20 March 2014
EMA/CHMP/231978/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pegasys

International non-proprietary name: PEGINTERFERON ALFA-2A

Procedure No. EMEA/H/C/000395/II/0073

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Table of contents

List of abbreviations

BOC	Boceprevir
CHB	Chronic hepatitis B
CHC	Chronic hepatitis C
DAA	Direct acting antiviral
DS	Delayed start
EMA	European Medicines Agency
EPAR	European Public Assessment Report
GCP	Good Clinical Practice
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IFN	Interferon
MAH	Marketing authorization holder
MPA	Medical Products Agency
P	Peg-IFN-alfa-2a
PD	Pharmacodynamics
PDCO	Paediatric Committee
PEG	Polyethylene glycol
PEG-IFN alfa-2a	Peginterferon alfa-2a
PEG-IFN/RBV	Pegylated interferon and ribavirin
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PLB	Placebo
PR	Peginterferon alfa and ribavirin
PTL	Product Team Leader
QW	Once a week
RAVs	Resistant-associated variants
RBV	Ribavirin
RGT	Response-guided therapy
RNA	Ribonucleic acid
SmPC	Summary of Product Characteristics
SoC	Standard-of-care
SVR	Sustained virologic response
T	Telaprevir
TID	Three times a day
TW	Treatment week

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 variation of Commission Regulation (EC) No 1234/2008, Roche Registration Ltd submitted to the European Medicines Agency on 4 December 2013 an application for a variation including an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Pegasys	PEGINTERFERON ALFA-2A	See Annex A

The following variation was requested:

Variation requested		**Type**
C.1.6 a)	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH proposed to extend the indication to include the use of HCV NS3/4A protease inhibitors for the treatment of HCV genotype 1. Section 4.1 is to be updated and cross reference to the SmPC's of the HCVNS3/4A protease inhibitors is to be made throughout the SmPC.

The Package Leaflet was proposed to be updated in accordance.

The variation proposed amendments to the SmPC and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decision P/0089/2013 on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP P/0089/2013 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder Co-Rapporteur: Concepcion Prieto Yerro

Submission date:	4 December 2013

Start of procedure:	22 December 2013
Rapporteur's preliminary assessment report circulated on:	21 January 2014
Co-Rapporteur's preliminary assessment report circulated on:	21 January 2014
PRAC RMP advice and assessment overview adopted by PRAC	5 February 2014
Joint Rapporteur's updated assessment report circulated on:	14 February 2014
Request for supplementary information and extension of timetable adopted by the CHMP on:	20 February 2014
MAH's responses submitted to the CHMP on:	24 February 2014
Joint Rapporteur's preliminary assessment report on the MAH's responses circulated on:	10 March 2014
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	14 March 2014
CHMP opinion:	20 March 2014

2. Scientific discussion

2.1. Introduction

Peginterferon alfa-2a (Pegasys) is a chemically modified alpha interferon (IFN) formed by the covalent attachment of a 40-kilodalton single branched methoxy polyethylene glycol (PEG) moiety to recombinant IFN alfa-2a. Pegasys alone or in combination with ribavirin (RBV) is currently indicated for the treatment of chronic hepatitis C (CHC), including coinfection with human immunodeficiency virus (HIV).

The approval of boceprevir (Victrelis) and telaprevir (Incivo) in combination with a peginterferon (2a or -2b) and ribavirin in the EU in 2011 led to a change in the standard of care for the treatment of CHC caused by the genotype 1 HCV virus.

Following this change in treatment paradigm, the marketing authorization holder (MAH) is proposing to update the Pegasys label to reflect the evolution in treatment of hepatitis C as follows: "Pegasys is indicated in combination with ribavirin and an approved Hepatitis C virus (HCV) NS3/4A protease inhibitor for the treatment of chronic hepatitis C genotype 1 infection in non-cirrhotic and cirrhotic patients with compensated liver disease who are previously untreated or who have failed previous therapy. "

The NS3/4A inhibitors telaprevir and boceprevir are indicated for use with either of the alfa-peginterferons and ribavirin, and have been studied in such combinations in the trials pivotal to their approval. To support the proposed extension of the indication of peginterferon alfa-2a to reciprocally include such combination use, the applicant refers to these pivotal studies. The relevant trials have previously been assessed by European regulators within the context of the approval procedures for boceprevir (EC Decision 18/07/2011) and telaprevir (EC Decision 19/09/2011).

As they currently stand, both the boceprevir and the telaprevir Summary of Product Characteristics (SmPCs) extensively cross-refer the treating physician or patient to the SmPC for the peginterferon alfa that is used in combination.

Of note the full data set for the authorisation of telaprevir and boceprevir are discussed in the respective EPAR's for these products available on the EMA website. The current report summarises the salient aspects of these dossiers relevant to the current extension of indication for Pegasys.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application. Given that the data have already been assessed in the context of the marketing authorisations for telaprevir and boceprevir this was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The MAH did not provide an ERA with this application. The extended indication does not increase the overall target population but is aimed at a specific subpopulation of patients already covered by the previous Pegasys indication. Therefore, the lack of an ERA is justified.

2.3. Clinical aspects

2.4. Clinical efficacy

2.4.1. Main studies

The pivotal phase III studies conducted for demonstrating the efficacy and the safety of boceprevir and telaprevir used with peginterferon alfa-2a and ribavirin is provided in Table 1.

Table 1. Overview of pivotal Studies that Evaluated Efficacy and Safety of Boceprevir and Telaprevir used with PEG-IFN Alfa-2a and Ribavirin

Study ID	Diagnosis Inclusion Criteria	Design	Study Posology	Subjects
Boceprevir				
P05685	Previous PEG/RBV treatment failures	This is a randomized, multicenter study, double blinded for boceprevir or placebo in combination with open-label peginterferon alfa-2a / ribavirin, in adult subjects with hepatitis C genotype 1 who demonstrated interferon responsiveness but failed to achieve sustained virologic response on prior treatment with peginterferon/ribavirin.	Boceprevir 800 mg three times daily (TID) was co-administered with PEG2a 180 µg/week SC plus ribavirin 1000 to 1200 mg/day PO BID, after the 4-week lead-in.	A total of 202 subjects were randomized and 201 received at least one dose of PEG2a/R, including 67 randomized to PEG2a/R control and 134 randomized to BOC/PEG2a/R

Study ID	Diagnosis Inclusion Criteria	Design	Study Posology	Subjects
Telaprevir[a]				
Study 108 (ADVANCE)	Treatment-naïve	**A Phase III** Study of 2 Dose Regimens of Telaprevir in Combination With Peginterferon Alfa-2a (Pegasys) and Ribavirin (Copegus) in Treatment-Naïve Subjects with Genotype 1 Chronic Hepatitis C	T8/PR T12/PR PLB/PR48	1088
Study 111 (ILLUMINATE)	Treatment-naïve	**A Phase III** Randomized Study of Stopping Treatment at 24 Weeks or Continuing Treatment to 48 Weeks in Treatment-Naïve Subjects with Genotype 1 Chronic Hepatitis C who Achieve an Extended Rapid Viral Response While Receiving Telaprevir, Peginterferon-alfa-2a (Pegasys), and Ribavirin (Copegus)	T12/PR[b]	540
Study C216 (REALIZE)	Previous PEG/RBV Treatment Failures	**A Phase III R**andomized, double-blind, placebo-controlled, Phase III trial of 2 regimens of telaprevir (with and without delayed start) combined with pegylated interferon alfa-2a (Pegasys) and ribavirin (Copegus) in subjects with chronic genotype 1 hepatitis C infection who failed prior pegylated interferon plus ribavirin treatment	T12/PR48[c] T12(DS)/PR48 [c] PLB/PR48	662

BOC: boceprevir; HCV=hepatitis C virus; P: Peg-IFN-alfa-2a; PLB = placebo; PR: Peginterferon alfa and ribavirin; QW=once a week; RBV = ribavirin; T: telaprevir; TID = three times a day;
[a]: In placebo-controlled studies, telaprevir matching placebo was administered to maintain double-blinding; [b]: The total duration of Peg-IFN and RBV treatment was 24 or 48 weeks based on subject's individual on-treatment virologic response and randomization; c: In both telaprevir groups, subjects received 12 weeks of telaprevir in combination with 48 weeks of Peg-IFN and RBV. In the T12(DS)/PR48 group, telaprevir treatment had delayed start (DS), i.e. telaprevir treatment started after 4 weeks treatment with Peg-IFN and RBV.

The efficacy of peginterferon alfa-2a in combination with an NS3/4A inhibitor

Telaprevir

Three pivotal studies supported the use of peginterferon alfa-2a in combination with telaprevir and ribavirin. In all studies, telaprevir was administered at a dose of 750 mg t.i.d, together with

peginterferon alfa-2a and ribavirin at standard doses. Patients had genotype 1 infection and were either treatment naive (studies -108 and -111) or treatment experienced (study -216). Patients with decompensated liver disease or HCV/HIV co-infection were not eligible to participate.

Study -108: A Phase 3 Study of 2 Dose Regimens of Telaprevir in Combination With Peginterferon Alfa-2a (Pegasys) and Ribavirin (Copegus) in Treatment-Naïve Subjects with Genotype 1 Chronic Hepatitis C

This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study. Patients included and female subjects between 18 to 70 years of age with genotype 1 chronic HCV infection who had not been previously treated for HCV. Decompensated liver disease or HBV/HCV co-infection were exclusion criteria.

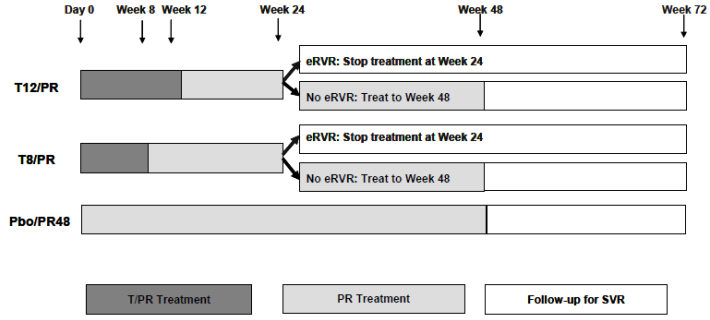
The treatment regimens were as follows:

Table 2. Treatment Groups

	Treatment		
Treatment Group	**Telaprevir Dosing Period**	**Telaprevir-matching Placebo Dosing Period**	**Peg-IFN-alfa-2a and RBV Dosing Period**
T8/PR	Day 1 through Week 8	Weeks 9 through 12	Day 1 through Week 24–with eRVR Day 1 through Week 48–without eRVR
T12/PR	Day 1 through Week 12	---	Day 1 through Week 24–with eRVR Day 1 through Week 48–without eRVR
Pbo/PR48	---	Weeks 1 through 12	Day 1 through Week 48

eRVR: extended rapid viral response (undetectable HCV RNA at Weeks 4 and 12); Pbo: placebo; PR: peginterferon alfa-2a (Pegasys®) and ribavirin (Copegus®); T: telaprevir.

Figure 1 Schematic of Study Design



eRVR: extended rapid viral response (undetectable HCV RNA at Weeks 4 and 12); Pbo: placebo; PR: peginterferon alfa-2a (Pegasys®) and ribavirin (Copegus®); T: telaprevir.

The primary efficacy measure was $SVR_{planned}$ (SVR 24 weeks after the planned end of treatment). Rates were as follows:

Table 3. $SVR24_{planned}$ Rates, Full Analysis Set

Variable	**T8/PR N = 364**	**T12/PR N = 363**	**Pbo/PR48 N = 361**
$SVR24_{planned}$[a]: n (%)	250 (68.7)	271 (74.7)	158 (43.8)
Odds ratio between each of the T/PR groups and Pbo/PR48	2.92	3.95	N/A
95% confidence intervals for the odds ratio	(2.14, 3.99)	(2.87, 5.45)	N/A
P value for odds ratio	<0.0001	<0.0001	N/A
Difference between each of the T/PR and Pbo/PR48 groups and 95% confidence intervals for the difference	24.9% (17.9%, 31.9%)	30.9% (24.1%, 37.7%)	N/A

N/A: not applicable; SVR: sustained viral response.
Note: Logistic regression analysis (2-sided) with $SVR24_{planned}$ as the dependent variable was used to determine the *P* value and and 95% confidence intervals with treatment, genotype, and baseline HCV RNA plasma level as factors. *P* value and 95% confidence intervals for the odds ratios are between T8/PR group (or T12/PR group) and Pbo/PR48 group.
Source: Table 14.2.1a

Thus, both telaprevir arms were significantly superior to placebo on the primary endpoint. The response in the T12/PR arm was numerically superior to that in the T8/PR arm. The placebo arm performed at the level of efficacy that would be expected. Both the 12-weeks and the 8 weeks telaprevir arm, with a subsequent peginterferon/ribavirin tail for a total of 24 or 48 weeks duration depending on eRVR (plasma viremia not detected at treatment weeks 4+12), were superior to 48 weeks of peginterferon/ribavirin with placebo. A higher on-treatment virological failure rate after telaprevir treatment completion was found in the 8 week telaprevir arm. As the viral genotype of these excess failures were wild-type or low-level resistant variants which might have been cleared by further telaprevir treatment, these data indicate a virological edge of twelve rather than eight weeks of telaprevir therapy. The advantage of telaprevir over placebo was evident regardless of viral subtype, degree of fibrosis, baseline viral load, sex, age, gender or race.

-111 A Randomized Study of Stopping Treatment at 24 Weeks or Continuing Treatment to 48 Weeks in Treatment-Naïve Subjects with Genotype 1 Chronic Hepatitis C who Achieve an Extended Rapid Viral Response While Receiving Telaprevir, Peginterferon-alfa-2a (Pegasys), and Ribavirin (Copegus)

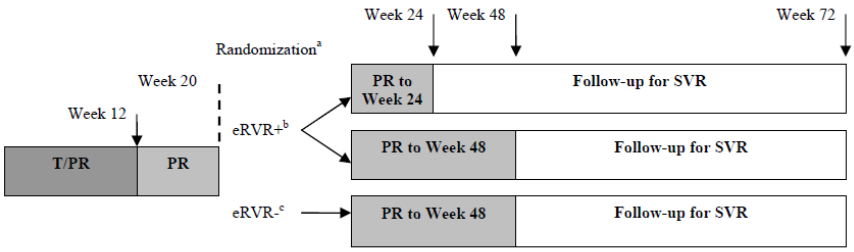
The study was designed to evaluate the SVR rates in subjects who achieved an eRVR (undetectable HCV RNA levels at Week 4 and Week 12 on treatment) with telaprevir in combination with Peg-IFN-alfa-2a and RBV.

The treatment regimens were 24 or 48 weeks in duration, with telaprevir administered in combination with Peg-IFN-alfa-2a and RBV for the first 12 weeks (i.e., T12/PR24 arm or T12/PR48 arms, respectively). Subjects who achieved an eRVR and completed the Week 20 visit were randomized in a 1:1 ratio to stop all study treatment at Week 24 or to continue treatment with Peg-IFN-alfa-2a and RBV to Week 48 (T12/PR48/eRVR+ group).

Subjects who did not achieve an eRVR were assigned a total treatment with Peg-IFN-alfa-2a and RBV for 48 weeks (T12/PR48/eRVR- group). Subjects who prematurely discontinued treatment before Week 20, were not randomized or assigned to a treatment regimen. These subjects were included in the group designated 'Other'.

The table below provides a summary of the treatment regimens in this study.

Table 4. Summary of Treatment



Abbreviations: eRVR: extended rapid viral response; PR: Peg-IFN-alfa-2a and RBV; SVR: sustained viral response; T: telaprevir
Note: Subjects who received at least 1 dose of study drug, but prematurely discontinued treatment before Week 20 were not randomized or assigned to a treatment regimen. These subjects were included in a group designated 'Other'.
[a] Randomization occurred after the Week 20 visit, but before the Week 24 visit. Randomization was blocked and stratified to optimize balance among the treatment groups with regard to genotype (1a, 1b, or unknown) and race (Black or non-Black; and self-identified).
[b] Subjects who achieved eRVR and completed the Week 20 visit were randomized in a 1:1 ratio to stop all study treatment at Week 24 (T12/PR24/eRVR+ group) or to continue treatment with Peg-IFN-alfa-2a and RBV to Week 48 (T12/PR48/eRVR+ group).
[c] Subjects who did not achieve eRVR and completed the Week 20 visit were assigned treatment with Peg-IFN-alfa-2a and RBV for 48 weeks (T12/PR48/eRVR- treatment group).
Source: clinical study protocol (Appendix 16.1.1)

The primary efficacy variable was the $SVR24_{planned}$ rate, defined as undetectable HCV RNA levels at the end of treatment (EOT) visit and at 24 weeks after the last planned dose of study treatment without any confirmed detectable HCV RNA levels in between those visits.

The T12/PR24 treatment regimen was to be declared non-inferior to the T12/PR48 treatment regimen if the lower limit of the 1-sided 97.5% CI on the observed difference between the T12/PR24/eRVR+ group and the T12/PR48/eRVR+ group was greater than -10.5% (i.e., the non-inferiority margin).

The 540 enrolled subjects had a median age of 51 years (range: 19 to 70); 60% of the subjects were male; 32% had a body mass index ≥ 30 kg/m^2; 14% were Black; 10% were Hispanic or Latino; 82% had baseline HCV RNA levels > 800,000 IU/ml; 16% had bridging fibrosis; 11% had cirrhosis; 72% had HCV genotype 1a; and 27% had HCV genotype 1b.

Primary outcomes (SVR)

Table 5. $SVR24_{planned}$ Rates, Full Analysis Set

	Randomized (eRVR+)		Assigned (eRVR-)	
Variable	T12/PR24 N = 162 n (%)	T12/PR48 N = 160 n (%)	T12/PR48 N = 118 n (%)	Other N = 100 n (%)
$SVR24_{planned}$: n (%)	149 (92.0)	140 (87.5)	76 (64.4)	23 (23.0)
Difference between T12/PR24/eRVR+ and T12/PR48/eRVR+ groups and 95% CI for the difference	4.5% (-2.1%, 11.1%)		N/A	N/A
Odds ratio between T12/PR24/eRVR+ and T12/PR48/eRVR+ groups and 95% CI intervals for the odds ratio	1.62 (0.77, 3.38)		N/A	N/A

Abbreviations: CI: confidence interval; eRVR: extended rapid viral response; N/A: not applicable; SVR: sustained viral response
Note: Subjects who received at least 1 dose of study drug, but prematurely discontinued treatment before Week 20 were not randomized or assigned to a treatment regimen.
Source: Table 14.2.1a

The SVR rate in those treated for 24 weeks was numerically higher and statistically non-inferior compared to that of subjects treated for 48 weeks (92% with T12/PR24 vs 88% with T12/PR48).

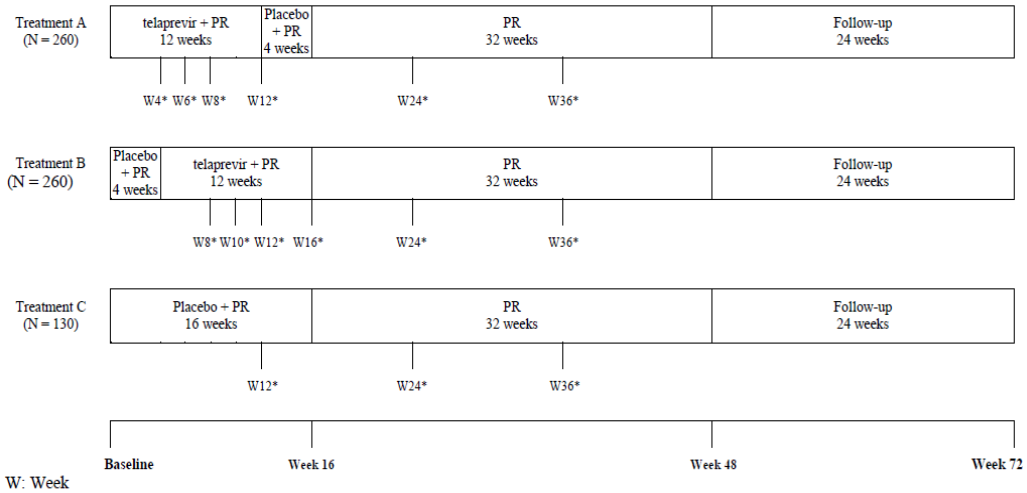
The primary outcome was consistent through the subgroups of age, gender, race, viral subtype and baseline viral load.

C216 A randomized, double-blind, placebo-controlled, Phase III trial of 2 regimens of telaprevir (with and without delayed start) combined with pegylated interferon alfa-2a (Pegasys) and ribavirin (Copegus) in subjects with chronic genotype 1 hepatitis C infection who failed prior pegylated interferon plus ribavirin treatment.

The study was designed to compare the efficacy, safety, and tolerability of 2 regimens of telaprevir (with and without delayed start (DS) of telaprevir) combined with Peg-IFN-alfa-2a and RBV versus standard treatment (Peg-IFN-alfa-2a and RBV).

Subjects were eligible to enrol in the study if they (1) had an undetectable hepatitis C virus (HCV) ribonucleic acid (RNA) level at the end of a prior course of Peg-IFN/RBV therapy but did not achieve sustained virologic response (SVR) (prior relapsers), or (2) never had an undetectable HCV RNA level during or at the end of a prior course of Peg-IFN/RBV therapy (prior non-responders).

Figure 1 Study Design



W: Week
PR: standard treatment, i.e., Peg-IFN-alfa-2a and RBV

N: planned number of subjects
* Time points at which treatment and procedural modifications could be made based on virologic response assessments (see Table 1)

Figure 1: Study Design

The main efficacy variable was SVR, defined as having undetectable HCV RNA 24 weeks after the last planned dose of study drug SVR24planned.

Approximately half the patients were prior relapsers and half non-responders, with a balanced distribution between treatment arms. 89% had baseline HCV RNA levels > 800,000 IU/ml; 22% had bridging fibrosis; 26% had cirrhosis; 54% had HCV genotype 1a; and 46% had HCV genotype 1b.

Primary endpoint (SVR)

Table 6. $SVR24_{planned}$ Rates and Statistical Comparison (Logistic Regression) for $SVR24_{planned}$ – Overall Population, FA Set

	Overall population		
Variable	**T12/PR48 N = 266**	**T12(DS)/PR48 N = 264**	**Pbo/PR48 N = 132**
$SVR24_{planned}$, n (%)	171 (64.3)	175 (66.3)	22 (16.7)
P value (in comparison to Pbo/PR48)[a]	<0.001	<0.001	N/A
Difference between each of T/PR and Pbo/PR48 groups[a]	46.8%	49.8%	
95% CI[a] for the difference	(36.8%, 56.7%)	(39.9%, 59.7%)	N/A
Difference between T12/PR48 and T12(DS)/PR48 and 95% CI[a] for the difference	-3.0% (-13.0%,7.0%)		N/A

N/A: not applicable
[a] as estimated in a logistic regression model including the following factors: treatment, type of prior response and their interaction, and baseline viral RNA as a covariate
N: number of subjects with data; n: number of subjects with SVR
Source: Display EFF.13, Display EFF.18

As the treatment duration was similar in all treatment groups, the planned assessment was at study week 72 (24 weeks after the end of therapy) for all patients. The superiority of both immediate and delayed start telaprevir based regimens over placebo was demonstrated, with point estimates for SVR in the full treatment population of 64% (telaprevir immediate start), 66% (telaprevir, delayed start) and 17% (peginterferon+ribavirin+placebo). Statistically significant superiority was demonstrated for each telaprevir regimen over placebo in the three subcategories of prior response patterns, relapsers, partial responders (at least 2 log 10 decline at week 12 of prior therapy with peginterferon+ribavirin) and null responders less than 2 log 10 decline at week 12 of prior therapy.

In prior relapsers, SVR rates in the telaprevir (immediate and delayed start) arms and in the control arm were 83%, 88% and 23.5% respectively. In prior partial responders, SVR rates in the telaprevir arms (immediate and delayed start) and in the control arm were 60%, 54% and 15% respectively. In prior null responders, SVR rates in the telaprevir (immediate and delayed start) arms and in the control arm were 30%, 33% and 5% respectively. The benefit of telaprevir appeared consistent over subgroups where n is large enough for direct conclusions, such as age, gender, viral subtype, baseline viral load, degree of fibrosis in the overall population. Though there is a likely advantage of telaprevir over placebo in all relevant subgroups, absolute SVR rates remain low in some population categories, despite the addition of telaprevir. These include, e.g., prior null responders with subtype 1a (27%) and prior null responders with cirrhosis (14%).

Boceprevir

While the bulk of the boceprevir development program was performed with peginteferon alfa-2b, the sponsor of that program conducted one pivotal trial to provide evidence for bridging assumptions with peginterferon alfa- 2a.

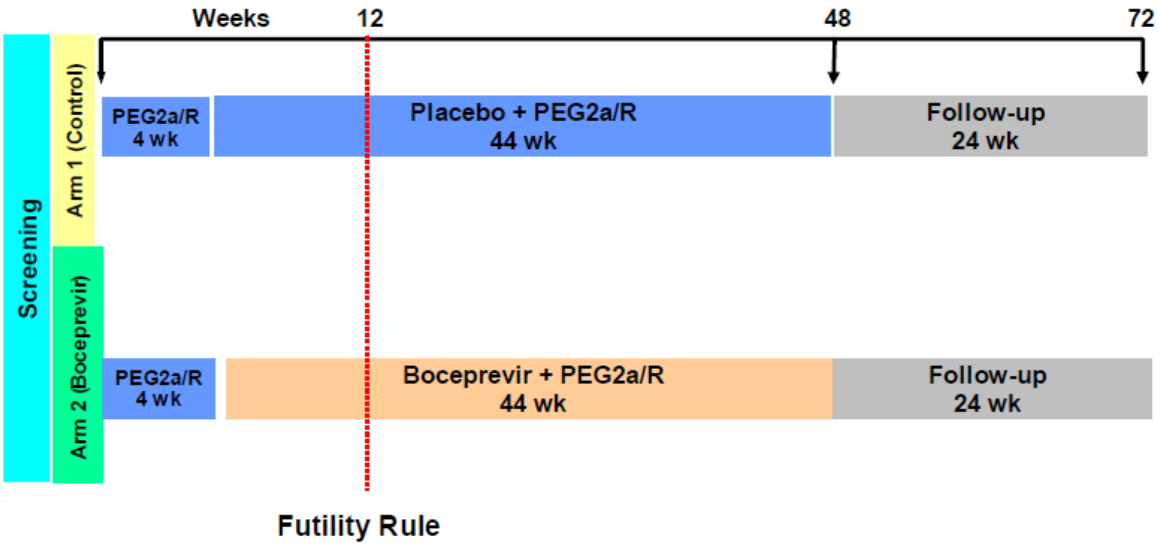
Study P05685, A Phase 3 Safety and Efficacy Study of Boceprevir in Combination With Peginterferon Alfa-2a and Ribavirin in Subjects With Chronic Hepatitis C Genotype 1 Who Failed Prior Treatment With Peginterferon/Ribavirin

This is a randomized, multicentre study, double-blinded for boceprevir or placebo in combination with open-label peginterferon alfa-2a / ribavirin, in adult subjects with hepatitis C genotype 1 who demonstrated interferon responsiveness but failed to achieve sustained virologic response on prior treatment with peginterferon/ribavirin. Patients with decompensated liver disease were not eligible for this study.

The primary objective was to compare the efficacy of boceprevir in combination with peginterferon alfa-2a (PEG2a) plus ribavirin (PEG2a/R) to the same PEG2a/R regimen without boceprevir for 48 weeks in adult subjects with chronic hepatitis C (CHC) genotype 1 with demonstrated interferon responsiveness who failed prior treatment with peginterferon/ribavirin. A secondary objective was to evaluate the safety of boceprevir when used in combination with PEG2a/R.

Subjects with HCV (genotype 1) who failed to achieve SVR on prior adequate treatment with any peginterferon alfa and ribavirin but demonstrated interferon responsiveness (a decrease in hepatitis C virus-ribonucleic acid (HCV-RNA) viral load ≥2 log10 by treatment week (TW) 12 or undetectable HCV-RNA at End of Treatment [EOT]) were selected for the study.

The primary efficacy endpoint was the achievement of SVR24.



A total of 202 subjects were randomized and 201 received at least one dose of PEG2a/R, including 67 randomized to PEG2a/R control and 134 randomized to BOC/PEG2a/R.

In this study, 70% (140/201) of the treated randomized subjects were male and 90% (181/201) were non-black. The mean age was 53 years (range, 29-70 years), and the mean weight was 85 kg. All subjects had genotype 1 (45% [90/201] subtype 1a, 47% [95/201] subtype 1b by TRUGENE™ assay), and 77% (155/201) had high viral load (>800,000 IU/mL), with a 6.32 mean log10 baseline viral load. 16% of patients had F4 cirrhosis.

Efficacy outcomes (SVR rates) in the full analysis set, including all patients randomised and treated, were as follows:

	FAS[a]	
	Arm 1 PEG2a/R n=67	Arm 2 BOC/PEG2a/R n=134
	Overall Response	
EOT (Undetectable HCV-RNA), n (%)	28 (41.8)	99 (73.9)
SVR[b], n (%)	14 (20.9)	86 (64.2)
ΔSVR[c, d]	-	43.3
95% CI for Δ	-	30.6, 56.0
P value[c]	-	<0.0001
Relapse[e], n/N (%)	7/21 (33.3)	11/95 (11.6)

Thus, the addition of boceprevir to the PEG2a/R backbone led to a significant increase in SVR from 21% to 64%. Using historical classification of previous response, both relapsers (SVR=70%) and non responders (SVR=47%) had large increases in SVR compared with controls (28% and 5%, respectively). No subgroup of subjects was identified for whom PEG2a/R therapy was superior to triple therapy with boceprevir plus PEG2a/R.

The efficacy results of the P05685 study, which was performed in a treatment experienced population, supported the a priori hypothesis that using boceprevir and ribavirin with peginterferon alfa-2a would be at least equally effective as the use of the same drugs with peginterferon alfa-2b.

Discussion of Clinical efficacy

The NS3/4A inhibitors telaprevir and boceprevir are indicated for use with either of the alfa-peginterferons and ribavirin, and have been studied in such combinations in the trials pivotal to their approval. To support the proposed extension of the indication of peginterferon alfa-2a to reciprocally include such combination use, the applicant refers to these pivotal studies. The relevant trials have previously been assessed by European regulators within the context of the approval procedures for telaprevir (19/09/2011) and boceprevir (18/07/2011). These trials indicate that the SVR rate in treatment naive patients that get peginterferon alfa-2a+ribavirin bitherapy is somewhat higher than 40%, which is in agreement with other results obtained with such regimens. Furthermore, in treatment naive patients, the addition of telaprevir led to an absolute increment in response rates of more than 30 percent.

In patients that have previously failed on peginterferon alfa+ribavirin therapy, and thus are preselected “poor interferon responders”, the absolute response rates when using peginterferon alfa-2a+ribavirin bitherapy in the control arms of the abovementioned pivotal trials was lower, as anticipated. Also, the absolute response rates to triple therapy including telaprevir or boceprevir in studies of such patients were lower than in studies of treatment naive patients. However, the proportional increment in SVR rates when adding a NS3/4A inhibitor to peginterferon alfa-2a+ribavirin in such poorer interferon responders tended to be higher than seen in the treatment naive.

The safety of peginteferon alfa-2a in combination with a first generation NS3/4A inhibitor and ribavirin

Safety in combination with telaprevir

The pooled placebo-controlled phase II/III studies with telaprevir, forming the core of the safety database at the time of approval of this drug, included 1823 subjects that received a telaprevir regimen of 8, 12 or 24 weeks. Median time on telaprevir was 12.1 weeks. Thirty six percent of the patients were female, 11% were non-white, 1.5% were >65 years of age, 13.3% had cirrhosis. Virtually no patients had CrCL <50 ml/min.

Adverse events

Treatment-emergent treatment-related AEs reported more frequently when telaprevir is added to peginterferon alfa-2a+ribavirin include rash, pruritus, anemia, nausea, diarrhoea, vomiting, dysgeusia and haemorrhoids.

Serious adverse events, deaths and other significant events

The incidence of serious adverse events on telaprevir treatment was 6.6%, compared to 2.9% in the placebo group. The most frequently reported SAEs in the T12/PR group were anemia (1.6%) and rash (0.7%).

Table 7. Placebo-Controlled Phase 2-3 Studies: Incidence of Serious Adverse Events That Occurred in More than 0.5% of Subjects in any Treatment Group by System Organ Class and Preferred Term – *Telaprevir/Placebo Treatment Phase*

System Organ Class Preferred Term, n (%)	T12/PR (750 mg q8h) N = 1346	Any T/PR N = 1823	Pbo/PR N = 764
Any SAE	93 (6.9)	121 (6.6)	22 (2.9)
Blood and lymphatic system disorders			
Anaemia	21 (1.6)	34 (1.9)	3 (0.4)
Skin and subcutaneous tissue disorders			
Rash	10 (0.7)	12 (0.7)	0

N: number of subjects with data; n: number of subjects with observations
Note: If a subject has multiple events within a SOC or preferred term, the subject is counted once.
Source: Module 5.3.5.3/VX-950-SCS/Display SAF.B47

There were no deaths during telaprevir treatment.

Rash is the most important side effect of telaprevir, and the most important adverse effect cause of discontinuation. In the phase III studies, the applicant implemented a "rash management plan", which remains the basis for recommendations in the extant SmPC for Incivo.

The other clinically major side effect is an additive effect on the anemia seen with peginterferon alfa-2a+ribavirin treatment which, if needed, is usually managed by ribavirin dose reduction.

Table 8. Placebo-Controlled Phase 2-3 Studies: Summary of Anemia SSC Events – *Telaprevir/Placebo Treatment Phase*

Number (%) of subjects with:	T12/PR (750 mg q8h) N = 1346	Any T/PR N = 1823	Any T/P N = 189	Pbo/PR N = 764
AEs	432 (32.1)	608 (33.4)	13 (6.9)	113 (14.8)
Deaths	0	0	0	0
SAEs	22 (1.6)	36 (2.0)	1 (0.5)	3 (0.4)
AEs of at least Grade 3	66 (4.9)	97 (5.3)	1 (0.5)	6 (0.8)
AEs leading to permanent discontinuation of				
T/Pbo	37 (2.7)	60 (3.3)	2 (1.1)	4 (0.5)
RBV	17 (1.3)	37 (2.0)	0	3 (0.4)
all study drugs at the same time[a]	12 (0.9)	25 (1.4)	-[b]	4 (0.5)
AEs leading to temporary discontinuation of RBV	63 (4.7)	88 (4.8)	0	10 (1.3)
AEs leading to RBV dose reduction	291 (21.6)	406 (22.3)	0	72 (9.4)
AEs at least possibly related to T/Pbo	362 (26.9)	536 (29.4)	13 (6.9)	101 (13.2)

[a] Post-hoc analysis
[b] Not calculated as subjects in the Any T/P group received only 2 drugs instead of 3.
N: number of subjects with data

Also, there is an additive effect on peginterferon platelet decrease and lymphopenia, but not on neutrophil counts.

When treating with telaprevir there was a transient and reversible rise in serum creatinine. It remains unclear whether the increase in creatinine represents a decreased glomerular filtration or an otherwise altered creatinine disposition, though the identification of older age and hypertension as risk factors may indicate the former.

Hypothyroidism is a well-known side effect of peginterferon alfa, which occurs in up to 5% of patients treated with peginterferon alfa+ribavirin in clinical trials. Increased TSH levels were more common when treating with telaprevir than with placebo, in combination with peginterferon alfa-2a and ribavirin. Also, “hypothyroidism” was reported at a considerably higher frequency in telaprevir-treated patients – and at a comparably low rate in patients treated with peginterferon and ribavirin. As the frequency of TSH increases overall with telaprevir or placebo in the regimen is similar, it may be that TSH increases occur earlier with telaprevir therapy. Furthermore, most cases pertain to patients with a history of thyroid disease and/or thyroid replacement therapy. Thus it may be that telaprevir affects the disposition of T3 and T4.

Discontinuation due to AES

Approximately 10% of patients treated with telaprevir+peginterferon alfa-2a+ribavirin discontinued their entire treatment regimen due to adverse effects, compared to 7% in the control group treated only with peginterferon alfa-2a and ribavirin. Approximately 15% discontinued telaprevir due to AE, while 4% discontinued placebo.

Safety in combination with boceprevir

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

The bulk of the boceprevir drug development program was performed in combination with peginterferon alfa-2b rather than -2a. However, the application dossier included the aforementioned P05685 study, which served to bridge data for the use of boceprevir in combination with either peginterferon, which is how the label for Victrelis is stated.

Adverse events

In the P05685 study, where boceprevir was used in combination with peginteferon alfa-2a, the most common AEs were those previously reported with peginterferon alfa-2a+ribavirin therapy, such as, e.g., fatigue, myalgia, influenza-like symptoms, cytopenias. Treatment-emergent treatment-related AEs reported more frequently in the boceprevir-containing arm compared with the control arm were blood and lymphatic system disorders, including anemia, neutropenia, and leukopenia; rash; myalgia; and gastrointestinal disorders, including dysgeusia, nausea, diarrhoea, and vomiting.

Serious adverse events, deaths and other significant events

Serious adverse events were reported with similar frequency in the boceprevir-containing and control arms (13% vs 10%, respectively). Only the SAE of neutropenia was reported in more than one subject (n=2), both in the boceprevir+peginteferon alfa-2a+ribvairin arm. Various different infection SAEs were reported in 7 of the 134 subjects in the boceprevir-containing arm and none of the 67 in the control arm; however, 2 of these 7 subjects with infections were assigned to receive boceprevir but had only received PEG2a/R before the development of their infections. No subject had Grade 3 or 4 neutropenia within 14 days of the onset of a severe or life-threatening infection.

There were two deaths on study, both in the BOC/PEG2a/R arm: one due to cardiac failure, which the investigator considered unlikely related to study medication, and one due to multi-organ failure secondary to Staphylococcal pneumonia, which was considered possibly related to study medication.

The following table illustrates comparative safety when boceprevir was used with peginterferon alfa-2a in treatment experienced patients in the P05685 study, and when used in a similar population with peginterferon alfa-2b in the pivotal P05101 study.

	Study P05685		Study P05101	
	PegIFN alfa2a/RBV	PegIFN alfa 2a/RBV/BOC	PegIFN alfa2b/RBV	PegIFN alfa2b/RBV/BOC
	N=67	N=334	N= 80	N= 161
Treatment duration (mean)	105 days	334 days	104 days	336 days
AE	100%	100%	96%	100%
SAE	10%	13%	5%	14%
Death	0	2 (1%)	0	0
Drug discontinuation	4%	17%	3%	12%
Dose modification	22%	43%	14%	33%
Anaemia as AE	33%	50%	20%	47%
Hb<10g/dl	22%	37%	24%	35%
Hb<8.5g/dl	4%	13%	1%	14%
Use of EPO	30%	47%	21%	46%
Dysgueusia	25%	39%	11%	45%
Neutropenia as AE	18%	**31%**	10%	14%
Neutrophils<750/mm3 Grade3-4	18%	**28%**	9%	20%
Neutrophils<500/mm3 Grade4	3%	**14%**	4%	7%
Thrombocytopenia as AE	6%	7%	0%	6%
Platelets < 50 (Grade3)	7%	10%	0	5%
Platelets <25 (Grade 4)	0	1%	0	0

The most salient aspect of the safety profile of the drug is marked by the high rate of anaemia and dysgueusia that occurred in 49% and 37% of boceprevir-treated subjects respectively, versus 29% and 17% of patients treated only with peginterferon alfa-2b and ribavirin. Thus, overall, the main adverse effect burden associated with the use of boceprevir is due to the marked increase of anemia as compared to the already significant rate of anemia with peginterferon+ribavirin.

The risk of neutropenia (including grade3/4) is markedly increased when boceprevir is combined to alfa 2a. As a consequence, the Victrelis SmPC contains a statement that, as compared to the combination of Victrelis with peginterferon alfa–2b and ribavirin, the combination of Victrelis with peginterferon alfa–2a and ribavirin was associated with a higher rate of neutropenia (including grade 4 neutropenia) and a higher rate of infections.

Of note, neutropenia is an identified risk as per the RMP of Victrelis. In September 2013 var II/19 was adopted, approving recommendations on additional monitoring of neutrophils while treated with boceprevir-based triple therapy. This was not prompted by any specific concerns relating to the use of peginterferon alfa-2a rather than -2b, but was based on further analysis of data from trials where the latter was used.

Discontinuation due to AES

Common AEs that resulted in discontinuation included events known to be associated with PEG2a/R therapy, including asthenia and fatigue. Although there was an increased incidence of treatment-related anemia in boceprevir-treated subjects compared with control subjects (50% vs 33%, respectively), none of the anemia AEs was considered serious, and only one resulted in drug discontinuation.

Conclusion on clinical safety

The two first NS3/4A inhibitors both have an additive impact to well-known haematological adverse effects attributed to the combination of peginterferon+ribavirin, and in particular anemia. Furthermore, there are additional side effects characteristic of each NS3/4A inhibitors such as rash (telaprevir), anal complaints (telaprevir) and dysgeusia (boceprevir). In summary, the documentation submitted by the company for this application does not contain any data that have not been thoroughly assessed by European regulators within the approval procedures of telaprevir and boceprevir. According to the outcome of these, as well as through subsequent PSUR cycles, the benefit-risk of co-administering these drugs with peginterferon alfa-2a, according to the labels of Incivo and Victrelis, has been deemed positive.

Risk management plan

PRAC Advice:

Based on the PRAC review of the Risk Management Plan version 5, the PRAC considers by consensus that the risk management system for peginterferon alfa-2a (Pegasys) in the proposed indication is acceptable.

Safety concerns

There are no new identified or potential risks since the previous revision of the RMP. The data in support for an extension of indication for use in combination with NS3/4A protease inhibitors do not indicate any new risks to be required for inclusion into the RMP.

PhV Plan

Table 9. Table of on-going and planned studies in the Post-authorization Pharmacovigilance Development Plan

Study	Protocol Version	Protocol Status	Planned Date for Submission of Interim Data	Planned Date for Submission of Final Data
GUARD-C; post-appproval commitment:SAEs reports of adult patients receiving more than 48 weeks Pegasys to be analyzed	MV22255	Study active but further recruitment stopped due to recent approval of new direct acting antiviral agents	Q1 2012	March 2014
HCV long-term follow-up (PEDS-C)	NR17424 version D	Protocol approved	Not applicable	Q4 2013
HBV immune-tolerant long-term follow-up (Vergani)	NV25361 version 5 [EudraCT Number 2006-000977-31]	Active	Not applicable	Primary endpoint Q4 2014 5-year follow-up planned for Q4 2019
HBV immune active	YV25718 (protocol C) (previously known as WV18447) – HBV Pediatric IMAC study-version A	Protocol approved	Not applicable	Primary endpoint Q2 2014 5- year follow-up planned for Q2 2016
HCV Pediatric Study Ages 3-5 years	BV28334 protocol A	Submitted to the FDA; comments received; protocol to be initiated post bioequivalency study of Copegus® (ribavirin) solution and /tablets	Q4 2019	Q1 2023

The PRAC having considered the data submitted, is of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

Risk minimisation measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Important identified risks:		
Psychiatric and	Because of the potential for psychiatric or CNS reactions, Section 4.4 of	None

CNS Adverse Events	the Pegasys SPC contains a black box describing the spectrum of neuropsychiatric reactions: **Psychiatric and Central Nervous System (CNS):** Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during Pegasys therapy, and even after treatment discontinuation mainly during the 6-month follow-up period. Other CNS effects including aggressive behavior (sometimes directed against others such as homicidal ideation), bipolar disorders, mania, confusion and alterations of mental status have been observed with alpha interferons. All patients should be closely monitored for any signs or symptoms of psychiatric disorders. In particular, pediatric patients with a prior history of or concurrent psychiatric disorders should be monitored for evidence of depression. If symptoms of psychiatric disorders appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric symptoms persist or worsen, or suicidal ideation is identified, it is recommended that treatment with Pegasys be discontinued, and the patient followed, with psychiatric intervention as appropriate. *Patients with existence of, or history of severe psychiatric conditions:* If treatment with Pegasys is judged necessary in patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualized diagnostic and therapeutic management of the psychiatric condition. In addition, all above adverse events are listed in SPC Section 4.8 (Undesirable effects).	proposed
Blood and Lymphatic System Adverse Events	Warning in Section 4.4 of the SPC describing the spectrum of hematological abnormalities, and recommendations for management: *"Prior to beginning Pegasys therapy, standard hematological and biochemical laboratory tests are recommended for all patients.* *The following may be considered as baseline values for initiation of treatment:* - *Platelet count ≥ 90,000/mm^3* - *Absolute neutrophil counts ≥ 1500/mm^3* *Hematological tests should be repeated after 2 and 4 weeks and biochemical tests should be performed at 4 weeks. Additional testing should be performed periodically during therapy.* *In clinical trials, Pegasys treatment was associated with decreases in both total white blood cell (WBC) count and absolute neutrophil count (ANC), usually starting within the first 2 weeks of treatment (see Section 4.8). Progressive decreases after 8 weeks of therapy were infrequent. The decrease in ANC was reversible upon dose reduction or cessation of therapy (see Section 4.2), reached normal values by 8 weeks in the majority of patients and returned to baseline in all patients after about 16*	None proposed

	weeks. *Pegasys treatment has been associated with decreases in platelet count, which returned to pre-treatment levels during the post-treatment observation period (see Section 4.8). In some cases, dose modification may be necessary (see Section 4.2).* *The occurrence of anemia (hemoglobin <10 g/dl) has been observed in up to 15% of chronic hepatitis C patients in clinical trials on the combined treatment of Pegasys with ribavirin. The frequency depends on the treatment duration and the dose of ribavirin (see Section 4.8,). The risk of developing anemia is higher in the female population.* *As with other interferons, caution should be exercised when administering Pegasys in combination with other potentially myelosuppressive agents.* *The use of Pegasys and ribavirin combination therapy in chronic hepatitis C patients who failed prior treatment has not been adequately studied in patients who discontinued prior therapy for hematological adverse events. Physicians considering treatment in these patients should carefully weigh the risks versus the benefits of re-treatment."* Instructions in Section 4.2 of the SPC discuss the occurrence of the hematological event, and provide recommendations for dose management based upon changing hematological parameters.	
Endocrine System Adverse Events	Warning in Section 4.4 of the SPC describing the spectrum of such disorder: *"Thyroid function abnormalities or worsening of pre-existing thyroid disorders have been reported with the use of alpha interferons, including Pegasys. Prior to initiation of Pegasys® therapy, TSH and T4 levels should be evaluated. Pegasys treatment may be initiated or continued if TSH levels can be maintained in the normal range by medication. TSH levels should be determined during the course of therapy if a patient develops clinical symptoms consistent with possible thyroid dysfunction (see Section 4.8). As with other interferons, hypoglycemia, hyperglycemia and diabetes mellitus have been observed with Pegasys® (see Section 4.8). Patients with these conditions who cannot be effectively controlled by medication should not begin Pegasys monotherapy or Pegasys/ribavirin combination therapy. Patients who develop these conditions during treatment and cannot be controlled with medication should discontinue Pegasys or Pegasys/ribavirin therapy."* In addition, these adverse events are listed in SPC Section 4.8 (Undesirable effects).	None proposed
Cardiovascular Adverse Events	Contraindication in Section 4.3 of the SPC indicates: *A history of severe pre-existing cardiac disease including unstable or uncontrolled cardiac disease in the previous six months.* Warning in Section 4.4 of the SPC describing the spectrum of such disorders:	None proposed

	Hypertension, supraventricular arrhythmias, congestive heart failure, chest pain and myocardial infarction have been associated with alpha interferon therapies, including Pegasys. It is recommended that patients who have pre-existing cardiac abnormalities have an electrocardiogram prior to initiation of Pegasys therapy. If there is any deterioration of cardiovascular status, therapy should be suspended or discontinued. In patients with cardiovascular disease, anemia may necessitate dose reduction or discontinuation of ribavirin. In addition, above cardiovascular adverse events are listed in SPC Section 4.8 (undesirable effects).	
Ischemic Cardiac Events in Setting of Ribavirin-induced Anemia	Warning in Section 4.4 of the Copegus® SPC describing the spectrum of ischemic cardiac events as a result of anemia, and suggestions for management: *"Although ribavirin has no direct cardiovascular effects, anemia associated with Copegus may result in deterioration of cardiac function, or exacerbation of the symptoms of coronary disease, or both. Thus, Copegus must be administered with caution to patients with pre-existing cardiac disease. Cardiac status must be assessed before start of therapy and monitored clinically during therapy; if any deterioration occurs, stop therapy (see section 4.2). Patients with a history of congestive heart failure, myocardial infarction, and/or previous or current arrhythmic disorders must be closely monitored. It is recommended that those patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of therapy."* Instructions in Section 4.2 of the SPC discuss the occurrence of the hematological event, and provide recommendations for dose management based upon cardiovascular events.	None proposed
Hepatobiliary Adverse Events	Contraindication in Section 4.3 of the SPC indicates: • *Autoimmune hepatitis* • *Severe hepatic dysfunction or decompensated cirrhosis of the liver* • *Initiation of Pegasys is contraindicated in HIV-HCV patients with cirrhosis and a Child-Pugh score ≥6, except if only due to indirect hyperbilirubinemia caused by drugs such as atazanavir and indinavir.* Warning in Section 4.4 of the SPC describing the spectrum of occurrence of the liver decompensation, and suggestions for management: "*In patients who develop evidence of hepatic decompensation during treatment, Pegasys should be discontinued. As with other alpha interferons, increases in ALT levels above baseline have been observed in patients treated with Pegasys, including patients with a viral response.*	None proposed

	When the increase in ALT levels is progressive and clinically significant, despite dose reduction, or is accompanied by increased direct bilirubin, therapy should be discontinued (see Sections 4.2 and 4.8). *In chronic hepatitis B, unlike chronic hepatitis C, disease exacerbations during therapy are not uncommon and are characterized by transient and potentially significant increases in serum ALT. In clinical trials with Pegasys in HBV, marked transaminase flares have been accompanied by mild changes in other measures of hepatic function and without evidence of hepatic decompensation. In approximately half the case of flares exceeding 10 times the upper limit of normal, Pegasys dosing was reduced or withheld until the transaminase elevations subsided, while in the rest therapy was continued unchanged. More frequent monitoring of hepatic function was recommended in all instances."* Instructions in Section 4.2 of the SPC discuss the occurrence of the event, and provide recommendations for dose management based upon liver function parameters: In addition, these adverse events are listed in SPC Section 4.8 (Undesirable effects).	
Hypersensitivity Reaction Adverse Events	Contraindication in Section 4.3 of the SPC indicates: *Hypersensitivity to the active substance, alpha interferons, or to any of the excipients.* Warning in Section 4.4 of the SPC: *"Serious, acute hypersensitivity reaction (eg, urticaria, angioedema, bronchoconstriction, anaphylaxis) have been rarely observed during alpha interferon therapy. If this occurs, therapy must be discontinued and appropriate medical therapy instituted immediately. Transient rashes do not necessitate interruption of treatment."* In addition, these adverse events are listed in SPC Section 4.8 (Undesirable effects).	None proposed
Autoimmune Adverse Events	Warning in Section 4.4 of the SPC describing the possibility of development of auto-antibodies and autoimmune disorder during alpha-interferon monotherapy or Pegasys/ ribavirin combination therapy: *"The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed."* In addition, these types of adverse events are listed in SPC Section 4.8 (Undesirable effects).	None proposed
Ocular Adverse Events	Warning in Section 4.4 of the SPC describing the spectrum of occurrence of the ocular events, and suggestions for management: *"As with other interferons retinopathy including retinal hemorrhages,*	None proposed

	cotton wool spots, papilloedema, optic neuropathy and retinal artery or vein obstruction which may result in loss of vision have been reported in rare instances with Pegasys. All patients should have a baseline eye examination. Any patient complaining of decrease or loss of vision must have a prompt and complete eye examination. Patients with preexisting ophthalmologic disorders (eg, diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams during Pegasys® therapy. Pegasys treatment should be discontinued in patients who develop new or worsening ophthalmologic disorders." In addition, above ocular adverse events are listed in SPC Section 4.8 (Undesirable effects).	
Pulmonary Adverse Events	Warning in Section 4.4 of the SPC describing the spectrum of such events and recommendation to discontinue treatment if events persist or are unexplained. *"As with other alpha interferons, pulmonary symptoms, including dyspnea, pulmonary infiltrates, pneumoniae, and pneumonitis have been reported during therapy with Pegasys. In case of persistent or unexplained pulmonary infiltrates or pulmonary function impairment, treatment should be discontinued."* In addition, above adverse events are listed in SPC Section 4.8 (Undesirable effects).	None proposed
Serious and Severe Infections (bacterial, viral, fungal) Adverse Events	Safety information in Section 4.4 of the SPC. *"While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever, particularly serious infections (bacterial, viral, fungal) must be ruled out, especially in patients with neutropenia. Serious infections (bacterial, viral, fungal) and sepsis have been reported during treatment with alpha interferons including Pegasys. Appropriate anti-infective therapy should be started immediately and discontinuation of therapy should be considered."* In addition, above adverse events are listed in SPC Section 4.8 (Undesirable effects).	None proposed
Skin Disorder	Warning in Section 4.4 of the SPC describing the spectrum of such events and recommendation to discontinue treatment if events persist or worsen: *"Use of alpha interferons has been associated with exacerbation or provocation of psoriasis and sarcoidosis. Pegasys must be used with caution in patients with psoriasis, and in cases of onset or worsening of psoriatic lesions, discontinuation of therapy should be considered."* In addition, skin adverse events are listed in SPC Section 4.8 (Undesirable effects).	None proposed
Teratogenic and Carcinogenicity Risk Adverse	Warning in Section 4.4 of the Copegus SPC discussing the need of using contraception during treatment with ribavirin.	None proposed

Events	*"Prior to initiation of treatment with ribavirin the physician must comprehensively inform the patient of the teratogenic risk of ribavirin, the necessity of effective and continuous contraception, the possibility that contraceptive methods may fail and the possible consequences of pregnancy should it occur during treatment with ribavirin. For laboratory monitoring of pregnancy please refer to Laboratory tests."* **Carcinogenicity:** *Ribavirin is mutagenic in some in vivo and in vitro genotoxicity assays. A potential carcinogenic effect of ribavirin cannot be excluded (see Section 5.3).* Additional safety information about pregnancy and lactation are listed in SPC Section 4.6 (pregnancy and lactation).	
Potential Risks:		
Possible persistence or *de novo* development of neuropsychiatric events after stopping treatment.	Because of the potential for psychiatric or CNS reactions, Section 4.4 of the Pegasys SPC contains a black box describing the spectrum of neuropsychiatric reactions	None proposed
Possible persistence or *de novo* development of thyroid dysfunction after stopping treatment and its potential impact on growth.	The Pegasys USPI has been updated with information on growth impairment in the pediatric population. The following proposed boxed warning in the SPC describing the pediatric growth impairment findings on treatment, based on the safety results from the PEDS-C study: *Growth and development (children and adolescents):* *During the course of therapy lasting up to 48 weeks in patients aged 5 through to 17 years, weight loss and growth inhibition were common (see sections 4.8 and 5.1).* *At 2 years post-treatment with Pegasys, 16% of pediatric subjects remained 15 percentiles or more below their baseline weight curve and 11% remained 15 percentiles or more below their baseline height curve.* *Case by case benefit/risk assessment in children* *The expected benefit of treatment should be carefully weighed against the safety findings observed for children and adolescents in the clinical trials (see sections 4.8 and 5.1).* *- It is important to consider that the combination therapy induced a growth inhibition, the reversibility of which is uncertain.* *- This risk should be weighed against the disease characteristics of the child, such as evidence of disease progression (notably fibrosis), co-morbidities that may negatively influence the disease progression (such*	None proposed

	as HIV co-infection), as well as prognostic factors of response (HCV genotype and viral load). *Whenever possible the child should be treated after the pubertal growth spurt, in order to reduce the risk of growth inhibition. There are no data on long term effects on sexual maturation.*	
Medication Errors in Pediatrics	Dosing by BSA category and dosing graph included in the EU SmPC.	None proposed
Missing Information:		
Efficacy and safety of Pegasys/ribavirin in pediatric HCV patients who are 3 to 5 years old	Section 4.2 of the EU SmPC states "Only limited safety and efficacy data are available in children and adolescents (6-18 years)"	None proposed
Efficacy and safety of Pegasys/ribavirin in pediatric patients with HIV/HCV coinfection	Section 4.2 of the EU SmPC states "Only limited safety and efficacy data are available in children and adolescents (6-18 years)"	None proposed
Efficacy and safety of Pegasys/ribavirin in pediatric HCV patients in whom previous treatment has failed	Section 4.2 of the EU SmPC states "Only limited safety and efficacy data are available in children and adolescents (6-18 years)"	None proposed
Use of Pegasys in pediatric patients with renal impairment	Section 4.2 of the EU SmPC states "Only limited safety and efficacy data are available in children and adolescents (6-18 years)"	None proposed

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

Summary of activities in the risk management plan by medicinal product

There has been the addition of information related to the use of Pegasys with NS3/4A protease inhibitor for adults with chronic hepatitis C caused by genotype 1 virus in the summary of treatment benefits as well as in the summary of unknowns regarding benefit. The Revisions are endorsed by PRAC.

The CHMP endorsed the PRAC Advice without changes.

PSUR cycle

The PSUR cycle remains unchanged

2.5. Update of the Product information

As a consequence of this new indication, sections 4.1 and 4.2, of the SmPC have been updated.

In addition the CHMP took the opportunity of this variation to request that information pertaining to liver histology prior to therapy be deleted. Given the evolution of the hepatitis C treatment field, including the widespread use of non-invasive methods for the evaluation of degree of fibrosis, the information is no longer relevant (EASL guidelines 2012).

The full product information is included in Attachment 1 to this report. The wording of the new indication is specified hereafter:

Section 4.1 Therapeutic indications

Pegasys is indicated in combination with other medicinal products, for the treatment of chronic hepatitis C (CHC) in patients with compensated liver disease (see sections 4.2, 4.4 and 5.1).

For hepatitis C virus (HCV) genotype specific activity, see sections 4.2 and 5.1.

Of note information which further defines the target population, notably patients with compensated liver disease is retained in the updated indication. The CHMP supports this inclusion as the specification of compensated liver disease correlates with the corresponding and extant contraindication in decompensated liver disease.

Discussion on the Benefit-Risk Balance

Benefits

Beneficial effects

The addition of first generation NS3/4A inhibitor telaprevir to peginterferon alfa-2a in treatment naive patients increases response rates from around 40-50% with peginterferon alfa-2a+ribavirin to 70-80% as seen with telaprevir+peginterferon alfa-2a+ribavirin. Studies where boceprevir is added to peginterferon alfa-2b, which mainly differs from peginteferon alfa-2a insofar that the PEG-moiety has a lower molecular weight and half-life therefore is shorter, have shown similar increases in SVR rates with boceprevir is added to peginterferon alfa-2b+ribavirin in treatment naive patients.

In patients with experience of previous failure to reach SVR with peginterferon alfa-2a+ribavirin (and thus preselected as a subpopulation with lower response to peginterferon), that are retreated with telaprevir or boceprevir in combination with peginterferon alfa-2a or ribavirin, the absolute response rates are lower than in a treatment naive patients; however, the proportional increment in SVR rates tends to be greater, as illustrated by an absolute increment of more than 40 percentage units in the full populations of the studies pivotal to the present variation.

Risks

Unfavourable effects

Both telaprevir and boceprevir add to the haematological side effects that are characteristic of peginterferon alfa-2a+ribavirin treatment. Furthermore, they add some other adverse reactions to the

total side effects burden, the most important of which is telaprevir-associated rash. The product information for peginterferon alfa-2a contain a considerable section the selection of patients for treatment and on the management of haematological adverse effects. Further information of the appropriate selection of patients, as well as on monitoring and management of such events are found in the SmPCs for Incivo and Victrelis, to which cross reference is proposed.

Discussion on the benefit-risk balance

The benefit risk balance of the combination of an NS3/4A inhibitor and ribavirin with peginterferon alfa-2a has been previously evaluated by the CHMP in the context of the evaluations of the Marketing Authorisations of Incivo and Victrelis and has been found positive according to the conditions specified in the EPAR's and product information for these products. Therefore, the benefit-risk of combining peginterferon alfa-2a with ribavirin and an NS3/4A inhibitor (two of which are presently approved) is considered to be positive.

Very considerable changes have taken place in the field of HCV therapeutics within the last few years. The combination of a pegylated alfa-interferon and ribavirin was considered the standard of care for HCV genotype 1 (GT1) infection until 2011, when boceprevir and telaprevir were approved, and for the other HCV genotypes until the very recent approval of Sovaldi (sofosbuvir) the NS5B inhibitor which received approval by the European commission in January 2014. One recommended regimen for the use of Sovaldi is in combination with peginterferon and ribavirin.

The first DAAs approved, telaprevir and boceprevir, had exclusively been investigated in phase II/III trials in genotype 1 at the time of licensure. Both of these drugs have salient side effect profiles that need to be balanced against incremental efficacy. Furthermore, at least telaprevir is clearly not pangenotypically active. Hence, the CHMP adopted a specific indication for those products (i.e. GT1 infected patients, in combination with peginterferon alfa and ribavirin).

To further understand the rationale for this indication, it must be considered that, at the time of approval of these drugs in Europe, it had only very recently been demonstrated for products in development that SVR could be reached without an interferon (Lok et al, abstract presented at EASL, Berlin, March 2011, and subsequently published in N Engl J Med 2012), and there were no large studies on going with interferon-free regimens. Thus, the only drugs for which combination therapy could be relevant for these DAAs, were peginterferon alfa (-2a or -2b) and ribavirin, both of which were needed for reasonable efficacy.

Presently there is evidence from compounds in development that numerous combination regimens, with or without interferon, can be used to obtain SVR. DAAs of four distinct classes (NS3/4A protease inhibitors, NS5A inhibitors, non-nucleoside and nucleos(t)ide inhibitors of the NS5B polymerase) are currently in phase III trials or approved. Developmental drugs of all of these classes have been studied in various combinations; agents of each class having shown efficacy contributions in the development phase when combined with the others.

In this respect, the treatment landscape now bears similarity to that in HIV, where the beneficial antiviral effect of combining agents that lack evidence of cross resistance is well established. Also, it is anticipated that regimen selection for patients with experience of failure on regimens containing direct acting antivirals will be individualized based on an understanding of resistance and cross-resistance, like in the HIV field. In summary, the evolving field of hepatitis C therapeutics is similar to that of antiretroviral therapy in the following aspects:

- Combination therapy is anticipated in all cases

- Agents with different mechanisms of action or lack of cross resistance consistently show additive antiviral effects
- Failure of antiviral therapy is in many cases associated with selection of drug resistant viral variants which may impact future therapeutic option. Furthermore, in hepatitis C, there are naturally occurring viral polymorphisms that impact the activity of some agents.
- Consequently, individual viral drug susceptibility will need to be taken into account when selecting an appropriate combination regimen

Antiretrovirals used against HIV are generally approved for use "in combination with other agents", with the particular information needed for rational regimen selection provided in relevant sections of the SmPC. The emerging treatment landscape indicates that the same approach would be appropriate for hepatitis C medicines.

For these reasons the CHMP, has recommended in October 2013 that, in the general case, the indication (section 4.1. of the SmPC) for drugs against HCV infection should be as follows:

"[*TRADENAME] is indicated in combination with other agents for the treatment of chronic hepatitis C (CHC) in adults (see sections 4.2., 4.4. and 5.1.)"*

Further information relevant to viral genotypic specificity and to the appropriate and safe use of the drugs should be stated in the other sections of the SmPC.

Overall the benefit risk balance for the use of peginterferon alfa-2a in combination with ribavirin and an NS3/4A inhibitor is positive. The CHMP considers that the indication in adult patients with hepatitis C infection can be extended taking into account the above suggestion from the IDWP and the general format of the product information of recently approved products for the treatment of Hepatitis C.

This expansion of the indication is based on an interpretation of the scope of the external validity of the proprietary data of the MAH, that is the extent to which the data can be generalized in relation to the current state of the field and present treatment paradigm for hepatitis C.

Final Outcome

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

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

Extension of Indication for Pegasys to include the use of other products used for the treatment of Hepatitis C. The package leaflet is updated accordingly.

The requested variation proposed amendments to the SmPC and Package Leaflet.