EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

# Assessment report

## Victrelis

boceprevir

**Procedure No.:** EMEA/H/C/002332/II/0005

## Note

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



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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 June 2012
EMA/CHMP/389856/2012

Committee for Medicinal Products for Human Use (CHMP)

# CHMP Type II variation assessment report

Invented name Victrelis

Procedure No. EMEA/H/C/002332/II/0005

Marketing authorisation holder (MAH): Merck Sharp & Dohme Ltd.



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# 1. Background information on the procedure

## *1.1. Requested Type II variation*

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme Ltd. submitted to the European Medicines Agency on 6 March 2012 an application for a variation.

This application concerns the following medicinal product:

| **Medicinal product:** | **International non-proprietary name:** | **Presentations:** |
|---|---|---|
| Victrelis | boceprevir | See Annex A |

The following variation was requested:

| **Variation requested** | | **Type** |
|---|---|---|
| C.I.4 | Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data | II |

The MAH proposed the update of section 4.3 of the SmPC with a new contraindication with simvastatin and lovastatin and section 4.5 of the SmPC with information on interactions with cyclosporine, tacrolimus, sirolimus, escitalopram, atorvastatin and pravastatin. The Package Leaflet is updated in accordance. Change to section 4.6 of the SmPC with new information on contraceptive measures and to section 5.1 of the SmPC with updated information on resistance were also introduced.

Changes were also made to the SmPC, Annex II, Labelling and PL to bring it in line with the current QRD template. In addition, the list of local representatives in the PL has been revised to amend contact details for the representatives of Ireland, Iceland, Italy, Hungary, Malta, Netherlands and Portugal.

In addition, translation mistakes were corrected in the product information for all EU languages.

The requested variation proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet.

Rapporteur: Philippe Lechat

## *1.2. Steps taken for the assessment*

| | |
|---|---|
| Submission date: | 6 March 2012 |
| Start of procedure: | 25 March 2012 |
| Rapporteur's preliminary assessment report circulated on: | 16 May 2012 |
| Request for Supplementary Information adopted by the CHMP on: | 24 May 2012 |
| Responses submitted by the MAH on: | 30 May 2012 |
| Rapporteur's preliminary assessment report circulated on: | 08 June 2012 |

| | |
|---|---|
| Rapporteur's updated assessment report circulated on: | 15 June 2012 |
| CHMP opinion: | 21 June 2012 |

# 2. Scientific discussion

## *2.1. Introduction*

Boceprevir (Victrelis, SCH 503034) is an inhibitor of the HCV NS3 protease. Boceprevir 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. Boceprevir 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.

This application results from a Drug-Drug Interaction (DDI) study (P08124) characterizing the pharmacokinetic interactions between boceprevir and cyclosporine, tacrolimus, escitalopram, atorvastatin and pravastatin. This study is also one of the pharmacovigilance activities as detailed in the Pharmacovigilance Plan and agreed in the RMP for Victrelis.

Moreover, the MAH proposed to revise the contraindication for co-administration of boceprevir 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 to include simvastatin and lovastatin.

## *2.2. Clinical Pharmacology aspects*

### 2.2.1. Methods – analysis of data submitted

**Study design (P08124)**

This study was a single-center, 5-part, open label, drug-drug-interaction trial in healthy adult subjects. Each part of the study had a fixed-sequence design.

The MAH stated that the study was conducted in conformance with Good Clinical Practices standards and applicable country or local requirements regarding ethical committee review.

| **Protocol** | **P08124: A Multi-Part Trial to Characterize the Pharmacokinetic Interactions between SCH 503034 (Boceprevir) and Cyclosporine, Tacrolimus, Escitalopram, Atorvastatin and Pravastatin** |
|---|---|
| Objectives | **Part 1 and 2: cyclosporine/tacrolimus**<br>- Primary objective: To determine pharmacokinetic interaction between boceprevir and the tested drug at the level of AUC.<br>- Secondary objective 1: To determine pharmacokinetic interaction between boceprevir and the tested drug at the level of Cmax<br>- Secondary objective 2: To evaluate the safety and tolerability of steady-state boceprevir when co-administered with single-dose of the tested drug in healthy subjects.<br><br>**Part 3, 4 and 5 : escitalopram/atorvastatin/pravastatin**<br>- Primary objective: To determine the effect of steady-state boceprevir on the exposure of the tested drug.<br>- Secondary objective 1: To determine the effect of steady-state boceprevir on the |

| Protocol | P08124: A Multi-Part Trial to Characterize the Pharmacokinetic Interactions between SCH 503034 (Boceprevir) and Cyclosporine, Tacrolimus, Escitalopram, Atorvastatin and Pravastatin |
|---|---|
| | Cmax of the tested drug.<br>- Secondary objective 2: To explore the effect of the tested drug on the pharmacokinetic profile of boceprevir<br>- Secondary objective 3: To evaluate the safety and tolerability of steady-state boceprevir when co-administered with the tested drug in healthy subjects. |
| **Design** | Single center, open-label, five-period, fixed-sequence study in healthy subjects. Subjects were given multiple dose boceprevir and single dose of the substrate drug under investigation. However, the effect of single dose cyclosporine and tacrolimus on single dose boceprevir level was also investigated.<br><br>All treatments were administered with food.<br><br>**General Study Plan for all study parts (except Part 2B)**<br>To qualify for the study, subjects were evaluated during the 4-week screening period to ensure they met all of the inclusion criteria and none of the exclusion criteria.<br>Subjects started their first confinement period the evening before the first dose (Day -1) for baseline assessments to confirm eligibility. The next morning (Day 1), after an overnight fast followed by a standard breakfast, the subjects were assigned a subject number and received a single dose of cyclosporine (Part 1), tacrolimus (Part 2), escitalopram (Part 3), atorvastatin (Part 4) or pravastatin (Part 5) within 30 minutes after the initiation of breakfast. Pharmacokinetic samples were obtained predose and at multiple time points after the single dose on Day 1. The subjects of Part 1 also received single dose boceprevir (Day 3) and concomitant SD administration of boceprevir and cyclosporine (Day 4) followed by subsequent PK sampling.<br>After the last PK sample was obtained, safety assessments were performed and subjects were discharged. The duration of subject confinement depended upon the drug administered on Day 1. At discharge the subjects received boceprevir for intake at home and a diary to record this administration. The subjects were instructed on the day of first boceprevir intake (dependent on wash-out period of medication taken on Day 1). The subjects of Part 5 (pravastatin) could take the first boceprevir dose in the clinic, after the last PK sample was obtained and before discharge. Subjects had telephone contacts on each scheduled boceprevir intake to certify adherence to the scheduled time points of boceprevir administration. If logistics required, the time between the two dosing periods could be increased to a maximum of 1 week.<br>Subjects took 800 mg boceprevir in 8 hour intervals: in the morning (at approximately 8 AM) following breakfast and in the afternoon (at approximately 4 PM) and at night (approximately 12 midnight) after a snack. The precise time of day could be individualized for each subject, but the individual subjects were to adhere to the identical dosing schedule for each day.<br>A second confinement period started in the afternoon (before p.m. dosing) of the fourth day of boceprevir use. The diary was checked to verify medication intake at home. After an overnight fast, followed by a standard breakfast, the subjects received their 13th dose of boceprevir. PK samples for steady state boceprevir determination (diastereomers SCH 534128 and SCH 534129, and metabolite SCH 629144) were obtained predose (trough level) and up until 8 hrs post dose (Part 3, 4 and 5 only). Boceprevir TID administration was continued during the entire confinement period.<br>The next morning, the 16th dose of boceprevir was administered concomitantly with a single dose of cyclosporine (Part 1), tacrolimus (Part 2A), escitalopram (Part 3), atorvastatin (Part 4) or pravastatin (Part 5). Pharmacokinetic samples for cyclosporine (Part 1), tacrolimus (Part 2), escitalopram and metabolite (Part 3), atorvastatin and metabolites (Part 4) or pravastatin (Part 5) were obtained predose and at multiple time points after the co-administration. In addition PK samples for boceprevir determination (SCH 534128, SCH 534129, and SCH 629144) were obtained predose (trough level) and up until 8 hrs post morning dose (Part 3, 4 and 5 only). For Part 1 and Part 2 morning trough level samples for boceprevir determination were taken until discharge. After the last PK-sample was taken, |

| Protocol | P08124: A Multi-Part Trial to Characterize the Pharmacokinetic Interactions between SCH 503034 (Boceprevir) and Cyclosporine, Tacrolimus, Escitalopram, Atorvastatin and Pravastatin |
|---|---|
| | safety assessments were performed and subjects were discharged.<br>During hospitalization the subjects were provided standard meals.<br>On the first day of each PK sampling period, the subjects received a standard breakfast (after an overnight fast of at least 8 hours) to be consumed within 20 minutes. The subjects took the morning medication with 240 mL of water at 30 min after initiation of breakfast. Water was restricted 1 hour prior to and 1 hour after drug intake, and subjects fasted for 4 hours post morning dose.<br>Safety assessments (safety labs, ECG, vital signs, adverse events and Columbia Suicide Severity Rating Scale (C-SSRS, Part 3 only) were performed throughout the study as described in the Study Flow Chart. Subjects returned to the clinic approximately 7 days after the last PK sample collection for final safety assessments.<br><br>**Study Plan for Part 2 Cohort B tacrolimus (inhibitor):**<br>To qualify for the study, subjects were evaluated during the 4-week screening period to ensure they met all of the inclusion criteria and none of the exclusion criteria.<br>Subjects started confinement in the evening before the first dose (Day -1) for baseline assessments to confirm eligibility.<br>The next morning (Day 1), the subjects received a standard breakfast (after an overnight fast of at least 8 hours) to be consumed within 20 minutes. The subjects were assigned a Subject number and took a single 800 mg PO dose of boceprevir at 30 min after the initiation of breakfast. Study medication was given with 240 mL of water. Water was restricted 1 hour prior to and 1 hour after drug intake, and subjects fasted for 4 hours post dose. PK samples for boceprevir determination (diastereomers SCH 534128 and SCH 534129 and metabolite SCH 629144) were obtained predose and up until 24 hrs post dose. On Day 2 (after the PK sample at 24-hr post Day 1 dosing was taken), subjects received another single dose of 800 mg boceprevir together with a single dose of 0.5 mg of tacrolimus on the same food and time restrictions as on Day 1. PK samples for boceprevir (in the presence of tacrolimus) were collected from Day 2 predose up until the morning of Day 3 (= 24 hrs post dose). During hospitalization the subjects received standard meals unless otherwise specified. Safety assessments (safety labs, ECG, vital signs and adverse events (AE)) were performed throughout the study as described in the Study Flow Chart. On Day 3, after the last PK sample was taken, safety assessments were performed and subjects were discharged. On Day 10 (+/- 3 days) the subjects returned to the clinic for final safety assessments. |
| **Population** | Healthy subjects of either sex and of any race between the ages of 18 and 55 years, inclusive, having a Body Mass Index (BMI) between 18 and 32, inclusive. |
| **Treatment** | Part 1: Cyclosporine 100 mg (Neoral [Novartis], soft gelatin capsules 100 mg, Lot # F4141A, expiry date: 2013), oral administration; SCH 503034 (boceprevir) 800 mg (4 x 200 mg capsules, Lot # K-H11095) oral administration TID.<br><br>Part 2:<br>Cohort A: Tacrolimus 0.5 mg (Prograf [Astellas], capsule 0.5 mg, Lot # 040881, expiry date: 10/2013), oral administration; SCH 503034 (boceprevir) 800 mg (4 x 200 mg capsules, Lot # K-H11095) oral administration, single dose and TID.<br>Cohort B: Tacrolimus 0.5 mg (Prograf [Astellas], capsule 0.5 mg, Lot # 040881, expiry date: 10/2013); SCH 503034 (boceprevir) 800 mg (4 x 200 mg capsules, Lot # K-H11095) oral administration single dose.<br><br>Part 3: Escitalopram 10 mg (Cipralex/ Lexapro [Forest Pharm], tablet 10 mg, Lot # SL110204, expiry date: 11/2004), oral administration; SCH 503034 (boceprevir) 800 mg (4 x 200 mg capsules, Lot # K-H11095) oral administration TID.<br><br>Part 4: Atorvastatin 40 mg (Lipitor [Pfizer], tablet 40 mg, Lot # 0901011, expiry date: 12/10/2013), oral administration; SCH 503034 (boceprevir) 800 mg (4 x 200 mg capsules, Lot # K-H11095) oral administration TID.<br><br>Part 5: Pravastatin 40 mg, (Lipostat/ Pravachol [Bristol Myers Squibb], tablet 40 |

| Protocol | P08124: A Multi-Part Trial to Characterize the Pharmacokinetic Interactions between SCH 503034 (Boceprevir) and Cyclosporine, Tacrolimus, Escitalopram, Atorvastatin and Pravastatin |
|---|---|
| | mg, Lot # 0D59705A, expiry date: 04/2013), oral administration; SCH 503034 (boceprevir) 800 mg (4 x 200 mg capsules, Lot # K-H11095) oral administration TID. |

## 2.2.2. Results

***Study P08124***

**IMMUNOSUPPRESSANTS**

**SUBJECT DISPOSITION:**

- Part 1: 10 healthy adult subjects were enrolled. All 10 subjects completed treatment (boceprevir and cyclosporine) and finished the study as planned.
- Part 2a: 12 healthy adult subjects were enrolled. All 12 subjects completed the study as planned.
- Part 2b: 10 healthy adult subjects were enrolled. All 10 subjects the study as planned.

**PK RESULTS:**

Pharmacokinetic Interaction of Cyclosporine and Boceprevir

The mean elimination half-life increased from 11.3 hr to 15.7 hr while the mean CL/F decreased by >2-fold from 58.8 to 21.0 L/hr.

**Table 1.** Summary Statistics Data for Cyclosporine and Boceprevir PK Parameters Following a Single Oral 100 mg Cyclosporine Dose Administered Alone or a Single Oral 800 mg Boceprevir Dose Administered Alone or Concomitant Administration of a Single Oral 100 mg Cyclosporine Dose and Multiple Oral 800 mg TID Boceprevir Doses to Healthy Subjects (Part 1)

Protocol No. P08124

| Analyte | Parameter | Treatment | N | Geometric Mean[a] | Comparison | GMR | 90% CI for GMR | rMSE[b] |
|---|---|---|---|---|---|---|---|---|
| Cyclosporine | $C_{max}$ (ng/mL) | Cyclosporine + Boceprevir | 10 | 712 | Cyclosporine + Boceprevir vs. Cyclosporine Alone | 2.01 | 1.69-2.40 | 0.21 |
| | | Cyclosporine Alone | 10 | 354 | | | | |
| | $AUC_{last}$ (ng.hr/mL) | Cyclosporine + Boceprevir | 10 | 4481 | Cyclosporine + Boceprevir vs. Cyclosporine Alone | 2.59 | 2.34-2.86 | 0.12 |
| | | Cyclosporine Alone | 10 | 1731 | | | | |
| | $AUC_{inf}$ (ng.hr/mL) | Cyclosporine + Boceprevir | 9 | 4762 | Cyclosporine + Boceprevir vs. Cyclosporine Alone | 2.68 | 2.38-3.03 | 0.13 |
| | | Cyclosporine Alone | 9 | 1774 | | | | |
| Boceprevir | $C_{max}$ (ng/mL) | Boceprevir + Cyclosporine | 10 | 2209 | Boceprevir + Cyclosporine vs. Boceprevir Alone | 1.08 | 0.967-1.20 | 0.13 |
| | | Boceprevir Alone | 10 | 2052 | | | | |
| | $AUC_{last}$ (ng.hr/mL) | Boceprevir + Cyclosporine | 10 | 9678 | Boceprevir + Cyclosporine vs. Boceprevir Alone | 1.21 | 1.13-1.29 | 0.08 |
| | | Boceprevir Alone | 10 | 8015 | | | | |
| | $AUC_{inf}$ (ng.hr/mL) | Boceprevir + Cyclosporine | 10 | 9777 | Boceprevir + Cyclosporine vs. Boceprevir Alone | 1.16 | 1.06-1.26 | 0.10 |
| | | Boceprevir Alone | 9 | 8459 | | | | |

CI = Confidence Interval; GMR = Ratio of geometric least-squares means

a: Model-based (least squares) geometric mean: based on mixed effect model extracting the effect due to Treatment as fixed effect and Subject as the random effect

b: Square root of conditional mean squared error (residual error) from the linear mixed effect model. rMSEx100% approximate the within-subject CV% on the raw scale

Pharmacokinetic Interaction of Tacrolimus and Boceprevir

The mean elimination half-life increased from 36.7 hr to 61.5 hr whereas the mean CL/F decreased by approximately 18-fold from 29.6 to 1.60 L/hr.

**Table 2.** Summary Statistics Data for Tacrolimus and Boceprevir PK Parameters Following a Single Oral 0.5 mg Tacrolimus Dose Administered Alone or a Single Oral 800 mg Boceprevir Dose Administered Alone or Concomitant Administration of a Single Oral 0.5 mg Tacrolimus Dose and Multiple Oral 800 mg TID Boceprevir Doses to Healthy Subjects (Part 2)

Protocol No. P08124

| Analyte | Parameter | Treatment | N | Geometric Mean[a] | Comparison | GMR | 90% CI for GMR | rMSE[b] |
|---|---|---|---|---|---|---|---|---|
| Tacrolimus | $C_{max}$ (ng/mL) | Tacrolimus + Boceprevir | 12 | 7.58 | Tacrolimus + Boceprevir vs. Tacrolimus Alone | 9.90 | 7.96-12.3 | 0.30 |
| | | Tacrolimus Alone | 12 | 0.77 | | | | |
| | $AUC_{last}$ (ng.hr/mL) | Tacrolimus + Boceprevir | 12 | 265 | Tacrolimus + Boceprevir vs. Tacrolimus Alone | 16.9 | 13.3-21.7 | 0.33 |
| | | Tacrolimus Alone | 12 | 15.6 | | | | |
| | $AUC_{inf}$ (ng.hr/mL) | Tacrolimus + Boceprevir | 12 | 328 | Tacrolimus + Boceprevir vs. Tacrolimus Alone | 17.1 | 14.0-20.8 | 0.27 |
| | | Tacrolimus Alone | 12 | 19.2 | | | | |
| Boceprevir | $C_{max}$ (ng/mL) | Boceprevir + Tacrolimus | 10 | 1839 | Boceprevir + Tacrolimus vs. Boceprevir Alone | 0.972 | 0.837-1.13 | 0.18 |
| | | Boceprevir Alone | 10 | 1892 | | | | |
| | $AUC_{last}$ (ng.hr/mL) | Boceprevir + Tacrolimus | 10 | 6985 | Boceprevir+ Tacrolimus vs. Boceprevir Alone | 0.991 | 0.936-1.05 | 0.07 |
| | | Boceprevir Alone | 10 | 7048 | | | | |
| | $AUC_{inf}$ (ng.hr/mL) | Boceprevir + Tacrolimus | 10 | 7104 | Boceprevir + Tacrolimus vs. Boceprevir Alone | 0.999 | 0.946-1.06 | 0.07 |
| | | Boceprevir Alone | 10 | 7111 | | | | |

CI = Confidence Interval; GMR = Ratio of geometric least-squares means

a: Model-based (least squares) geometric mean: based on mixed effect model extracting the effect due to Treatment as fixed effect and Subject as the random effect

b: Square root of conditional mean squared error (residual error) from the linear mixed effect model. rMSEx100% approximate the within-subject CV% on the raw scale

**SAFETY RESULTS**

There were no deaths or serious AEs. No clinically significant changes in blood chemistry or hematological parameters, vital signs, or ECGs occurred in any treatment group.

**ESCITALOPRAM**

**SUBJECT DISPOSITION:**

- Part 3: 10 healthy adult subjects were enrolled. 9 subjects completed the study as planned while 1 subject was discontinued due to non-compliance with protocol.

**PK RESULTS**

Pharmacokinetic Interaction of Escitalopram and Boceprevir

**Table 3.** Summary Statistics Data for Escitalopram and Boceprevir PK Parameters Following a Single Oral 10 mg Escitalopram Dose Administered Alone or Multiple Oral 800 mg TID Boceprevir Doses Administered Alone or Concomitant Administration of a Single Oral 10 mg Escitalopram Dose and Multiple Oral 800 mg TID Boceprevir Doses to Healthy Subjects (Part 3)

Protocol No. P08124

| Analyte | Parameter | Treatment | N | Geometric Mean[a] | Comparison | GMR | 90% CI for GMR | rMSE[b] |
|---|---|---|---|---|---|---|---|---|
| Escitalopram | $C_{max}$ (ng/mL) | Escitalopram + Boceprevir | 9 | 6.73 | Escitalopram + Boceprevir vs. Escitalopram Alone | 0.812 | 0.760-0.869 | 0.08 |
| | | Escitalopram Alone | 10 | 8.28 | | | | |
| | $AUC_{last}$ (ng.hr/mL) | Escitalopram + Boceprevir | 9 | 176 | Escitalopram + Boceprevir vs. Escitalopram Alone | 0.824 | 0.756-0.899 | 0.10 |
| | | Escitalopram Alone | 10 | 214 | | | | |
| | $AUC_{inf}$ (ng.hr/mL) | Escitalopram + Boceprevir | 9 | 218 | Escitalopram + Boceprevir vs. Escitalopram Alone | 0.787 | 0.714-0.870 | 0.11 |
| | | Escitalopram Alone | 10 | 276 | | | | |
| Boceprevir | $C_{max}$ (ng/mL) | Boceprevir + Escitalopram | 9 | 2175 | Boceprevir + Escitalopram vs. Boceprevir Alone | 0.911 | 0.814-1.02 | 0.13 |
| | | Boceprevir Alone | 9 | 2388 | | | | |
| | $AUC_{\tau}$ (ng.hr/mL) | Boceprevir + Escitalopram | 9 | 6580 | Boceprevir+ Escitalopram vs. Boceprevir Alone | 1.02 | 0.959-1.08 | 0.07 |
| | | Boceprevir Alone | 9 | 6461 | | | | |

**SAFETY RESULTS**

There were no deaths or serious AEs. No clinically significant changes in blood chemistry or hematological parameters, vital signs, or ECGs occurred in any treatment group.

**HMG-CoA REDUCTASE INHIBITORS**

**SUBJECT DISPOSITION:**

- Part 4: 10 healthy adult subjects were enrolled. All 10 subjects completed the study as planned.
- Part 5: 10 healthy adult subjects were enrolled. 9 subjects completed the study as planned while 1 subject was discontinued due to non-compliance with protocol.

**PK RESULTS**

Pharmacokinetic Interaction of Atorvastatin and Boceprevir

**Table 4.** Summary Statistics Data for Atorvastatin and Boceprevir PK Parameters Following a Single Oral 40 mg Atorvastatin Dose Administered Alone or Multiple Oral 800 mg TID Boceprevir Doses Administered Alone or Concomitant Administration of a Single Oral 40 mg Atorvastatin Dose and Multiple Oral 800 mg TID Boceprevir Doses to Healthy Subjects (Part 4)

Protocol No. P08124

| Analyte | Parameter | Treatment | N | Geometric Mean[a] | Comparison | GMR | 90% CI for GMR | rMSE[b] |
|---|---|---|---|---|---|---|---|---|
| Atorvastatin | $C_{max}$ (ng/mL) | Atorvastatin + Boceprevir | 10 | 24.7 | Atorvastatin + Boceprevir vs. Atorvastatin Alone | 2.66 | 1.81-3.90 | 0.47 |
| | | Atorvastatin Alone | 10 | 9.29 | | | | |
| | $AUC_{last}$ (ng.hr/mL) | Atorvastatin + Boceprevir | 10 | 198 | Atorvastatin + Boceprevir vs. Atorvastatin Alone | 2.33 | 1.85-2.93 | 0.2[illegible] |
| | | Atorvastatin Alone | 10 | 85.1 | | | | |
| | $AUC_{inf}$ (ng.hr/mL) | Atorvastatin + Boceprevir | 10 | 200 | Atorvastatin + Boceprevir vs. Atorvastatin Alone | 2.30 | 1.84-2.88 | 0.28 |
| | | Atorvastatin Alone | 10 | 86.8 | | | | |
| Boceprevir | $C_{max}$ (ng/mL) | Boceprevir + Atorvastatin | 10 | 1969 | Boceprevir + Atorvastatin vs. Boceprevir Alone | 1.04 | 0.888-1.21 | 0.19 |
| | | Boceprevir Alone | 10 | 1900 | | | | |
| | $AUC_{\tau}$ (ng.hr/mL) | Boceprevir + Atorvastatin | 10 | 6938 | Boceprevir + Atorvastatin vs. Boceprevir Alone | 0.953 | 0.896-1.01 | 0.08 |
| | | Boceprevir Alone | 10 | 7282 | | | | |

Pharmacokinetic Interaction of Pravastatin and Boceprevir

**Table 5.** Summary Statistics Data for Pravastatin and Boceprevir PK Parameters Following a Single Oral 40 mg Pravastatin Dose Administered Alone or Multiple Oral 800 mg TID Boceprevir Doses Administered Alone or Concomitant Administration of a Single Oral 40 mg Pravastatin Dose and Multiple Oral 800 mg TID Boceprevir Doses to Healthy Subjects (Part 5)

Protocol No. P08124

| Analyte | Parameter | Treatment | N | Geometric Mean[a] | Comparison | GMR | 90% CI for GMR | rMSE[b] |
|---|---|---|---|---|---|---|---|---|
| Pravastatin | $C_{max}$ (ng/mL) | Pravastatin + Boceprevir | 9 | 44.7 | Pravastatin + Boceprevir vs. Pravastatin Alone | 1.49 | 1.03-2.14 | 0.42 |
| | | Pravastatin Alone | 10 | 30.1 | | | | |
| | $AUC_{last}$ (ng.hr/mL) | Pravastatin + Boceprevir | 9 | 131 | Pravastatin + Boceprevir vs. Pravastatin Alone | 1.50 | 1.20-1.87 | 0.26 |
| | | Pravastatin Alone | 10 | 87.6 | | | | |
| | $AUC_{inf}$ (ng.hr/mL) | Pravastatin + Boceprevir | 6[c] | 144 | Pravastatin + Boceprevir vs. Pravastatin Alone | 1.63 | 1.01-2.62 | 0.30 |
| | | Pravastatin Alone | 6[c] | 88.4 | | | | |
| Boceprevir | $C_{max}$ (ng/mL) | Boceprevir + Pravastatin | 9 | 1806 | Boceprevir + Pravastatin vs. Boceprevir Alone | 0.928 | 0.828-1.04 | 0.13 |
| | | Boceprevir Alone | 9 | 1947 | | | | |
| | $AUC_{\tau}$ (ng.hr/mL) | Boceprevir + Pravastatin | 9 | 6499 | Boceprevir + Pravastatin vs. Boceprevir Alone | 0.941 | 0.883-1.01 | 0.07 |
| | | Boceprevir Alone | 9 | 6889 | | | | |

CI = Confidence Interval; GMR = Ratio of geometric least-squares means

a: Model-based (least squares) geometric mean: based on mixed effect model extracting the effect due to Treatment as fixed effect and Subject as the random effect.

b: Square root of conditional mean squared error (residual error) from the linear mixed effect model. rMSEx100% approximate the within-subject CV% in the raw scale

c: Six of 10 subjects for the pravastatin alone treatment had reportable $AUC_{inf}$, 6 of 9 subjects for the pravastatin+boceprevir treatment had reportable $AUC_{inf}$

## SAFETY RESULTS

There were no deaths or serious AEs. No clinically significant changes in blood chemistry or hematological parameters, vital signs, or ECGs occurred in any treatment group.

### *SIMVASTATIN AND LOVASTATIN*

Boceprevir is an inhibitor of the cytochrome P450 isoform CYP3A4. Coadministration of boceprevir and drugs primarily metabolized by CYP3A4 may result in increased plasma concentrations of the other drug, which could increase or prolong its therapeutic and adverse effects. Based on in vitro data in human liver microsomes, boceprevir does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP2E1. In vivo, boceprevir administration increases the AUC of co-administered drugs which are CYP3A4 substrates, with midazolam increasing 5.30-fold; cyclosporine, 2.68-fold; and tacrolimus, 17.1-fold.

## 2.2.3. Discussion

Although complex due to its multipart design, the study design is overall suitable. Boceprevir was administered at the recommended dose of 800mg TID, except when required to be given at single dose. Of note, most of the interaction studies provided in the marketing authorisation application had been conducted with a lower than recommended dose of boceprevir.

All drugs were given with food in this study. This is consistent with the food requirement of boceprevir and adequate for escitalopram, atorvastatin and pravastatin that could be given with or without food. Bioavailability of tacrolimus and cyclosporine are known to be decreased by food. In this study, immunosuppressive drugs were taken within 30 minutes after the initiation of breakfast. This is not optimal on a PK point of view and will have to be taken into account in the interpretation of the interaction results.

A 5 days delay has been anticipated to reach maximal inhibitory effect on CYP3A4, which is appropriate. A washout period of minimum 7 days has been applied between the different dosing period which is in accordance with the mean plasma half-life of boceprevir of 3.4 hours. Dose of the co-administered substrate were adequately justified and chosen to provide robust PK profile while mitigating potential safety concerns.

A fixed-sequence design was chosen by the MAH on the basis of the long apparent terminal half-lives of most of the interacting drugs and the absence of subjective and/or time-dependent pharmacodynamic or safety variables.

All co-administered drugs were given at single dose. Interacting effect may be studied at single dose for drugs having a linear PK; however, the MAH did not comment on this aspect.

**IMMUNOSUPPRESSANTS**

PK results are consistent with the known strong inhibitor effect of boceprevir on CYP3A4.

The concomitant administration of boceprevir and cyclosporine led to significant changes in cyclosporine pharmacokinetics (Cmax increased by 101% and AUC by 168%). Cyclosporine half-life was increased from 11 to 16h and tacrolimus half-life from 37 to 62h.

The AUC and Cmax of tacrolimus increased in an even more substantial manner (Cmax increases by 890% and AUC by 1610%) when combined with boceprevir.

Boceprevir PK was not significantly altered by cyclosporine or tacrolimus in this study. Of note, however, a 2-fold increase in Cmax and AUC of the metabolite SCH 629144 (inactive major metabolite) was observed following co-administration of boceprevir and cyclosporine (not shown in table 1). The underlying mechanism is unknown.

Given the significant difference in the magnitude of the interaction observed in this study (3 fold increase in cyclosporine AUC and 17 fold increase in tacrolimus AUC when coadministered with boceprevir), distinction in recommendations between cyclosporine and tacrolimus was discussed. However, the CHMP felt that the administration of immunosupressants is made under well controlled circumstances in clinical practice and clinicians treating transplant patients are fully experienced with the management of dose adjustment of immunosuppressants notably when co-administered with strong CYP3A4 inhibitors. Therefore, similar recommendations for both compounds are made in the SmPC: dose adjustment with close monitoring of concentration, renal function and side effects to all immunosuppressants. In addition, the results obtained with these immunosuppressants were extrapolated to sirolimus. The recommendations were aligned with those for the other

immunosuppressants by including monitoring of renal function and sirolimus-related side-effects (see section 2.4).

**ESCITALOPRAM**

Escitalopram is metabolised in the liver to demethylated and didemethylated metabolites. Biotransformation of escitalopram is mediated primarily by CYP2C19. Some contribution by the enzymes CYP3A4 and CYP2D6 is possible. Boceprevir is a strong inhibitor of CYP3A4/5 but does not inhibit CYP2C19.

Boceprevir PK was not significantly altered by escitalopram. On the other hand, escitalopram exposure and Cmax were reduced by 21% and 19% respectively, when coadministered with boceprevir.

The mechanism underlying the decrease in exposure of escitalopram is not clear.

Selective serotonin reuptake inhibitors such as escitalopram have a wide therapeutic index, and as such the observed decrease of 21% in exposure and of 19% in Cmax is generally not thought to be of clinically significance. However, it is possible that for individual patients, doses may need to be adjusted when combined with boceprevir to preserve full therapeutic benefit.

Therefore, the CHMP agreed on the MAH's proposal to highlight the need for clinicians to consider a dose adjustment of escitalopram when given together with boceprevir in the SmPC (see section 2.4).

**HMG-CoA REDUCTASE INHIBITORS**

Pharmacokinetic Interaction of Atorvastatin and Boceprevir

Consistent with the known strong inhibitor effect of boceprevir on CYP3A4, boceprevir significantly increased the exposure (AUC by 130% and Cmax by 166%) of atorvastatin. According to the MAH, atorvastatin may have P-gp inhibitory effects at concentration much higher than therapeutic concentrations.

In this study, atorvastatin had no effect on PK parameters of boceprevir.

Of note, dose of 40mg atorvastatin was used in this study (whereas usual dose are 10 or 20mg/day with maximal recommended dose of 80mg).

In line with these findings, dose reduction of atorvastatin should be considered when co-administrated with boceprevir. Additional clinical monitoring is recommended when daily doses of atorvastatin exceed 40 mg (see section 2.4).

Pharmacokinetic Interaction of Pravastatin and Boceprevir

The exposure of pravastatin is increased when co-administered with boceprevir (AUC by 63% and Cmax by 49%).Given the metabolism pathway of pravastatin, a significant impact was not expected.

As expected, pravastatin did not affect the exposure of boceprevir.

In line with these findings, treatment with pravastatin can be initiated at the recommended dose when co-administered with boceprevir. However, close clinical monitoring is warranted (see section 2.4).

Lovastatin and simvastatin

HMG-CoA reductase inhibitors which are highly dependent on CYP3A4 metabolism, such as lovastatin and simvastatin, are expected to have markedly increased plasma concentrations when co-administered with drugs which are CYP3A4 inhibitors. The interaction of boceprevir with lovastatin or

simvastatin has not been studied; however, boceprevir inhibits CYP3A4 and as a result is expected to markedly increase the plasma concentrations of these HMG-CoA reductase inhibitors. Since increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis, the combination of lovastatin or simvastatin with boceprevir is not recommended (see section 2.4).

## *2.3. Risk management plan*

This submission of the results from a Drug-Drug Interaction (DDI) study (P08124) characterizing the pharmacokinetic interactions between boceprevir and cyclosporine, tacrolimus, escitalopram, atorvastatin and pravastatin was one of the pharmacovigilance activities as detailed in the Pharmacovigilance Plan and agreed in the RMP for Victrelis. An updated RMP incorporating these results (version 3.0) was submitted in March 2012 and the review is currently on-going.

## *2.4. Changes to the Product Information*

During the procedure, the CHMP requested further amendments to the SmPC (addition / ~~deletion~~):

**4.3 Contraindications**

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 and triazolam, bepridil, pimozide, lumefantrine, halofantrine, tyrosine kinase inhibitors, simvastatin, lovastatin, and ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine) (see section 4.5).

**4.5 Interaction with other medicinal products and other forms of interaction**

Victrelis, in combination with peginterferon alfa 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 and triazolam, bepridil, pimozide, lumefantrine, halofantrine, tyrosine kinase inhibitors, simvastatin, lovastatin, and ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine) (see section 4.3).

Table 2
Pharmacokinetic interactions data

| Medicinal products by therapeutic areas | Interaction*<br>(postulated mechanism of action, if known) | Recommendations concerning co-administration |
|---|---|---|
| *ANTI-DEPRESSANTS* | | |
| Escitalopram<br>(escitalopram 10 mg single dose + Victrelis 800 mg three times daily) | boceprevir AUC ↔ 9%<br>boceprevir $C_{max}$ ↔ 2%<br>escitalopram AUC ↓ 21%<br>escitalopram $C_{max}$ ↔ 19% | Exposure of escitalopram was slightly decreased when co-administered with Victrelis. No dose adjustment of escitalopram is anticipated. ~~Selective serotonin reuptakeinhibitors such as escitalopram have a wide therapeutic index,~~but doses may need to be adjusted |

| Medicinal products by therapeutic areas | Interaction*<br><br>(postulated mechanism of action, if known) | Recommendations concerning co-administration |
|---|---|---|
| | | based on clinical effect ~~when combined with Victrelis~~. |
| *ANTI-INFECTIVES* | | |
| *Antifungals* | | |
| Ketoconazole<br>(ketoconazole 400 mg two times daily +<br>Victrelis 400 mg single dose)<br><br>Itraconazole, Posaconazole, Voriconazole | boceprevir AUC ↑ 131%<br>boceprevir $C_{max}$ ↑ 41%<br>boceprevir $C_{min}$ N/A<br><br>(CYP3A4/5 inhibition and/or P-gp inhibition)<br><br>Not studied | Caution should be exercised when boceprevir is combined with ketoconazole or azole antifungals (itraconazole, posaconazole, voriconazole). |
| *Antiretroviral* | *Antiretroviral* | *Antiretroviral* |
| Efavirenz<br>(efavirenz 600 mg daily + Victrelis 800 mg three times daily) | boceprevir AUC ↔ 19%**<br>boceprevir Cmax ↔ 8%<br>boceprevir Cmin ↓ 44%<br><br>efavirenz AUC ↔ 20%<br>efavirenz Cmax ↔ 11%<br><br>(CYP3A4 induction effect on boceprevir) | 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. |
| Ritonavir<br><br>(ritonavir 100 mg daily + Victrelis 400 mg three times daily) | boceprevir AUC ↔ 19%<br><br>boceprevir $C_{max}$ ↓ 27%<br><br>boceprevir $C_{min}$ ↔ 4%<br><br>(CYP3A inhibition) | When boceprevir is administered with ritonavir alone, boceprevir concentrations are decreased. |
| *HMG CoA REDUCTASE INHIBITORS* | | |
| Atorvastatin<br><br>(atorvastatin 40 mg single dose + Victrelis 800 mg three times daily)<br><br>**~~Statins~~** ~~(e.g., simvastatin and atorvastatin).~~ | boceprevir AUC ↔ 5%<br><br>boceprevir $C_{max}$ ↔ 4%<br><br>atorvastatin AUC ↑ 130%<br><br>atorvastatin $C_{max}$ ↑ 166%<br><br>(CYP3A and OATPB1 inhibition) | Exposure to atorvastatin was increased when administered with Victrelis. When co-administration is required, starting with the lowest possible dose of atorvastatin should be considered with titration up to desired clinical effect while monitoring for safety. For patients currently taking atorvastatin, dose reduction of atorvastatin should be considered when starting Victrelis. Additional clinical monitoring is recommended when daily doses of atorvastatin exceed |

| Medicinal products by therapeutic areas | Interaction*<br><br>(postulated mechanism of action, if known) | Recommendations concerning co-administration |
|---|---|---|
| | | 40 mg.<br><br>~~Dose reduction of atorvastatin should be considered. Therapeutic monitoring is recommended when administering Victrelis with simvastatin or atorvastatin, CYP3A4/5 substrates that have a narrow therapeutic window. Individual patients may require additional titration of their statin dosage when Victrelis is started or stopped to ensure clinically effective blood levels~~ |
| Pravastatin<br><br>(pravastatin 40 mg single dose + Victrelis 800 mg three times daily) | boceprevir AUC ↔ 6%<br><br>boceprevir Cmax ↔ 7%<br><br>pravastatin AUC ↑ 63%<br><br>pravastatin Cmax ↑ 49%<br><br>(OATPB1 inhibition) | Concomitant administration of pravastatin with Victrelis increased exposure to pravastatin. Treatment with pravastatin can be initiated at the recommended dose when co-administered with Victrelis. Close clinical monitoring is warranted. |
| *IMMUNOSUPPRESSANTS* | | |
| Cyclosporine<br><br>(cyclosporine 100 mg single dose + Victrelis 800 mg single dose)<br><br>(cyclosporine 100 mg single dose + Victrelis 800 mg three times daily multiple doses) | boceprevir AUC ↔ 16%<br><br>boceprevir $C_{max}$ ↔ 8%<br><br>cyclosporine AUC ↑ 168%<br><br>cyclosporine $C_{max}$ ↑ 101%<br><br>(CYP3A inhibition - effect | Dose adjustments of cyclosporine should be anticipated when administered with Victrelis and should be guided by close monitoring of cyclosporine blood concentrations, and frequent assessments of renal function and cyclosporine-related side effects. |

| Medicinal products by therapeutic areas | Interaction*<br><br>(postulated mechanism of action, if known) | Recommendations concerning co-administration |
|---|---|---|
| | on cyclosporine) | |
| Tacrolimus<br><br>(tacrolimus 0.5 mg single dose + Victrelis 800 mg single dose)<br><br><br><br><br>(tacrolimus 0.5 mg single dose + Victrelis 800 mg three times daily multiple doses) | boceprevir AUC ↔ no change<br><br>boceprevir $C_{max}$ ↔ 3%<br><br><br><br><br><br>tacrolimus AUC ↑ 1610%<br><br>tacrolimus $C_{max}$ ↑ 890%<br><br><br>(CYP3A inhibition - effect on tacrolimus) | Concomitant administration of Victrelis with tacrolimus requires significant dose reduction and prolongation of the dosing interval of tacrolimus, with close monitoring of tacrolimus blood concentrations and frequent assessments of renal function and tacrolimus-related side effects. |
| Sirolimus | Not studied<br><br>(CYP3A inhibition) | Blood concentrations of sirolimus are expected to increase significantly when administered with Victrelis. Close monitoring of sirolimus blood concentrations is recommended, and frequent assessments of renal function and sirolimus-related side effects. |
| *NARCOTIC ANALGESIC* | | |
| Methadone | Not studied<br><br>(CYP3A inhibition) | 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 |

| Medicinal products by therapeutic areas | Interaction*<br><br>(postulated mechanism of action, if known) | Recommendations concerning co-administration |
|---|---|---|
| | | levels. |

Of note, at the CHMP request, the mechanistic explanation for the drug-drug interactions (when understood) has been included in Table 2 of section 4.5 (i.e. ketaconazole, ritonavir, efavirenz, midazolam, triazolam, alprazolam, midazolam, triazolam, methadone, cyclosporine, tacrolimus, sirolimus, atorvastatin, pravastatin).

### 4.6 Fertility, pregnancy and lactation

Section 4.6 was updated to take into account the recent revisions made to soften the requirement for double contraception in the Rebetol SmPC and patient leaflet:

**"Pregnancy**

~~Treated patients and their partners must use two effective forms of contraceptive methods when boceprevir is used in combination with peginterferon alfa and ribavirin.~~

Due to the combined treatment with peginterferon alfa and ribavirin, extreme care must be taken to avoid pregnancy in female patients or in female partners of male patients. Therefore, female patients of childbearing potential must use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients or their female partners must use an effective contraceptive during treatment and for 7 months after treatment has been concluded."

### 5.1 Pharmacodynamic properties

Section 5.1 was updated to delete redundant information regarding the association of the presence of baseline RAVs with treatment response in subjects receiving the combination of Victrelis with peginterferon alfa-2b and ribavirin:

"However, among poorly interferon-responsive patients to peginterferon alfa–2b/ribavirin during the 4-week lead-in period, the efficacy of Victrelis appeared to be reduced for those who had variants V36M, T54A, T54S, V55A or R155K detected at baseline. Subjects with these baseline variants and reduced response to peginterferon alfa–2b/ribavirin represented approximately 1% of the total number of subjects treated with Victrelis. ~~The presence of baseline RAVs did not appear to have a notable association with treatment response in subjects receiving the combination of Victrelis with peginterferon alfa-2b and ribavirin."~~

Changes were also made to the PI to bring it in line with the current QRD template.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative(s) of Ireland, Iceland, Italy, Hungary, Malta, Netherlands, Portugal.



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

The changes to the product information were acceptable to the CHMP. The overall B/R balance for boceprevir remains positive.

# 4. Recommendations

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

| **Variation accepted** | | **Type** |
|---|---|---|
| C.I.4 | Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data | II |

Update of section 4.3 of the SmPC with a new contraindication with simvastatin and lovastatin and section 4.5 of the SmPC with information on interactions with cyclosporine, tacrolimus, sirolimus, escitalopram, atorvastatin and pravastatin. The Package Leaflet is updated in accordance. Change to section 4.6 of the SmPC with new information on contraceptive measures and to section 5.1 of the SmPC with updated information on resistance were also introduced.

Changes were also made to the SmPC, Annex II, Labelling and PL to bring it in line with the current QRD template. In addition, the list of local representatives in the PL has been revised to amend contact details for the representatives of Ireland, Iceland, Italy, Hungary, Malta, Netherlands and Portugal.

In addition, translation mistakes were corrected in the product information for all EU languages.

The requested variation proposed amendments to the update of Summary of Products Characteristics, Annex II, Labelling and Package Leaflet.