 2-log10 HCV-RNA decline by treatment week 12 during prior therapy with peginterferon alpha and ribavirin (null responders). If considered for treatment, these subjects should receive 4 weeks of peginterferon alpha and ribavirin followed by 44 weeks of VICTRELIS 800 mg orally three times daily in combination with peginterferon alpha and ribavirin. Discontinuation of therapy is recommended in patients with prior null response on previous therapy who have detectable HCV-RNA at TW12; if a patient has detectable HCV-RNA at TW24 discontinuation of therapy is recommended.

Patients with Cirrhosis

Patients with compensated cirrhosis should receive 4 weeks peginterferon alpha and ribavirin followed by 44 weeks Victrelis 800 mg orally three times daily in combination with peginterferon alpha and ribavirin. Discontinuation of therapy is recommended in previously untreated patients who have detectable HCV-RNA at TW24. Discontinuation of therapy is recommended in patients who failed therapy with detectable HCV-RNA at TW12; if a patient has detectable HCV-RNA at TW24, discontinuation of therapy is recommended.

Dose Interruption

If a patient misses a dose and it is less than 2 hours before the next dose is due, the missed dose should be skipped.

If a patient misses a dose and it is 2 or more hours before the next dose is due, the patient should take the missed dose with food and resume the normal dosing schedule.

Dose Modification

Dose reduction of VICTRELIS is not recommended.

If a patient has a serious adverse reaction potentially related to peginterferon alpha and/or ribavirin, the peginterferon alpha and/or ribavirin dose should be reduced. Refer to the Product Information for peginterferon alpha and ribavirin for additional information about how to reduce and/or discontinue the peginterferon alpha and/or ribavirin dose.

VICTRELIS must not be administered in the absence of peginterferon alpha and ribavirin.

Renal impairment

No dose adjustment of VICTRELIS is required in patients with any degree of renal impairment (see PHARMACOLOGY).

Hepatic impairment

No dose adjustment of VICTRELIS is required for patients with mild, moderate or severe hepatic impairment. VICTRELIS, in combination with peginterferon alpha and ribavirin, is contraindicated in cirrhotic patients with a Child-Pugh score > 6 (class B and C) (see CONTRAINDICATIONS).

Organ transplant recipients: The safety and efficacy of VICTRELIS alone or in combination with peginterferon alpha and ribavirin for the treatment of Chronic Hepatitis C genotype 1 infection in liver or other organ transplant recipients have not been studied.

Patients co-infected with HCV/HIV: The safety and efficacy of VICTRELIS alone or in combination with peginterferon alpha and ribavirin for the treatment of Chronic Hepatitis C genotype 1 infection have not been established in patients co-infected with Human Immunodeficiency Virus (HIV) and HCV.

Patients co-infected with HCV/HBV: The safety and efficacy of VICTRELIS alone or in combination with peginterferon alpha and ribavirin for the treatment of Chronic Hepatitis C genotype 1 infection in patients co-infected with hepatitis B Virus (HBV) and HCV have not been studied.

Patients having HCV genotypes other than genotype 1: The safety and efficacy of VICTRELIS alone or in combination with peginterferon alpha and ribavirin for the treatment of chronic hepatitis C genotypes other than genotype 1 infection have not been established.

OVERDOSAGE

Daily doses up to 3,600 mg have been taken by healthy volunteers for 5 days without untoward symptomatic effects. There is no specific antidote for overdose with VICTRELIS Capsules. Ingestion of VICTRELIS at higher than recommended doses may potentially increase the risk of adverse events from drug-drug interactions associated with concomitantly administered medications that are metabolized via the CYP3A4 pathway. Treatment of overdose with VICTRELIS Capsules should consist of general supportive measures, including monitoring of vital signs, and observation of the patient's clinical status.

PRESENTATION

VICTRELIS 200 mg Capsules are comprised of a yellowish-brown, opaque cap with an "MSD" logo imprinted in red ink and off-white, opaque body with the code "314" imprinted in red ink.

The capsules are packaged in blisters. Each blister tray contains three pouches with each pouch containing four capsules. The available pack size is 336 capsules (four week pack).

STORAGE

Store VICTRELIS Capsules in a refrigerator at 2-8°C until dispensed to the patient. For patient use, VICTRELIS Capsules may be stored in the refrigerator until the expiration date printed on the label. VICTRELIS Capsules can also be stored below 30°C for up to 3 months. Store in the original container.

SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited
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Australia

POISON SCHEDULE OF THE DRUG

Schedule 4

Prescription Only Medicine

This Product Information was approved by the Therapeutic Goods Administration on 22 December 2011

Version 1