ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Victrelis 200 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 200 mg of boceprevir.

Excipient with known effect
Each capsule contains 56 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

Each capsule has 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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 (see sections 4.4 and 5.1).

4.2 Posology and method of administration

Treatment with Victrelis should be initiated and monitored by a physician experienced in the management of chronic hepatitis C.

Posology

Victrelis must be administered in combination with peginterferon alfa and ribavirin. The Summary of Product Characteristics of peginterferon alfa and ribavirin (PR) must be consulted prior to initiation of therapy with Victrelis.

The recommended dose of Victrelis is 800 mg administered orally three times daily (TID) with food (a meal or light snack). Maximum daily dose of Victrelis is 2,400 mg. Administration without food could be associated with a net loss of efficacy due to sub-optimal exposure.

Patients without cirrhosis who are previously untreated or who have failed previous therapy
The following dosing recommendations differ for some subgroups from the dosing studied in the Phase 3 trials (see section 5.1).

Table 1

Duration of therapy using Response-Guided Therapy (RGT) guidelines in patients without cirrhosis who are previously untreated or who have failed previous therapy to interferon and ribavirin therapy

	ASSESSMENT* (HCV-RNA Results†)		**ACTION**
	At Treatment Week 8	**At Treatment Week 24**	
Previously Untreated Patients	Undetectable	Undetectable	*Treatment duration = 28 weeks* 1. Administer peginterferon alfa and ribavirin for 4 weeks, and then 2. Continue with all three medicines (peginterferon alfa and ribavirin [PR] + Victrelis) and finish through Treatment Week 28 (TW 28).
	Detectable	Undetectable	*Treatment duration = 48 weeks*‡ 1. Administer peginterferon alfa and ribavirin for 4 weeks, and then 2. Continue with all three medicines (PR + Victrelis) and finish through TW 36; and then 3. Administer peginterferon alfa and ribavirin and finish through TW 48.
Patients Who have Failed Previous Therapy	Undetectable	Undetectable	*Treatment duration = 48 weeks* 1. Administer peginterferon alfa and ribavirin for 4 weeks, and then 2. Continue with all three medicines (PR + Victrelis) and finish through TW 36, and then 3. Administer peginterferon alfa and ribavirin and finish through TW 48.
	Detectable	Undetectable	

***Stopping rules**

If the patient has hepatitis C virus ribonucleic acid (HCV-RNA) results greater than or equal to 1,000 IU/mL at TW 8; then discontinue three-medicine regimen.

If the patient has HCV-RNA results greater than or equal to 100 IU/mL at TW 12; then discontinue three-medicine regimen.

If the patient has confirmed, detectable HCV-RNA at TW 24; then discontinue three-medicine regimen.

†In clinical trials, HCV-RNA in plasma was measured with the Roche COBAS Taqman 2.0 assay with a limit of detection of 9.3 IU/mL and a limit of quantification of 25 IU/mL.

‡This regimen has only been tested in subjects who have failed previous therapy who were late responders (see section 5.1).

All cirrhotic patients and null responders

- Recommended treatment duration is 48 weeks: 4 weeks of bitherapy with peginterferon alfa+ ribavirin + 44 weeks of tritherapy with peginterferon alfa + ribavirin + Victrelis. (Refer to the stopping rule in Table 1 for all patients.)
    - The duration of the tritherapy after the first 4 weeks of bitherapy should not be less than 32 weeks. Given the incremental risk of adverse events with Victrelis (anaemia notably); in case the patient cannot tolerate the treatment, consideration could be given to pursue with 12 weeks of bitherapy for the final 12 weeks of treatment instead of tritherapy (see sections 4.8 and 5.1). For additional information on use of Victrelis in patients with advanced liver disease, see section 4.4.

Poorly interferon-responsive patients

In poorly interferon responsive patients (defined as < 1-$\log_{10}$ decline in HCV-RNA at TW 4) the use of triple therapy should be considered on a case by case basis, as the likelihood of achieving sustained virologic response (SVR) with triple therapy is lower in these patients (see section 5.1).

Missed doses

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 reduction

Dose reduction of Victrelis is not recommended.

If a patient has a serious adverse reaction potentially related to peginterferon alfa and/or ribavirin, the peginterferon alfa and/or ribavirin dose should be reduced. Refer to the Summary of Product Characteristics for peginterferon alfa and ribavirin for additional information about how to reduce and/or discontinue the peginterferon alfa and/or ribavirin dose. Victrelis must not be administered in the absence of peginterferon alfa and ribavirin.

Stopping rules

Discontinuation of therapy is recommended in all patients with 1) HCV-RNA levels of greater than or equal to 1,000 IU per mL at TW 8; or 2) HCV-RNA levels of greater than or equal to 100 IU per mL at TW 12; or 3) confirmed, detectable HCV-RNA levels at TW 24.

Special populations

Elderly

Clinical studies of boceprevir 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 older and younger patients (see section 5.2).

Renal impairment

No dose adjustment of Victrelis is required in patients with any degree of renal impairment (see section 5.2).

Hepatic impairment

No dose adjustment of Victrelis is required for patients with mild, moderate or severe hepatic impairment. Boceprevir has not been studied in patients with decompensated cirrhosis (see section 5.2). For additional information on use of Victrelis in patients with advanced liver disease, see section 4.4.

Paediatric population
The safety and efficacy of Victrelis in children aged below 18 years have not yet been established. No data are available.

Method of administration

To obtain the hard capsules the foil of the blister should be peeled off. Victrelis is to be taken orally with food (a meal or light snack).

4.3 Contraindications

- Hypersensitivity to the active substance or any of the excipients listed in section 6.1.
- Patients with autoimmune hepatitis.
- 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, lurasidone, lumefantrine, halofantrine, tyrosine kinase inhibitors, simvastatin, lovastatin, quetiapine, alfuzosin, silodosin, and ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine) (see section 4.5).
- Pregnancy (see section 4.6).

Refer to the Summary of Product Characteristics for peginterferon alfa and ribavirin for additional information.

4.4 Special warnings and precautions for use

Anaemia

The onset of anaemia has been reported with peginterferon alfa and ribavirin therapy by Treatment Week 4. The addition of boceprevir to peginterferon alfa and ribavirin is associated with an additional decrease in haemoglobin concentrations of approximately 1 g/dL by Treatment Week 8 compared to standard of care (see section 4.8). In clinical trials with the combination of Victrelis, peginterferon alfa-2b and ribavirin compared to peginterferon alfa-2b and ribavirin alone, the median time from the initiation of therapy to onset of haemoglobin less than 10 g/dL was similar (71 days with a range of 15-337 days, and 71 days with a range of 8-337 days, respectively). Complete blood counts (with white blood cell differential counts) should be obtained at pretreatment, and at Treatment Weeks 2, 4, 8, 12 and should be monitored closely at other time points, as clinically appropriate. If haemoglobin is < 10 g/dL (or < 6.2 mmol/L) management of anaemia may be warranted (see section 4.8).

Ribavirin dose reduction is the preferred strategy for managing treatment-emergent anaemia (see section 5.1). Refer to the Summary of Product Characteristics for ribavirin for information regarding dose reduction and/or discontinuation of ribavirin. If permanent discontinuation of ribavirin is required, then peginterferon alfa and Victrelis must also be discontinued.

In a study comparing the use of ribavirin dose reduction and erythropoesis stimulating agents in the management of treatment-emergent anaemia, the use of erythropoesis stimulating agents was associated with an increased risk of thromboembolic events (see section 5.1).

Neutropenia

The addition of boceprevir to peginterferon alfa–2b and ribavirin resulted in higher incidences of neutropenia and Grade 3-4 neutropenia compared with peginterferon alfa–2b and ribavirin alone (see section 4.8).

The frequency of severe or life threatening infections tends to be higher in boceprevir-containing arms than the control arm. Complete blood counts (with white blood cell differential counts) should be obtained at pretreatment, and at Treatment Weeks 2, 4, 8, 12, and should be monitored closely at other time points, as clinically appropriate. Decreases in neutrophil counts may require dose reduction of peginterferon alfa or discontinuation of therapy. If permanent discontinuation of peginterferon alfa is required, then ribavirin and Victrelis must also be discontinued. Prompt evaluation and treatment of infections is recommended.

Combined use with peginterferon alfa–2a as compared to alfa–2b:
As compared to the combination of boceprevir with peginterferon alfa–2b and ribavirin, the combination of boceprevir with peginterferon alfa–2a and ribavirin was associated with a higher rate of neutropenia (including grade 4 neutropenia) and a higher rate of infections.

Please refer to the Summary of Product Characteristics for peginterferon alfa.

Pancytopenia

Cases of pancytopenia have been reported in patients receiving Victrelis in combination with peginterferon alfa and ribavirin. Complete blood counts (with white blood cell differential counts) should be obtained at pretreatment, and at Treatment Weeks 2, 4, 8, and 12, and should be monitored closely at other time points, as clinically appropriate.

Hypersensitivity

Serious, acute hypersensitivity reactions (e.g., urticaria, angioedema) have been observed during combination therapy with Victrelis, peginterferon alfa, and ribavirin. If such reaction occurs, combination therapy should be discontinued and appropriate medical therapy immediately instituted (see section 4.3 and 4.8).

Patients with advanced liver disease

Safety and efficacy of Victrelis, in combination with peginterferon alfa and ribavirin, have not been studied in patients with decompensated cirrhosis.

Please refer to the Summary of Product Characteristics for peginterferon alfa for the contraindication in patients with decompensated liver disease.

Hypoalbuminemia and low platelet count, as well as severe infections, have been identified as predictive factors of severe complications of liver disease.

Victrelis in combination with peginterferon alfa and ribavirin is not recommended in patients who have platelet count < 100,000/mm^3 and/or serum albumin < 35 g/L and/or signs of coagulopathy (International Normalized Ratio (INR) > 1.7) at baseline. If therapy is initiated, a very close monitoring for signs of infections and worsening liver function is warranted.

Drospirenone-containing medicines

Caution should be exercised in patients taking drospirenone-containing medicines with conditions that predispose them to hyperkalaemia or patients taking potassium-sparing diuretics. Alternative contraceptives should be considered (see section 4.5).

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 (see section 5.1).

It is unknown what effect therapy with Victrelis will have on the activity of subsequently administered HCV protease inhibitors, including re-treatment with Victrelis.

Laboratory testing

Refer to the Summary of Product Characteristics for peginterferon alfa and ribavirin for baseline, on-treatment and post-treatment laboratory testing recommendations including haematology, biochemistry (including hepatic function tests), and pregnancy testing.

HCV-RNA levels should be monitored at Treatment Weeks 8, 12, and 24, and for other time points as clinically indicated.

Complete blood counts (with white blood cell differential counts) should be obtained at pretreatment, and at Treatment Weeks 2, 4, 8, and 12, and should be monitored closely at other time points as clinically appropriate.

Use in patients with HIV co-infection

Boceprevir, in combination with peginterferon alfa and ribavirin, was evaluated in a total of 98 patients (64 in the boceprevir arm) co-infected with Human Immunodeficiency Virus (HIV) and HCV genotype 1 who were previously untreated for chronic HCV infection (see section 4.8 and 5.1). For data regarding drug-drug interactions with antiretroviral agents, see section 4.5.

Use in patients with HBV co-infection

The safety and efficacy of Victrelis alone or in combination with peginterferon alfa 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.

Cases of HBV reactivation, some of them fatal, have been reported during or after treatment with direct-acting antivirals not given in combination with peginterferon alfa and ribavirin. Some cases have also been reported in patients coinfected with hepatitis B and C viruses treated with interferon (refer to the Summary of Product Characteristics for peginterferon alfa for more information on HBV reactivation in patients coinfected with HBV and HCV treated with interferon). HBV screening should be performed in all patients before initiation of treatment. HBV/HCV co-infected patients are at risk of HBV reactivation, and should therefore be monitored and managed according to current clinical guidelines.

Use in patients with an organ transplant

The safety and efficacy of Victrelis alone or in combination with peginterferon alfa and ribavirin for the treatment of chronic hepatitis C genotype 1 infection in liver or other organ transplant recipients have not been studied (see section 4.5).

Use in patients having HCV genotypes other than genotype 1

The safety and efficacy of Victrelis alone or in combination with peginterferon alfa and ribavirin for the treatment of chronic hepatitis C genotypes other than genotype 1 have not been established.

Use in patients who have previously failed treatment with an HCV protease inhibitor

The safety and efficacy of Victrelis alone or in combination with peginterferon alfa and ribavirin for the treatment of chronic hepatitis C genotype 1 infection has not been studied in patients who have failed previous therapy with Victrelis or other HCV protease inhibitors.

Potent CYP3A4 inducers

The concomitant use of Victrelis with potent CYP3A4 inducers (rifampicin, carbamazepine, phenobarbital, phenytoin) is not recommended (see section 4.5).

Alpha-1 adrenoreceptor antagonists

Co-administration of Victrelis with alfuzosin and silodosin is contraindicated (see section 4.3). The concomitant use of Victrelis with doxazosin and tamsulosin is not recommended (see section 4.5).

Proarrhythmic effects:
The data available (see section 5.3) warrant caution in patients at risk of QT prolongation (long congenital QT, hypokalaemia).

Use in patients with rare hereditary disorders

Victrelis contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of 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 reactions (see Table 2). Victrelis does not inhibit or induce the other enzymes of the CYP450.

Boceprevir has been shown to be a p-glycoprotein (P-gp) and breast cancer resistant protein (BCRP) substrate *in vitro*. There is potential for inhibitors of these transporters to increase concentrations of boceprevir; the clinical implications of these interactions are not known. A clinical drug interaction study with digoxin demonstrated that boceprevir is a mild P-gp inhibitor *in vivo*, increasing digoxin exposure by 19%. An increase in plasma concentrations of substrates of the P-gp efflux transporter, such as digoxin or dabigatran, should be anticipated (see table 2).

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 (see section 4.4). 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, lurasidone, lumefantrine, halofantrine, tyrosine kinase inhibitors, simvastatin, lovastatin, quetiapine, alfuzosin, silodosin, and ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine) (see section 4.3).

Boceprevir is primarily metabolized by aldoketo reductase (AKR). In medicine interaction trials conducted with AKR inhibitors diflunisal and ibuprofen, boceprevir exposure did not increase to a clinically significant extent. Victrelis may be co-administered with AKR inhibitors.

The concomitant use of Victrelis with rifampicin or anticonvulsants (such as phenytoin, phenobarbital or carbamazepine) may significantly reduce the plasma exposure of boceprevir. No data are available; therefore, the combination of boceprevir with these medicines is not-recommended (see section 4.4).

The concomitant use of Victrelis with doxazosin or tamsulosin may increase plasma concentrations of these medicines. The combination of boceprevir with these medicines is not recommended (see section 4.4).

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

As liver function may change during treatment with Victrelis, a close monitoring of International Normalised Ratio (INR) values is recommended in patients treated with vitamin K antagonists.

Table 2 provides dosing recommendations as a result of drug interactions with Victrelis. These recommendations are based on either drug interaction studies (indicated with *) or predicted interactions due to the expected magnitude of interaction and potential for serious adverse reactions or loss of efficacy.

The percent change and arrows (↑ = increase, ↓ = decrease, ↔ = no change) are used to show the magnitude and direction of change in mean ratio estimate for each pharmacokinetic parameter.

Table 2
Pharmacokinetic interactions data

Medicinal products by therapeutic areas	**Interaction (postulated mechanism of action, if known)**	**Recommendations concerning co-administration**
ANALGESIC		
Narcotic analgesic/Opioid Dependence		
Buprenorphine/Naloxone* (buprenorphine/naloxone 8/2 – 24/6 mg daily + Victrelis 800 mg three times daily)	buprenorphine AUC ↑ 19% buprenorphine C_{max} ↑ 18% buprenorphine C_{min} ↑ 31% naloxone AUC ↑ 32% naloxone C_{max} ↑ 9% (CYP3A inhibition)	No dose adjustment of buprenorphine/naloxone or Victrelis is recommended. Patients should be monitored for signs of opiate toxicity associated with buprenorphine.
Methadone* (methadone 20-150 mg daily + Victrelis 800 mg three times daily)	*R*-methadone AUC ↓ 15% *R*-methadone C_{max} ↓ 10% *R*-methadone C_{min} ↓ 19% *S*-methadone AUC ↓ 22% *S*-methadone C_{max} ↓ 17% *S*-methadone C_{min} ↓ 26%	Individual patients may require additional titration of their methadone dosage when Victrelis is started or stopped to ensure clinical effect of methadone.
ANTI-ARRYTHMICS		
Digoxin* (0.25 mg digoxin single dose + Victrelis 800 mg three times daily)	digoxin AUC ↑ 19% digoxin C_{max} ↑ 18% (effect on P-gp transport in the gut)	No dose adjustment of digoxin or Victrelis is recommended. Patients receiving digoxin should be monitored appropriately.
ANTI-DEPRESSANTS		
Escitalopram* (escitalopram 10 mg single dose + Victrelis 800 mg three times daily)	boceprevir AUC ↓ 9% boceprevir C_{max} ↑ 2% escitalopram AUC ↓ 21% escitalopram C_{max} ↓ 19%	Exposure of escitalopram was slightly decreased when co-administered with Victrelis. No dose adjustment of escitalopram is anticipated, but doses may need to be adjusted based on clinical effect.

Medicinal products by therapeutic areas	Interaction (postulated mechanism of action, if known)	Recommendations concerning co-administration
ANTI-INFECTIVES		
Antifungals		
Ketoconazole* (ketoconazole 400 mg two times daily + Victrelis 400 mg single dose) Itraconazole, Posaconazole, Voriconazole	boceprevir AUC ↑ 131% boceprevir C_{max} ↑ 41% boceprevir C_{min} N/A (CYP3A inhibition and/or P-gp inhibition) Not studied	Caution should be exercised when boceprevir is combined with ketoconazole or azole antifungals (itraconazole, posaconazole, voriconazole).
Antiretroviral		
HIV Nucleoside Reverse Transcriptase Inhibitor (NRTI)		
Tenofovir* (tenofovir 300 mg daily + Victrelis 800 mg three times daily)	boceprevir AUC ↑ 8%** boceprevir C_{max} ↑ 5% boceprevir C_{min} ↑ 8% tenofovir AUC ↑ 5% tenofovir C_{max} ↑ 32%	No dose adjustment required for Victrelis or tenofovir.
HIV Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI)		
Efavirenz* (efavirenz 600 mg daily + Victrelis 800 mg three times daily)	boceprevir AUC ↓ 19%** boceprevir C_{max} ↓ 8% boceprevir C_{min} ↓ 44% efavirenz AUC ↑ 20% efavirenz C_{max} ↑ 11% (CYP3A 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.
Etravirine* (etravirine 200 mg every 12 hours + Victrelis 800 mg three times daily)	boceprevir AUC ↑ 10% boceprevir C_{max} ↑ 10% boceprevir C_{min} ↓ 12% etravirine AUC ↓ 23% etravirine C_{max} ↓ 24% etravirine C_{min} ↓ 29%	The clinical significance of the reductions in etravirine pharmacokinetic parameters and boceprevir C_{min} in the setting of combination therapy with HIV antiretroviral medicines, which also affect the pharmacokinetics of etravirine and/or boceprevir, has not been directly assessed. Increased clinical and laboratory monitoring for HIV and HCV suppression is recommended.

Medicinal products by therapeutic areas	Interaction (postulated mechanism of action, if known)	Recommendations concerning co-administration
Rilpivirine* (rilpivirine 25 mg every 24 hours + Victrelis 800 mg three times daily)	boceprevir AUC ↓ 6%** boceprevir C_{max} ↓ 2% boceprevir C_{8h} ↑ 4% rilpivirine AUC ↑ 39% rilpivirine C_{max} ↑ 15% rilpivirine C_{min} ↑ 51% (CYP3A inhibition - effect on rilpivirine)	No dose adjustment of Victrelis or rilpivirine is recommended.
HIV Protease Inhibitor (PI)		
Atazanavir/Ritonavir* (atazanavir 300 mg / ritonavir 100 mg daily + Victrelis 800 mg three times daily)	boceprevir AUC ↓ 5% boceprevir C_{max} ↓ 7% boceprevir C_{min} ↓ 18% atazanavir AUC ↓ 35% atazanavir C_{max} ↓ 25% atazanavir C_{min} ↓ 49% ritonavir AUC ↓ 36% ritonavir C_{max} ↓ 27% ritonavir C_{min} ↓ 45%	Co-administration of atazanavir/ritonavir with boceprevir resulted in lower exposure of atazanavir which may be associated with lower efficacy and loss of HIV control. This co-administration might be considered on a case by case basis if deemed necessary, in patients with suppressed HIV viral loads and with HIV viral strain without any suspected resistance to the HIV regimen. Increased clinical and laboratory monitoring for HIV suppression is warranted.
Darunavir/Ritonavir* (darunavir 600 mg / ritonavir 100 mg two times daily + Victrelis 800 mg three times daily)	boceprevir AUC ↓ 32% boceprevir C_{max} ↓ 25% boceprevir C_{min} ↓ 35% darunavir AUC ↓ 44% darunavir C_{max} ↓ 36% darunavir C_{min} ↓ 59% ritonavir AUC ↓ 27% ritonavir C_{max} ↓ 13% ritonavir C_{min} ↓ 45%	It is not recommended to co-administer darunavir/ritonavir and Victrelis.

Medicinal products by therapeutic areas	Interaction (postulated mechanism of action, if known)	Recommendations concerning co-administration
Lopinavir/Ritonavir* (lopinavir 400 mg / ritonavir 100 mg two times daily + Victrelis 800 mg three times daily)	boceprevir AUC ↓ 45% boceprevir C_{max} ↓ 50% boceprevir C_{min} ↓ 57% lopinavir AUC ↓ 34% lopinavir C_{max} ↓ 30% lopinavir C_{min} ↓ 43% ritonavir AUC ↓ 22% ritonavir C_{max} ↓ 12% ritonavir C_{min} ↓ 42%	It is not recommended to co-administer lopinavir/ritonavir and Victrelis.
Ritonavir* (ritonavir 100 mg daily + Victrelis 400 mg three times daily)	boceprevir AUC ↓ 19% boceprevir C_{max} ↓ 27% boceprevir C_{min} ↑ 4% (CYP3A inhibition)	When boceprevir is administered with ritonavir alone, boceprevir concentrations are decreased.
Integrase Inhibitor		
Raltegravir* (raltegravir 400 mg single dose + Victrelis 800 mg three times daily) (raltegravir 400 mg every 12 hours + Victrelis 800 mg three times daily)	raltegravir AUC ↑ 4%*** raltegravir C_{max} ↑ 11% raltegravir C_{12h} ↓ 25% boceprevir AUC ↓ 2% boceprevir C_{max} ↓ 4% boceprevir C_{8h} ↓ 26%	No dose adjustment required for Victrelis or raltegravir. However, since the clinical relevance of the boceprevir C_{8h} decrease has not been established, increased clinical and laboratory monitoring for HCV suppression is recommended.
CCR5 Receptor Antagonists		
Maraviroc* (maraviroc 150 mg two times daily + Victrelis 800 mg three times daily)	maraviroc AUC_{12h} ↑ 202% maraviroc C_{max} ↑ 233% maraviroc C_{12h} ↑ 178% (CYP3A inhibition – effect on maraviroc)	Boceprevir concentrations are not likely to be affected by maraviroc co-administration (based on elimination pathway of boceprevir). Maraviroc 150 mg twice daily when co-administered with boceprevir.

Medicinal products by therapeutic areas	Interaction (postulated mechanism of action, if known)	Recommendations concerning co-administration
ANTIPSYCHOTICS		
Quetiapine	Not studied (CYP3A inhibition – effect on quetiapine)	Concomitant administration of Victrelis and quetiapine may increase plasma concentrations of quetiapine leading to quetiapine-related toxicity, including coma. Co-administration of quetiapine with Victrelis is contraindicated (see section 4.3).
CALCIUM CHANNEL BLOCKERS		
Calcium channel blockers such as amlodipine, diltiazem, felodipine, nicardipine, nifedipine, nisoldipine, verapamil	Not studied (CYP3A inhibition)	Plasma concentrations of calcium channel blockers may increase when administered with Victrelis. Caution is warranted and clinical monitoring of patients is recommended.
CORTICOSTEROIDS		
Prednisone* (prednisone 40 mg single dose + Victrelis 800 mg three times daily)	prednisone AUC ↑ 22% prednisone C_{max} ↓ 1% prednisolone AUC ↑ 37% prednisolone C_{max} ↑ 16%	No dose adjustment is necessary when co-administered with Victrelis. Patients receiving prednisone and Victrelis should be monitored appropriately.

Medicinal products by therapeutic areas	Interaction (postulated mechanism of action, if known)	Recommendations concerning co-administration
HMG CoA REDUCTASE INHIBITORS		
Atorvastatin* (atorvastatin 40 mg single dose + Victrelis 800 mg three times daily)	boceprevir AUC ↓ 5% boceprevir C_{max} ↑ 4% atorvastatin AUC ↑ 130% atorvastatin C_{max} ↑ 166% (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 without exceeding a daily dose of 20 mg. For patients currently taking atorvastatin, the dose of atorvastatin should not exceed a daily dose of 20 mg during co-administration with Victrelis.
Pravastatin* (pravastatin 40 mg single dose + Victrelis 800 mg three times daily)	boceprevir AUC ↓ 6% boceprevir C_{max} ↓ 7% pravastatin AUC ↑ 63% pravastatin C_{max} ↑ 49% (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* (cyclosporine 100 mg single dose + Victrelis 800 mg single dose) (cyclosporine 100 mg single dose + Victrelis 800 mg three times daily multiple doses)	boceprevir AUC ↑ 16% boceprevir C_{max} ↑ 8% cyclosporine AUC ↑ 168% cyclosporine C_{max} ↑ 101% (CYP3A inhibition - effect on cyclosporine)	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 (postulated mechanism of action, if known)	Recommendations concerning co-administration
Tacrolimus* (tacrolimus 0.5 mg single dose + Victrelis 800 mg single dose) (tacrolimus 0.5 mg single dose + Victrelis 800 mg three times daily multiple doses)	boceprevir AUC ↔ boceprevir C_{max} ↓ 3% tacrolimus AUC ↑ 1610% tacrolimus C_{max} ↑ 890% (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* (sirolimus 2 mg single dose + Victrelis 800 mg three times daily)	boceprevir AUC ↓ 5% boceprevir C_{max} ↓ 6% sirolimus $AUC_{0-\infty}$ ↑ 712% sirolimus C_{max} ↑ 384% (CYP3A inhibition – effect on sirolimus)	Concomitant administration of Victrelis with sirolimus requires significant dose reduction and prolongation of the dosing interval for sirolimus, with close monitoring of sirolimus blood concentrations and frequent assessments of renal function and sirolimus-related side effects.
ORAL ANTICOAGULANTS		
Dabigatran	Interaction not studied. (effect on P-gp transport in the gut)	No dose adjustment of dabigatran is recommended. Patients receiving dabigatran should be monitored appropriately.
Vitamin K antagonists	Interaction not studied.	Close monitoring of INR is recommended with all vitamin K antagonists. This is due to liver function changes during treatment with Victrelis.

Medicinal products by therapeutic areas	Interaction (postulated mechanism of action, if known)	Recommendations concerning co-administration
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 - CYP3A inhibition)	Caution should be exercised in patients with conditions that predispose them to hyperkalaemia or patients taking potassium-sparing diuretics (see section 4.4). Alternative contraceptives should be considered for these patients.
Norethindrone†/Ethinyl estradiol: (norethindrone 1 mg daily + ethinyl estradiol 0.035 mg daily + Victrelis 800 mg three times daily)	norethindrone AUC ↓4% norethindrone C_{max} ↓17% ethinyl estradiol AUC ↓ 26% ethinyl estradiol C_{max} ↓ 21%	Co-administration of Victrelis with an oral contraceptive containing ethinyl estradiol and at least 1 mg of norethindrone is unlikely to alter the contraceptive effectiveness. Indeed, serum progesterone, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels indicated that ovulation was suppressed during co-administration of norethindrone 1 mg/ethinyl estradiol 0.035 mg with Victrelis (see section 4.6). The ovulation suppression activity of oral contraceptives containing lower doses of norethindrone/ethinyl estradiol and of other forms of hormonal contraception during co-administration with Victrelis has not been established. Patients using oestrogens as hormone replacement therapy should be clinically monitored for signs of oestrogen deficiency.

Medicinal products by therapeutic areas	Interaction (postulated mechanism of action, if known)	Recommendations concerning co-administration
PROTON PUMP INHIBITOR		
Omeprazole*: (omeprazole 40 mg daily + Victrelis 800 mg three times daily)	boceprevir AUC ↓ 8%** boceprevir C_{max} ↓ 6% boceprevir C_{min} ↑ 17% omeprazole AUC ↑ 6%** omeprazole C_{max} ↑ 3% omeprazole C_{8h} ↑ 12%	No dose adjustment of omeprazole or Victrelis is recommended.
SEDATIVES		
Midazolam* (oral administration) (4 mg single oral dose + Victrelis 800 mg three times daily) **Triazolam** (oral administration)	midazolam AUC ↑ 430% midazolam C_{max} ↑ 177% (CYP3A inhibition) Interaction not studied (CYP3A inhibition)	Co-administration of oral midazolam and oral triazolam with Victrelis is contraindicated (see section 4.3).
Alprazolam, midazolam, triazolam (intravenous administration)	Interaction not studied (CYP3A 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.
** 0-8 hours *** 0-12 hours † Also known as norethisterone.		

4.6 Fertility, pregnancy and lactation

Pregnancy

Victrelis in combination with ribavirin and peginterferon alfa is contraindicated in women who are pregnant (see section 4.3).

No effects on foetal development have been observed in rats and rabbits (see section 5.3). There are no data on the use of Victrelis in pregnant women.

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.

Refer to Summary of Product Characteristics for ribavirin and peginterferon alfa for additional information.

Breast-feeding

Boceprevir/metabolites are excreted in rat milk (see section 5.3). It is not known whether boceprevir is excreted in human breast milk.
A risk to the newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy with Victrelis taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No human data on the effect of Victrelis on fertility are available. Effects on fertility and Sertoli cells have been observed in rats but not in mice and monkeys. Clinical data (semen analyses and inhibin B levels – [a glycoprotein produced by Sertoli cells – used as a surrogate marker of testicular function]) showed no evidence of altered testicular function. Available pharmacodynamic/toxicological data in rats have shown effects of boceprevir/metabolites on fertility, which in females have been shown to be reversible (see section 5.3).

4.7 Effects on ability to drive and use machines

Combination therapy of Victrelis, peginterferon alfa and ribavirin may influence some patients' ability to drive and use machines. Patients should be informed that fatigue, dizziness, syncope, blood pressure fluctuations and blurred vision have been reported (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

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: one in patients who were previously untreated, and one in patients who had failed prior therapy (see section 5.1).

The most frequently reported adverse reactions were fatigue, anaemia (see section 4.4), nausea, headache, and dysgeusia.

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.

Tabulated list of adverse reactions

Adverse reactions are listed by System Organ Class (see Table 3). Within each system organ class, adverse reactions are listed under headings of frequency using the categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); not known (cannot be estimated from the available data).

Table 3
Adverse reactions in combination with Victrelis with peginterferon alfa-2b and ribavirin reported during clinical trials[† and ‡]

System Organ Class	Adverse Reactions
Infections and infestations	
Common:	Bronchitis*, cellulitis*, herpes simplex, influenza, oral fungal infection, sinusitis
Uncommon:	Gastroenteritis*, pneumonia*, staphylococcal infection*, candidiasis, ear infection, fungal skin infection, nasopharyngitis, onychomycosis, pharyngitis, respiratory tract infection, rhinitis, skin infection, urinary tract infection
Rare:	Epiglottitis*, otitis media, sepsis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Rare:	Thyroid neoplasm (nodules)
Blood and lymphatic system disorders	
Very common:	Anaemia*, neutropenia*
Common:	Leukopenia*, thrombocytopenia*, pancytopenia, agranulocytosis
Uncommon:	Haemorrhagic diathesis, lymphadenopathy, lymphopenia
Rare:	Haemolysis
Immune system disorders	
Rare:	Sarcoidosis*, porphyria non-acute
Endocrine disorders	
Common:	Goitre, hypothyroidism
Uncommon:	Hyperthyroidism
Metabolism and nutrition disorders	
Very common:	Decreased appetite*
Common:	Dehydration*, hyperglycaemia*, hypertriglyceridaemia, hyperuricaemia
Uncommon:	Hypokalaemia*, appetite disorder, diabetes mellitus, gout, hypercalcaemia
Psychiatric disorders	
Very common:	Anxiety*, depression*, insomnia, irritability
Common:	Affect lability, agitation, libido disorder, mood altered, sleep disorder
Uncommon:	Aggression*, homicidal ideation*, panic attack*, paranoia*, substance abuse*, suicidal ideation*, abnormal behaviour, anger, apathy, confusional state, mental status changes, restlessness
Rare:	Bipolar disorder*, completed suicide*, suicide attempt*, hallucination auditory, hallucination visual, psychiatric decompensation
Nervous system disorders	
Very common:	Dizziness*, headache*
Common:	Hypoaesthesia*, paraesthesia*, syncope*, amnesia, disturbance in attention, memory impairment, migraine, parosmia, tremour, vertigo
Uncommon:	Neuropathy peripheral*, cognitive disorder, hyperaesthesia, lethargy, loss of consciousness, mental impairment, neuralgia, presyncope
Rare:	Cerebral ischaemia*, encephalopathy

System Organ Class	Adverse Reactions
Eye disorders	
Common:	Dry eye, retinal exudates, vision blurred, visual impairment
Uncommon:	Retinal ischaemia*, retinopathy*, abnormal sensation in eye, conjunctival haemorrhage, conjunctivitis, eye pain, eye pruritus, eye swelling, eyelid oedema, lacrimation increased, ocular hyperaemia, photophobia
Rare:	Papilloedema
Ear and labyrinth disorders	
Common:	Tinnitus
Uncommon:	Deafness*, ear discomfort, hearing impaired
Cardiac disorders	
Common:	Palpitations
Uncommon:	Tachycardia*, arrhythmia, cardiovascular disorder
Rare:	Acute myocardial infarction*, atrial fibrillation*, coronary artery disease*, pericarditis*, pericardial effusion
Vascular disorders	
Common:	Hypotension*, hypertension
Uncommon:	Deep vein thrombosis*, flushing, pallor, peripheral coldness
Rare:	Venous thrombosis
Respiratory, thoracic and mediastinal disorders	
Very common:	Cough*, dyspnoea*
Common:	Epistaxis, nasal congestion, oropharyngeal pain, respiratory tract congestion, sinus congestion, wheezing
Uncommon:	Pleuritic pain*, pulmonary embolism*, dry throat, dysphonia, increased upper airway secretion, oropharyngeal blistering
Rare:	Pleural fibrosis*, orthopnoea, respiratory failure
Gastrointestinal disorders	
Very common:	Diarrhoea*, nausea*, vomiting* dry mouth, dysgeusia
Common:	Abdominal pain*, abdominal pain upper*, constipation*, gastrooesophageal reflux disease*, haemorrhoids*, abdominal discomfort, abdominal distention, anorectal discomfort, aphthous stomatitis, cheilitis, dyspepsia, flatulence, glossodynia, mouth ulceration, oral pain, stomatitis, tooth disorder
Uncommon:	Abdominal pain lower*, gastritis*, pancreatitis*, anal pruritus, colitis, dysphagia, faeces discoloured, frequent bowl movements, gingival bleeding, gingival pain, gingivitis, glossitis, lip dry, odynophagia, proctalgia, rectal haemorrhage, salivary hypersecretion, sensitivity of teeth, tongue discolouration, tongue ulceration
Rare:	Pancreatic insufficiency
Hepatobiliary disorders	
Uncommon:	Hyperbilirubinaemia
Rare:	Cholecystitis*

System Organ Class	Adverse Reactions
Skin and subcutaneous tissue disorders	
Very common:	Alopecia, dry skin, pruritus, rash
Common:	Dermatitis, eczema, erythema, hyperhidrosis, night sweats, oedema peripheral, psoriasis, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, skin lesion
Uncommon:	Photosensitivity reaction, skin ulcer, urticaria (see section 4.4)
Not known:	Angioedema (see section 4.4), drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders	
Very common:	Arthralgia, myalgia
Common:	Back pain*, pain in extremity*, muscle spasms, muscular weakness, neck pain
Uncommon:	Musculoskeletal chest pain*, arthritis, bone pain, joint swelling, musculoskeletal pain
Renal and urinary disorders	
Common:	Pollakiuria
Uncommon:	Dysuria, nocturia
Not known:	Renal impairment
Reproductive system and breast disorders	
Common:	Erectile dysfunction
Uncommon:	Amenorrhoea, menorrhagia, metrorrhagia
Rare:	Aspermia
General disorders and administration site conditions	
Very common:	Asthenia*, chills, fatigue*, pyrexia*, influenza-like illness
Common:	Chest discomfort*, chest pain*, malaise*, feeling of body temperature change, mucosal dryness, pain
Uncommon:	Feeling abnormal, impaired healing, non-cardiac chest pain
Investigations	
Very common:	Weight decreased
Uncommon:	Cardiac murmur, heart rate increased
Not known:	Glomerular filtration rate decreased

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

† Since Victrelis is prescribed with peginterferon alfa and ribavirin, please also refer to the respective Summary of Product Characteristics of peginterferon alfa and ribavirin.

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

Description of selected adverse reactions

Anaemia (see section 4.4)

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 (see section 4.4). 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/haemolytic 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 clinical trials, the proportion of subjects who

received erythropoietin for the management of anaemia was 43% (667/1,548) of subjects in the Victrelis-containing arms compared to 24% (131/547) of subjects receiving peginterferon alfa-2b and ribavirin alone. The majority of the anaemia subjects received erythropoietin when haemoglobin levels were ≤ 10 g/dL (or 6.2 mmol/L). 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 (see section 4.4)
The proportion of subjects with decreased neutrophils was higher in the Victrelis-containing arms compared to subjects receiving only peginterferon alfa-2b and ribavirin. The percentage of patients with Grades 3-4 neutropenia (neutrophil counts < 0.75 x 10^9/L) was higher in boceprevir-treated patients (29%) than in placebo-treated patients (17%), in combination with 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 x 10^9/L (Grade 4 neutropenia) compared to 4% of subjects receiving only peginterferon alfa-2b and ribavirin.

Combined use with peginterferon alfa–2a see specific section in section 4.4.

Platelets
Platelet counts were decreased for subjects in the Victrelis containing-arms (3%) compared to subjects receiving peginterferon alfa-2b and ribavirin alone (1%). In both treatment arms, patients with cirrhosis were at a higher risk to experience Grade 3-4 thrombocytopenia compared with non cirrhotic patients.

Other laboratory findings
The addition of Victrelis to peginterferon alfa–2b and ribavirin was associated to higher incidences of increase in uric acid, triglycerides and cholesterol total compared to peginterferon alfa–2b and ribavirin only.

Patients with HIV co-infection
The safety profile of Victrelis in HCV/HIV-1 co-infected patients (n=64) was overall similar to the safety profile in mono-infected HCV patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Daily doses of 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. Treatment of overdose with Victrelis should consist of general supportive measures, including monitoring of vital signs, and observation of the patient's clinical status.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antivirals for systemic use, protease inhibitors, ATC code: J05AE12

Mechanism of action

Boceprevir 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.

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 genotype 1a and 1b HCV replicon system. The IC_{50} and IC_{90} values for boceprevir against different genotype 1b replicons ranged from 200 to 600 nM and 400 to 900 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-$\log_{10}$ drop in replicon RNA. Prolonged exposure resulted in a 2-log decrease in RNA levels by Day 15. In a genotype 1a replicon, the IC_{50} and IC_{90} values for boceprevir were 900 nM and 1,400 nM, respectively.

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

The activity of boceprevir against the HCV genotype 1a replicon was reduced (2- to 6-fold) by the following amino acid substitutions in the NS3 protease domain: V36A/L/M, Q41R, T54A/S, V55A, R155K and V158I. A greater than 10-fold reduction in boceprevir susceptibility was conferred by the amino acid substitutions R155T and A156S. The V55I and D168N single substitutions did not reduce sensitivity to boceprevir. The following double amino acid substitutions conferred more than 10-fold reduced sensitivity to boceprevir: V55A+I170V, T54S+R155K, R155K+D168N, R155T+D168N and V36M+R155K.

The activity of boceprevir against the HCV genotype 1b replicon was reduced (2- to 8-fold) by the following amino acid substitutions in the NS3 protease domain: V36A/M, F43S, T54A/G/S, V55A, R155K/G, V158I, V170M and M175I. A greater than 10-fold reduction in boceprevir susceptibility was conferred by the amino acid substitutions A156S/T/V, V170A, R155W+A156G and V36M+R155K. The D168V single substitution did not reduce sensitivity to boceprevir.

In a pooled analysis of subjects who were previously untreated and subjects who have failed previous therapy who received four weeks of peginterferon alfa-2b and ribavirin followed by boceprevir 800 mg three times daily in combination with peginterferon alfa-2b and ribavirin in two Phase III studies, post-baseline RAVs were detected in 15% of all subjects. In boceprevir-treated subjects who did not attain sustained virologic response (SVR) for whom samples were analysed, 53% had post-baseline RAVs detected.

The most frequently (> 25% of subjects) detected post-baseline RAVs in these subjects were amino acid substitutions V36M (61%) and R155K (68%) in subjects infected with genotype 1a viruses and T54A (42%), T54S (37%), A156S (26%) and V170A (32%) in subjects infected with genotype 1b viruses.

In subjects treated with boceprevir, interferon responsiveness (as defined by ≥ 1-$\log_{10}$ decline in viral load at Treatment Week 4) was associated with detection of fewer RAVs, with 6% of these subjects having RAVs compared to 41% of subjects with < 1-$\log_{10}$ decline in viral load at Treatment Week 4 (poorly interferon responsive).

In subjects treated with boceprevir who did not achieve SVR and with post-baseline samples analysed for RAVs, interferon responsiveness was associated with detection of fewer RAVs, with 31% of these

subjects having post-baseline RAVs compared to 69% of subjects with < 1-$\log_{10}$ decline in viral load at Treatment Week 4.

RAVs were detected in 8% of patients at baseline by population sequencing. Overall, the presence of baseline RAVs did not appear to have a notable association with treatment response in subjects receiving the combination of boceprevir 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 boceprevir appeared to be reduced for those who had variants V36M, 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 boceprevir.

Follow-up analysis of boceprevir-treated subjects who did not achieve SVR showed that the population of wild-type virus increased and the majority of boceprevir-resistant variants became undetectable over time after the end of boceprevir treatment. Of 314 treatment-naïve and previously treated subjects who did not achieve SVR from Phase 2/3 studies (P03523, P03659, P05216, and P05101) in whom boceprevir-resistant variants had emerged during treatment, 73% (228/314) of subjects no longer had any RAVs detected at the boceprevir-resistance associated loci by population sequencing within 3 years post-therapy. Among the variants, 91% of V36M, 98% of T54A, 71% of T54S, 78% of V55A, 76% of R155K, 92% of A156S, 96% of I/V170A, 71% of R155K+T54S and 95% of R155K+V36M were undetectable by population sequencing. The median time for all RAVs to become undetectable was 1.11 years.

Among the 314 subjects, 230 were infected with genotype 1a HCV and 84 were infected with genotype 1b HCV. Seventy percent (70%) (162/230) of genotype 1a subjects no longer had any RAVs detected at the boceprevir-resistance associated loci by population sequencing. The median time for all RAVs to become undetectable was 1.17 years for genotype 1a. The median times for the most relevant boceprevir-resistant variants observed in genotype 1a patients (> 10%) to become undetectable were as follows: R155K+V36M, 0.69 years; V36M, 0.89 years; R155K+T54S, 1.05 years; R155K, 1.08 years; and T54S, 1.14 years. In comparison, 79% (66/84) of genotype 1b subjects no longer had any RAVs detected at the boceprevir-resistance associated loci by population sequencing. The median time for all RAVs to become undetectable was 1.04 years for genotype 1b. The median times for the most relevant boceprevir-resistant variants observed in genotype 1b patients (> 10%) to become undetectable were as follows: I/V170A, 0.46 years; T54A, 0.47 years; V55A, 0.83 years; A156S, 0.89 years; and T54S, 1.11 years.

Efficacy

The efficacy of Victrelis as a treatment for chronic hepatitis C genotype 1 infection was assessed in approximately 1,300 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 alfa and ribavirin) significantly increased sustained virologic response (SVR) rates compared to the current standard of care alone. It should be noted that retrospective analyses bridging the data between the two pivotal studies have led to a recommended posology that differs from the regimen studied in some patient subgroups.

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 were randomized in a 1:1:1 ratio in two cohorts (Cohort 1 N=

938/non-Black and Cohort 2 /Black N=159) 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 also had undetectable HCV-RNA 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 undetectable 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).

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 medicine (Full-Analysis-Set population) and decreased the length of therapy to 28 weeks for early responders (see Table 4). 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 and a limit of quantification of 25 IU/mL.

Table 4
Sustained Virologic Response (SVR)*, End of Treatment (EOT) and Relapse† Rates for patients who are previously untreated

Study Cohorts	Victrelis-RGT	Victrelis-PR48	PR48
All subjects §	n=368	n=366	n=363
SVR‡ % (n/N) 95% CI	63 (233/368) (58.4, 68.2)	66 (242/366) (61.3, 71.0)	38 (137/363) (32.8, 42.7)
EOT(Undetectable HCV-RNA) % (n/N) 95% CI	71 (261/368) (66.3, 75.6)	76 (277/366) (71.3, 80.1)	53 (191/363) (47.5, 57.8)
Relapse† %(n/N) 95% CI	9 (24/257) (5.8, 12.9)	9 (24/265) (5.6, 12.5)	22 (39/176) (16.0, 28.3)

* The Full Analysis Set (FAS) consisted of all randomized subjects (N=1,097) who received at least one dose of any study medicine (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.

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

‡ SVR: defined as undetectable[1] plasma HCV-RNA at Follow-up Week (FW) 24. If other HCV-RNA values were available after FW 24, the last available value in the period after FW 24 was used. If there were no such values at and after FW 24, the FW 12 value was used. SVR rates with "missing=failure" approach were nearly identical to those in the table: 37% for Control, 62% for Victrelis-RGT, 65% for Victrelis-PR48.

§ The number of subjects with cirrhosis is limited (where 40 subjects were treated with Victrelis of the total of 53 subjects).

Interferon-responsiveness (as defined by ≥ 1-$\log_{10}$ decline in viral load at TW 4) was predictive of SVR. In subjects who demonstrated interferon responsiveness by TW 4, treatment with the combination of Victrelis with peginterferon alfa-2b and ribavirin resulted in SVR rates of 79-81%, compared to 51% in subjects treated with standard of care. 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 subjects treated with standard of care.

Sustained Virologic Response (SVR) in patients receiving similar therapy up to treatment week 28

Table 5 presents sustained virologic response per treatment arm in previously untreated patients who were early responders and late responders and that received similar therapy up to treatment week 28. Fifty-seven percent (208/368) of subjects in the Victrelis-RGT arm and 56% (204/366) of subjects in the Victrelis-PR48 arm had undetectable HCV-RNA at TW 8 compared with 17% (60/363) of subjects in the PR arm.

[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 and a limit of quantification of 25 IU/mL.

Table 5
Sustained Virologic Response (SVR), End of Treatment (EOT), and Relapse in previously untreated patients (early and late responders)

	Victrelis-RGT	**Victrelis-PR48**	**Point estimate of the difference (Victrelis-RGT minus Victrelis-PR48) [95% CI]**
Early Responders (N=323)			
SVR %, (n/N)	96.3 (156/162)	96.3 (155/161)	0.0 [-4.1, 4.1]
EOT %, (n/N)	100.0 (162/162)	98.8 (159/161)	-
Relapse %, (n/N)	3.1 (5/161)	1.3 (2/157)	-
Late responders (N=141)			
SVR %, (n/N)	66.2 (45/68)	75.3 (55/73)	-9.2 [-24.4, 6.3]
EOT %, (n/N)	76.5 (52/68)	90.4 (66/73)	-
Relapse %, (n/N)	13.5 (7/52)	14.1 (9/64)	-

As a conservative measure in view of the limitations of the data, in treatment naïve patients–late responders, the treatment duration of the tritherapy is recommended to be prolonged to 32 weeks as compared to the tested 24 weeks duration of the tritherapy, for a total treatment duration of 48 weeks.

Patients with HIV co-infection

P05411 was a phase II randomized, double-blind, placebo-controlled study comparing 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)] to PR alone in subjects co-infected with HIV and HCV genotype 1 who were previously untreated for chronic HCV infection. Subjects were treated with 4 weeks of PR followed by 44 weeks of Victrelis or placebo with PR. Subjects were on an antiretroviral regimen with stable HIV disease (HIV-1 viral load < 50 copies/mL and CD4 count ≥ 200 cells/µL). The majority of subjects (87%; 85/98) were taking a ritonavir-boosted HIV protease inhibitor (PI) combined with HIV nucleoside reverse transcriptase inhibitors (NRTIs). The most common HIV PI taken was atazanavir followed by lopinavir and darunavir. Subjects were randomized in a 2:1 ratio and stratified based on cirrhosis/fibrosis and baseline HCV-RNA (< 800,000 IU/mL vs. ≥ 800,000 IU/mL).

The SVR rate was 62.5% (40/64) in subjects treated with Victrelis in combination with PR and 29.4% (10/34) in subjects treated with PR alone (see Table 6).

In the limited number of co-infected subjects who did not achieve SVR and for whom population sequencing was performed, the prevalence of post-baseline RAVs was higher than that in mono-infected subjects in study SPRINT-2.

Table 6
Sustained Virologic Response (SVR)*, End of Treatment (EOT) and HCV Relapse Rates† in previously untreated subjects with HIV co-infection

	Victrelis-PR48	PR48
SVR‡ % (n/N)	62.5% (40/64)	29.4% (10/34)
EOT % (n/N)	65.6% (42/64)	29.4% (10/34)
Relapse %(n/N)	4.8% (2/42)	10% (1/10)

* The Full Analysis Set (FAS) consisted of all randomized subjects (N=98) who received at least one dose of any study medicine (peginterferon alfa–2b, ribavirin, or Victrelis). Mean age of subjects randomized was 43.6 years. The race distribution of subjects was as follows: 82% White, 18% Non-White, 14% Black, 3% Asian, and 1% Multiracial. The distribution of subjects by gender was 69% men and 31% women. The study included 5 subjects with cirrhosis and 4 were in the Victrelis arm.

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

‡ SVR: defined as undetectable[1] plasma HCV-RNA at Follow-up Week (FW) 24. The last available value in the period at and after FW 24. If there is no such value, the FW 12 value was carried forward.

Patients who have failed previous therapy: previous partial responders and relapsers to interferon and ribavirin 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 alfa and ribavirin. Null responders (as defined historically by a decrease in HCV-RNA viral load < 2 $\log_{10}$ by Week 12 to prior therapy) were excluded. Subjects were randomized in a 1:2:2 ratio and stratified based on response to their previous qualifying regimen (relapsers vs. partial 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).

[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 and a limit of quantification of 25 IU/mL.

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[1] 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 medicine (Full-Analysis-Set population) and decreased the length of therapy to 36 weeks for many previous treatment failures (see Table 7). 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 7). 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.

Table 7
Sustained Virologic Response (SVR)[*], End of Treatment (EOT), and Relapse[**] Rates for patients who have failed previous therapy

			Victrelis-EOT (N=162)	Victrelis-PR48 (N=161)	PR48 (N=80)
All Subjects[§]		SVR[‡‡] % (n/N) 95% CI	59 (95/162) (51.5, 66.2)	66 (107/161) (59.2, 73.8)	21 (17/80) (12.3, 30.2)
		EOT %, (n/N) 95% CI	70 (114/162) (63.3, 77.4)	77 (124/161) (70.5, 83.5)	31 (25/80) (21.1, 41.4)
		Relapse[**] %, (n/N) 95% CI	15 (17/111) (8.6, 22.0)	12 (14/121) (5.9, 17.3)	32 (8/25) (17.3, 50.3)
Previous Treatment Response	**Previous Partial Responders**[***]	SVR[‡‡] %, (n/N)	40 (23/57)	52 (30/58)	7 (2/29)
		EOT %, (n/N)	54 (31/57)	60 (35/58)	10 (3/29)
		Relapse[**] %, (n/N)	18 (5/28)	14 (5/35)	33 (1/3)
	Previous Relapsers[†]	SVR[‡‡] %, (n/N)	69 (72/105)	75 (77/103)	29 (15/51)
		EOT % (n/N)	79 (83/105)	86 (89/103)	43 (22/51)
		Relapse[**] %, (n/N)	14 (12/83)	10 (9/86)	32 (7/22)

[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 and a limit of quantification of 25 IU/mL.

			Victrelis-RGT (N=162)	Victrelis-PR48 (N=161)	PR48 (N=80)
Lead-In Response‡ (Viral Load Reduction)	**< 1-log$_{10}$ decline**	SVR‡‡ %, (n/N)	33 (15/46)	34 (15/44)	0 (0/12)
		EOT %, (n/N)	41 (19/46)	48 (21/44)	0 (0/12)
		Relapse** %, (n/N)	12 (2/17)	25 (5/20)	0 (0/0)
	≥ 1-log$_{10}$ decline	SVR‡‡ %, (n/N)	73 (80/110)	79 (90/114)	25 (17/67)
		EOT %, (n/N)	86 (95/110)	89 (101/114)	37 (25/67)
		Relapse** %, (n/N)	16 (15/94)	9 (9/99)	32 (8/25)

* The Full Analysis Set (FAS) consisted of all randomized subjects (N=403) who received at least one dose of any study medicine (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.

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

*** Previous Partial 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 and had detectable HCV-RNA at End of Treatment (EOT).

† 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.

‡‡ SVR: defined as undetectable[1] plasma HCV-RNA at Follow-up Week (FW) 24. If other HCV-RNA values were available after FW 24, the last available value in the period after FW 24 was used. If there were no such values at and after FW 24, the FW 12 value was used. SVR rates with "missing=failure" approach were 17/80 [21.3%] for PR48, 94/162 [58.0%] for Victrelis-RGT, 106/161 [65.8%] for Victrelis-PR48.

§ The number of subjects with cirrhosis is limited (where 39 subjects were treated with Victrelis of the total of 49 subjects).

Sustained Virologic Response (SVR) in patients receiving similar therapy up to treatment week 36

Table 8 presents sustained virologic response per treatment arm in patients who had failed previous therapy that were early responders and late responders and that received similar therapy up to treatment week 36.

[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 and a limit of quantification of 25 IU/mL.

Table 8
Sustained Virologic Response (SVR), End of Treatment (EOT) and Relapse in patients who had failed previous therapy (early and late responders)

	Victrelis-RGT	**Victrelis-PR48**	**Point estimate of the difference (Victrelis-RGT minus Victrelis-PR48) [95% CI]**
Early Responders (N=144)			
SVR %, (n/N)	88.7 (63/71)	97.3 (71/73)	-8.5 [-16.8, -0.3]
EOT %, (n/N)	98.6 (70/71)	98.6 (72/73)	-
Relapse %, (n/N)	10.1 (7/69)	0 (0/71)	-
Late responders (N=75)			
SVR %, (n/N)	80.0 (28/35)	72.5 (29/40)	7.5 [-11.7, 26.7]
EOT %, (n/N)	97.1 (34/35)	92.5 (37/40)	-
Relapse %, (n/N)	17.6 (6/34)	19.4 (7/36)	-

As a conservative measure in view of limitations of the data, in treatment experienced patients early responders, the total treatment duration is recommended to be prolonged to 48 weeks as compared to the tested 36 weeks total treatment duration (tested RGT), with a 12 weeks of peginterferon ribavirin consolidation phase after the end of the tritherapy at week 36.

A study with peginterferon alfa–2a in treatment experienced patients gave consistent results as compared to the study P05101 (see section 4.4).

Patients who failed previous therapy: prior null responders, partial responders and relapsers to interferon and ribavirin therapy

PROVIDE (P05514) was an open-label, single-arm study 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] in adult subjects with chronic hepatitis C (HCV) genotype 1 infection who did not achieve SVR while in the PR control arms of previous Phase 2 and 3 studies of combination therapy with Victrelis. Subjects who enrolled in PROVIDE within 2 weeks after the last dose of PR in the parent study received Victrelis 800 mg three times daily + PR for 44 weeks. Subjects who were not able to enrol in this study within 2 weeks received PR for 4 weeks followed by Victrelis 800 mg three times daily + PR for 44 weeks.

The subjects included 62% (104/168) genotype 1a and 38% (63/168) genotype 1b. Ten percent of subjects (17/168) were cirrhotic, including 3 (6%) prior null responders, 2 (7%) prior relapsers, and 12 (14%) prior partial responders.

The SVR rates for subjects who received at least one dose of any study medication (Intent-to-Treat population) are shown in Table 9. The SVR rates for those who received at least one dose of Victrelis (i.e. excluding patients who discontinued during PR lead-in) are 41% for null responders, 67% for partial responders and 96% for relapsers.

Table 9

Sustained Virologic Response (SVR)*, End of Treatment (EOT) and Relapse** Rates for subjects who failed previous therapy

	Null responders* in parent study (52)**	**Partial responders**** in parent study (85)**	**Relapsers† in the parent study (29)**	**All (168)**
SVR§ % (n/N)	38% (20/52)	67% (57/85)	93% (27/29)	63% (106/168)
EOT % (n/N)	44% (23/52)	82% (70/85)	97% (28/29)	73% (123/168)
Relapse** %(n/N)	13% (3/23)	15% (10/67)	0% (0/27)	11% (13/119)

* The Intent-to-Treat (ITT) population consisted of all subjects (N=168) who received at least one dose of any study medicine (peginterferon alfa-2b, ribavirin, or Victrelis). The race distribution of subjects was as follows: 84% white, 13% Black, 2% Asian, and 1% others. The distribution of subjects by gender was 67% men and 33% women.

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

*** Null responder: subject who had less than a 2-$\log_{10}$ HCV-RNA decline by treatment week 12 with peginterferon alfa-2b and ribavirin.

**** Partial Responder: subject who failed to achieve SVR after at least 12 weeks of previous treatment with peginterferon alfa-2b and ribavirin, but demonstrated a $\geq$2 $\log_{10}$ reduction in HCV-RNA by Week 12 and had detectable HCV-RNA at End of Treatment (EOT).

† Relapser: subject who failed to achieve SVR after at least 12 weeks of previous treatment with peginterferon alfa-2b and ribavirin, but had undetectable HCV-RNA at the end of treatment.

§ SVR: defined as undetectable[1] plasma HCV-RNA at Follow-up Week (FW) 24. If other HCV-RNA values were available after FW 24, the last available value in the period after FW 24 was used. If there were no such values at and after FW 24, the FW 12 value was used.

Long-term efficacy data

A 3-year follow-up study of subjects who achieved SVR with a Victrelis-based regimen showed that > 99% (693/696) of patients maintained their SVR (no relapse) through the available follow-up period (median duration of 3.4 years).

Exploratory pharmacogenomic analysis of IL28B in phase 3 studies of Victrelis

A genetic variant near the gene encoding interferon-lambda-3 (*IL28B* rs12979860, a C to T change) is a strong predictor of response to peginterferon alfa–2b/ribavirin. *IL28B* rs12979860 was genotyped in 653 of 1,048 (62%) subjects in SPRINT-2 (previously untreated) and 259 of 394 (66%) subjects in RESPOND-2 (previous treatment failure) [see section 5.1 for the clinical trial descriptions]. The results of this retrospective subgroup analysis should be viewed with caution because of the small sample size and potential differences of the sub-study population relative to the overall trial population.

The degree of added value of Victrelis on top of the bitherapy in C/C patients will depend on the likelihood of achieving SVR with the bitherapy only. In C/C patients receiving tritherapy 89% in treatment naive were HCV-RNA undetectable by TW 8 and eligible for shorter duration of therapy as compared to 52% in treatment naïve non C/C.

[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 and a limit of quantification of 25 IU/mL.

Table 10
Sustained Virologic Response (SVR) rates by *IL28B* rs12979860 genotype

Clinical Study	*IL28B rs12979860* Genotype	PR48* SVR, % (n/N)	Victrelis-RGT* SVR, % (n/N)	Victrelis-PR48* SVR, % (n/N)
SPRINT-2 (previously untreated subjects)	C/C	78 (50/64)	82 (63/77)	80 (44/55)
	C/T	28 (33/116)	65 (67/103)	71 (82/115)
	T/T	27 (10/37)	55 (23/42)	59 (26/44)
RESPOND-2 (subjects who have failed previous therapy)	C/C	46 (6/13)	79 (22/28)	77 (17/22)
	C/T	17 (5/29)	61 (38/62)	73 (48/66)
	T/T	50 (5/10)	55 (6/11)	72 (13/18)

*Please see section 5.1 clinical trial descriptions for each treatment arm.

Whether on treatment early viral response and/or IL28B genotype could reliably identify those patients who are unlikely to retrieve significant benefit of boceprevir (higher SVR rates or short course treatment duration) on top of the bitherapy is currently under investigation.

Use of ribavirin dose reduction versus erythropoietin in the management of anaemia in previously untreated subjects

A randomized, parallel-arm, open-label study (P06086) was conducted to compare two strategies for the management of anaemia (use of erythropoietin versus ribavirin dose reduction) in 687 subjects including 60 cirrhotic patients with previously untreated CHC genotype 1 infection who became anaemic during therapy with 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].

If serum haemoglobin concentrations continued to decrease to ≤ 8.5 g/dL, subjects could be treated with additional anaemia interventions, including the use of erythropoietin or ribavirin dose reduction.

The SVR rates in subjects randomized to receive ribavirin dose reduction and randomized to receive erythropoietin were comparable.

Table 11
Sustained Virologic Response (SVR) * and Relapse† Rates for using ribavirin dose reduction versus erythropoietin in the management of anaemia in previously untreated subjects

	Subjects randomized to receive ribavirin dose reduction (N=249)	Subjects randomized to receive erythropoietin (N=251)
SVR‡ % (n/N)	71.5% (178/249)	70.9% (178/251)
Relapse % (n/N)	9.7% (19/196)	9.6% (19/197)

* The Full Analysis Set (FAS) consisted of all subjects who became anaemic (serum haemoglobin of approximately ≤10 g/dL within the treatment period) and were randomized to using either ribavirin dose reduction or erythropoietin (N=500). Mean age of subjects randomized was 49 years. The race distribution of subjects was as follows: 77% White, 19% Black, and 4% others. The distribution of subjects by genders was 37% men and 63% women.

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

‡ SVR: defined as undetectable[1] plasma HCV-RNA at Follow-up Week (FW) 24. If other HCV-RNA values were available after FW 24, the last available value in the period after FW 24 was used. If there were no such values at and after FW 24, the FW 12 value was used. SVR rates with "missing=failure" approach were similar to those in the table: 69.9% (174/249) for subjects randomized to receive ribavirin dose reduction; 68.5% (172/251) for subjects randomized to receive erythropoietin.

There were 77 subjects who received ≥ 5 steps ribavirin dose reduction for the management of anaemia. For most of these subjects (n=54), the lowest dose of ribavirin received for at least 14 days was ≥ 600mg/day. A limited number of subjects (n=12) received ≤ 200mg/day of ribavirin for at least 14 days.

The treatment discontinuation rate due to anaemia was 2% (5/249) in subjects randomized to receive ribavirin dose reduction and 2% (6/251) in subjects randomized to receive erythropoietin. The transfusion rate was 4% (10/249) in subjects randomized to receive ribavirin dose reduction and 2% (5/251) in subjects randomized to receive erythropoietin.

The use of erythropoesis stimulating agents was associated with an increased risk of thromboembolic events including pulmonary embolism, acute myocardial infarction, cerebrovascular accident, and deep vein thrombosis.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Victrelis in one or more subsets of the paediatric population in chronic viral hepatitis C (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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.

[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 and a limit of quantification of 25 IU/mL.

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 Victrelis has not been studied.

Effects 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 is 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.

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. At steady-state, the exposure ratio for the two diastereomers is approximately 2:1, with the predominant diastereomer being pharmacologically active.

Biotransformation

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. 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. For additional information on use of Victrelis in patients with advanced liver disease, see section 4.4.

Renal impairment
No clinically significant differences in pharmacokinetic parameters were observed between patients with end-stage renal disease (ESRD) and healthy subjects. Boceprevir is not eliminated by dialysis. No dose adjustment is required in these patients and in patients with any degree of renal impairment.

Gender
No gender-related pharmacokinetic differences in the phase III studies 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.

5.3 Preclinical safety data

In an *in vitro* dog Purkinje fiber study, boceprevir prolonged the action potential duration with inverse frequency dependence; the clinical relevance remains uncertain.

In repeat-dose toxicity studies boceprevir showed testicular degeneration in rats at systemic exposures lower than those in humans at the recommended human therapeutic dose. This is not observed in mice or monkeys.

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

In 2-year carcinogenicity studies, no carcinogenicity was observed, but there was an increased incidence of hepatocellular adenomas in mice, which was not statistically significant, at systemic exposures 5.7-fold higher than those in humans at the recommended therapeutic dose. No carcinomas or adenomas were observed in rats. The hepatocellular tumours are considered due to enzyme induction and therefore not relevant for humans.

Boceprevir/medicine derived material was shown to be transferred into the milk of lactating rats. Exposure to boceprevir in nursing human infants is estimated to be less than 1% of the dose.

In rats, boceprevir induced reversible effects on fertility and early embryonic development in female rats at exposures 1.2-fold the human exposure at the recommended therapeutic dose. Decreased fertility was also observed in male rats, most likely as a consequence of testicular degeneration (no testicular degeneration has been observed in mice or monkeys). Boceprevir was shown to be devoid of embryonic or teratogenic potential in both rats and rabbits at maternotoxic dose levels.

Data obtained in juvenile rats suggest that the pharmacokinetic profile of boceprevir may be different than in adult rats, possibly due to immaturity of some metabolic pathways. No clinical paediatric exposure data is available (see section 4.2).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents:

Sodium lauryl sulfate
Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Pre-gelatinized starch
Magnesium stearate

Capsule shell:

Gelatin

Titanium dioxide (E171)
Yellow iron oxide (E172)
Red iron oxide (E172)

Red printing ink containing:

Shellac
Red iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Storage by the pharmacist
Store in a refrigerator (2°C – 8°C).

Storage by the patient

- Store in a refrigerator (2°C – 8°C) until expiry.

OR

- Store outside of the refrigerator at or below 30°C for a period of not more than 3 months until expiry. After this period, the medicinal product should be disposed.

Store in the original blister in order to protect from moisture.

6.5 Nature and contents of container

Clear polychlorotrifluoroethylene /PVC/aluminium blisters containing 4 hard capsules per blister cavity. Each blister cavity is heat sealed closed with the peelable lidding in a configuration of 3 blister cavities per blister card and packaged.
Pack sizes: carton of 84 hard capsules and multipack containing 336 (4 packs of 84) hard capsules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/704/001
EU/1/11/704/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 July 2011
Date of latest renewal: 18 February 2016

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency: http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

S-P Labo NV
Industriepark 30
B-2220 Heist-op-den-Berg
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

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

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

The PEM should contain the following key elements:

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton with Blue Box

1. NAME OF THE MEDICINAL PRODUCT

Victrelis 200 mg hard capsules
boceprevir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 200 mg boceprevir.

3. LIST OF EXCIPIENTS

Also contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 336 (4 packs of 84) hard capsules
84 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Do not push through blister.
Take with food.
Take 3 times per day; morning, afternoon and evening.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Storage by the pharmacist
Store in a refrigerator.

Storage by the patient
- Store in a refrigerator until expiry.

OR
- Store outside of the refrigerator at or below 30°C for a period of not more than 3 months until expiry.

Store in the original blister in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/704/001 336 hard capsules
EU/1/11/704/002 84 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Victrelis

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Inner carton without Blue Box

1. NAME OF THE MEDICINAL PRODUCT

Victrelis 200 mg hard capsules
boceprevir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 200 mg boceprevir.

3. LIST OF EXCIPIENTS

Also contains lactose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

84 hard capsules. Component of a multipack, can't be sold separately

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Do not push through blister.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

- Store in a refrigerator until expiry.

OR

- Store outside of the refrigerator at or below 30°C for a period of not more than 3 months until expiry.

Store in the original blister in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused product or waste material should be disposed of in accordance with local requirements

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/704/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Victrelis

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:

NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Victrelis 200 mg hard capsules
boceprevir

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Open here

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Victrelis 200 mg hard capsules
boceprevir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Victrelis is and what it is used for

What Victrelis is
Victrelis contains the active ingredient boceprevir which helps to fight against hepatitis C infection by stopping the virus multiplying. Victrelis must always be used together with two other medicines. These are called peginterferon alfa and ribavirin. Victrelis must not be used by itself.

What Victrelis is used for
Victrelis, in combination with peginterferon alfa and ribavirin, is used for chronic hepatitis C virus infection in adults (also called HCV infection).
Victrelis may be used in adults who are previously untreated for HCV infection or who have previously used medicines called 'interferons' and 'pegylated interferons'.

How Victrelis works
Victrelis inhibits the direct replication of the virus and contributes in this way to lowering the amount of hepatitis C virus in your body.

2. What you need to know before you take Victrelis

Do not take Victrelis in combination with peginterferon alfa and ribavirin if you:
- are **allergic** to boceprevir or any of the other ingredients of this medicine (listed in section 6)
- are **pregnant**
- have a condition called 'autoimmune hepatitis'
- are taking bepridil, pimozide, lurasidone, oral midazolam, oral triazolam, simvastatin, lovastatin, alfuzosin, silodosin, 'ergot' type medicines (such as dihydro-ergotamine, ergonovine, ergotamine or methylergonovine), lumefantrine, halofantrine, quetiapine, or tyrosine kinase inhibitors.

Do not take Victrelis if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Victrelis.
Reminder: Please also read the "Do not use" section of the Package Leaflets for peginterferon alfa and ribavirin before you start taking Victrelis.

Warnings and precautions
Talk to your doctor or pharmacist before taking your medicine if you:
- have ever had a blood problem such as **anaemia** (when you lack enough healthy red blood cells, which transport oxygen around your body)
- have ever had a blood problem such as neutropenia (lack of a certain type of white blood cells). Neutropenia affects the body's ability to fight off infections
- have ever had a blood problem such as pancytopenia (a combination of low platelet, red and white blood cell counts)
- have a current or previous infection with the hepatitis B virus, since your doctor may want to monitor you more closely
- have liver failure
- have another **liver** problem in addition to hepatitis C infection
- have **HIV** (human immunodeficiency virus) or have ever had any other problems with your immune system
- were an organ transplant recipient
- have hepatitis C other than genotype 1
- were a patient who has previously failed treatment with an HCV protease inhibitor
- have or anyone in your family has an irregular heartbeat, especially a condition called "QT prolongation"
- have low blood potassium (hypokalaemia)

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking Victrelis.

While taking the combination of Victrelis with ribavirin and peginterferon alpha, serious allergic reactions have been reported. Please see "Possible side effects" for more information.

Tests
Your doctor will have your blood tested regularly. These blood tests are done for a number of reasons:
- so your doctor knows if the treatment is working for you
- to help your doctor decide how long you will be treated with Victrelis.
- to check for side effects.

Other medicines and Victrelis
Tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines obtained without a prescription and herbal medicines.

In particular, do not take Victrelis if you are taking any of the following medicines:
- alfuzosin and silodosin – used to treat symptoms of an enlarged prostate
- bepridil – used for heart problems
- pimozide or lurasidone – used for mental health problems
- oral midazolam or oral triazolam – a sedative, given by mouth
- statins – simvastatin or lovastatin
- 'ergot' type medicines, such as dihydro-ergotamine, ergonovine, ergotamine or methylergonovine – used for migraine and cluster headaches
- lumefantrine and halofantrine – anti-malaria medicines
- quetiapine - used to treat schizophrenia, bipolar disorder and major depressive disorder
- tyrosine kinase inhibitors – used as anti-cancer medicines

Do not take Victrelis if you are taking any of the medicines above. If you are not sure, talk to your doctor or pharmacist before taking Victrelis.

Also, tell your doctor or pharmacist if you are taking any of the following:
- birth control medicines - drospirenone
- CYP3A4 inducer medicines (such as antibiotic medicine - rifampicin, and anticonvulsant medicines - carbamazepine, phenobarbital, phenytoin)
- antiarrhythmic medicines- amiodarone, quinidine
- antimicrobial medicine – pentamidine
- some neuroleptics
- antifungal medicines - ketaconazole, itraconazole, posaconazole, voriconazole
- HIV non-nucleoside reverse transcriptase inhibitor – efavirenz, etravirine
- HIV protease inhibitors – atazanavir, darunavir, lopinavir, ritonavir
- intravenous sedatives - benzodiazepines (e.g., alprazolam, midazolam, triazolam)
- immunosuppressants – tacrolimus, sirolimus, cyclosporine
- select statins - atorvastatin or pravastatin
- methadone
- hormonal replacement therapy - oestrogen-based medicines
- medicine used to decrease blood pressure - calcium channel blockers (e.g., amlodipine, diltiazem, felodipine, nicardipine, nifedipine, nisoldipine, verapamil)
- medicine used to treat symptoms of an enlarged prostate – doxazosin and tamsulosin
- warfarin and other similar medicines called vitamin K antagonists used to thin the blood. Your doctor may need to increase the frequency of your blood tests to check how well your blood can clot.

Pregnancy and breast-feeding
Pregnancy must be avoided due to the use of Victrelis with ribavirin. Ribavirin can be very damaging to an unborn baby. Therefore, you and your partner must take **special precautions** in sexual activity if there is any chance for pregnancy to occur:

- if you are a **woman** of childbearing age who is taking ribavirin:
you must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You must use an effective birth control during the time you are taking ribavirin and for 4 months after stopping treatment. This should be discussed with your doctor.
- if you are a **man** who is taking ribavirin:
do not have sex with a pregnant woman unless you **use a condom**. This will lessen the possibility for ribavirin to be left in the woman's body. If your female partner is not pregnant but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. You or your partner must use an effective birth control during the time you are taking ribavirin and for 7 months after stopping treatment. This should be discussed with your doctor.

It is possible that boceprevir is excreted in human milk. If you are breast-feeding, your doctor will advise you to discontinue breast-feeding or to discontinue Victrelis while breast-feeding.

Reminder: Please also read the “Pregnancy and breast-feeding” section of the Package Leaflets for peginterferon alfa and ribavirin before you start taking Victrelis.

Driving and using machines
Victrelis does not affect your ability to drive or use tools or machines. However, the combination therapy of Victrelis, peginterferon alfa and ribavirin may make you feel tired, faint, a sensation of your head spinning, changes in blood pressure, confused or difficulty seeing clearly. If this happens, do not drive or use any tools or machines.

Victrelis contains lactose
Victrelis contains lactose (a type of sugar). If you have been told by your doctor that you cannot tolerate or digest some sugars (you have an intolerance to some sugars), such as Lapp lactase deficiency, or glucose-galactose malabsorption, talk to your doctor before taking this medicine.

3. How to take Victrelis

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

How much to take
The recommended dose of Victrelis is 4 capsules three times a day (a total of 12 capsules a day). Take the capsules in the morning, afternoon and evening with a meal or light snack. The use without food could seriously compromise your chance of success of treatment.

How to take this medicine
- Peel back the tab to get to the capsule - do not push the capsule through the blister since pushing the capsule through the package may break the capsule.
- Take this medicine by mouth.
- This medicine should be taken with a meal or light snack.
- Victrelis is always taken in combination with peginterferon alfa and ribavirin.
- The duration of the administration of these medicines will depend on your response and treatment plan.

Reminder: Please also read the "Possible side effects" in the Package Leaflets for peginterferon alfa and ribavirin before you start taking Victrelis.

If you take more Victrelis than you should
If you take more Victrelis than you should, talk to a doctor or go to the nearest hospital emergency room straight away.

If you forget to take Victrelis
- If you forget a dose and it is more than 2 hours before your next dose is due, take the missed dose with food. Then continue taking your capsules as normal.
- However, if it is less than 2 hours before your next dose is due, skip the missed dose.
- Do not take a double dose to make up for a forgotten dose.

If you have any questions about what to do, talk to your doctor.

If you stop taking Victrelis
Do not stop taking Victrelis unless your doctor tells you to.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist because your treatment may not work.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects may happen with this medicine:
Stop taking Victrelis and see a doctor straight away if you notice any of the following serious side effects – you may need urgent medical treatment:
- difficulty breathing or swallowing, wheezing, hives, itching, swelling of your face, eyes, lips, tongue or throat – these are signs of an allergic reaction.

Other side effects include:

Very common (may affect more than 1 in 10 people)

General: headache; chills, fever; feeling sick (nausea); flu-like symptoms; feeling dizzy, low energy; not being able to sleep; low appetite, weight loss; shortness of breath

Mouth, nose or throat: cough; dry mouth; funny taste

Skin and hair: dry skin, itching, rash; hair loss or thinning of hair

Joints and muscles: unusual weakness; painful, swollen joints; muscle ache not caused by exercise

Stomach and gut: diarrhoea; being sick (vomiting)

Mental illness: feeling anxious; feeling of deep sadness or of being worthless (depression); feeling irritable, tense and restless

Blood: low red blood cell count (anaemia), drop in the number of red blood cells – the signs may include feeling tired, headaches, being short of breath when exercising; low neutrophil count (neutropenia), low number of white blood cells – the signs may include getting more infections than usual - including fever, severe chills, a sore throat or mouth ulcers

Common (may affect up to 1 in 10 people)

General: shaking; fainting; difficulty breathing; feeling thirsty; trouble sleeping; throbbing headache; generally feeling unwell; feeling like you are spinning

Eyes or ears: dry eyes; ringing in the ears; changes in your vision

Mouth, nose or throat: mouth pain, tooth ache; pain when swallowing; nose bleed, stuffy nose; a change in how things smell; sore and raised patches in the mouth; feeling very thirsty with a dry mouth or dry skin; swelling of the thyroid gland, neck or voicebox; underactive thyroid gland; sores or swelling in the mouth, burning feeling on the tongue; feeling of tension or fullness in the nose, cheeks and behind the eyes - sometimes with a throbbing ache, fever or stuffy nose (sinusitis)

Skin and hair: cold sores, tingling or numbness of the skin; reduced feeling or sense of touch; skin rash, patchy skin rash, red skin; red raised skin rash sometimes with pus-filled blisters; hot, tender and red skin, sometimes with fever and chills; increased sweating; skin disease with thick patches of red skin – often with silvery scales

Joints and muscles: muscle spasm; feeling tired, muscle weakness, feeling cold; back pain, neck pain, pain in the arms or legs

Stomach and gut: pain in stomach and in the upper right side of the stomach or back; a burning feeling in the stomach, upset stomach; feeling bloated, burping (belching)

Anus: wind (flatulence); piles (haemorrhoids); difficulty passing stools (constipation)

Urinary: going to the toilet to urinate more often than usual

Sexual: a decrease in sex drive; difficulty getting or keeping an erection

Mental illness: changes in mood, feeling agitated; memory loss, trouble concentrating

Chest: difficulty breathing; chest discomfort, chest pain; heavy feeling in the chest, with difficulty breathing or wheezing

Heart or circulation: fast or uneven heart-beat; high or low blood pressure

Blood: drop in the number of blood platelets – the signs may include bleeding or bruising more easily than usual; high sugar (glucose) levels in the blood; high triglycerides levels in the blood; high uric acid levels in the blood; a combination of low platelet, red and white blood cell counts (pancytopenia); a severe drop of neutrophil count (agranulocytosis)

Uncommon (may affect up to 1 in 100 people)

General: light-headedness, arthritis; increased tendency to bleed; swollen glands in neck or armpit or groin; intense burning or stabbing pain; increased sensitivity to light, sound, what is felt, or food one tastes; diabetes

Eyes or ears: pink eye; eye pain; deafness; trouble hearing; swelling around the eyelid; increased tearing; fluid draining from the ear or eye; abnormal feeling around the eye, red patch on the white of the eye; yellowing of the white part of the eyes or of the skin

Mouth, nose or throat: hoarseness, dry throat or lips; painful or bleeding gums; sensitive tooth or toothache; tongue swollen, discoloured, or has sores; blistering by the tongue; severe pain

when swallowing; chest pain close to the lungs; chest pain worsens when taking a deep breath; uncontrolled salivating; overactive thyroid gland
Skin and hair: hives; open sore; intolerance to heat; markedly red face; pale face; yellow skin; rash due to sunlight; wound not healing normally
Feet or hands or legs or arms: sensation of pain, numbness, tingling or prickling; blood clot in a vein; feeling cold in an arm or leg; painful inflammation of the joints most commonly in the foot (gout)
Stomach and gut: lower stomach pain; pancreatitis
Urinary: painful when urinating; burning feeling or difficulty urinating; get up several times during the night to urinate
Rectum or anus: anal itching; inability to pass stools or discoloured stools; more frequent bowel movements; bleeding from anus
Sexual: missing menstrual period; heavy or prolonged menstrual period; uterine bleeding (i.e., prolonged >7 days or excessive bleeding at irregular or more frequent than normal intervals, bleeding occurring in menopausal women at least 6 months to 1 year after cessation of cycles)
Mental illness: anger; hostile attitude or behaviour; threatening behaviour; substance abuse problems, abnormal behaviour; feeling of confusion; thoughts of suicide; sudden intense fear or apprehension; feeling you are being persecuted; difficulty solving problems
Muscles: pain in your bones; local or widespread pain
Chest: pneumonia
Heart or circulation: abnormal or rapid heart rate; heart disease caused by poor blood flow in the heart
Blood: low potassium levels in your blood; high calcium levels in the blood

Rare (may affect up to 1 in 1,000 people)
General: difficult breathing and swallowing; tumour of the thyroid; infection of the blood; swelling or lumps in organs of the body; disease which leads to increasing muscle paralysis; disease of the brain – signs may include headache and fever, paralysis of a part of the body, a stiff neck or being sensitive to light
Eyes or ears: ear ache
Skin and hair: reddening of the skin; bacterial skin infection
Stomach and gut: problems digesting food; vomiting blood; vomiting, diarrhoea, and severe right upper corner stomach (abdominal) pain
Sexual: drop in levels of sperm
Mental illness: change in mood; feeling like your life is falling apart; seeing, feeling or hearing things that are not real (hallucinations); thoughts of killing yourself (suicide), trying to kill yourself; feeling of great happiness (mania) and then a feeling of deep sadness or not being worthy
Chest: being short of breath when lying flat; serious lung infection like pneumonia; sharp chest pains which are worse when breathing; pain behind breast bone which can spread to neck and shoulders
Heart or circulation: heart attack; stopping breathing; blood clot in the leg or arm; decreased blood flow to parts of the brain (e.g., dizziness, double vision, or weakness on both sides of the body)

Not known (frequency cannot be estimated from the available data)
Skin and hair: Severe rash, which may be accompanied by fever, fatigue, swelling of the face or lymph glands, increase of eosinophils (type of white blood cells), effects on liver, kidney or lung (a reaction called DRESS); serious skin reaction, including blistering or peeling of the skin (a reaction called Stevens-Johnson syndrome)
Kidney: renal impairment (generally reversible after conclusion of treatment)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Victrelis

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blisterfoil after EXP. The expiry date refers to the last day of that month.

Storage by the pharmacist
Store in a refrigerator (2°C – 8°C).

Storage by the patient
- Store in a refrigerator (2°C – 8°C) until expiry.

OR
- Store outside of the refrigerator at or below 30°C for a period of not more than 3 months until expiry. After this period, the medicinal product should be disposed.

Store in the original blister in order to protect from moisture.

Do not throw away any medicine via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Victrelis contains
- The active substance is boceprevir. Each hard capsule contains 200 mg of boceprevir.
- The other ingredients are sodium lauryl sulfate, microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, pre-gelatinized starch, magnesium stearate, yellow iron oxide (E172), red iron oxide (E172), titanium dioxide (E171), gelatin, and shellac.

What Victrelis looks like and contents of the pack
The hard capsules have a yellowish-brown cap with the "MSD" logo printed in red ink and an off-white body with "534" printed in red ink.
Peelable blisters containing 12 hard capsules (3x4 capsule blister strip).
Pack sizes: carton of 84 hard capsules and multipack containing 336 (4 packs of 84) hard capsules.
Not all pack sizes may be marketed.

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Manufacturer
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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.