24 September 2015
EMA/CHMP/174072/2015
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Rebetol

International non-proprietary name: ribavirin

Procedure No. EMEA/H/C/000246/II/0074

## Note

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



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# Table of contents

# List of abbreviations

| | |
|---|---|
| AEs | Adverse Events |
| $AUC_{0-12h}$ | Area Under the plasma Concentration- time curve from 0 to 12 hours after dosing |
| $AUC_{0-tf}$ | Area Under the plasma Concentration-time curve from time zero to last measurable concentration |
| BW | Body Weight |
| CHC | Chronic Hepatitis C |
| CHMP | Committee for Medicinal Products for Human Use |
| CI | Confidence Interval |
| CL/F | Apparent Clearance |
| $CL_{hd}$ | Haemodialysis Clearance |
| $CL_r$ | Renal Clearance |
| $C_{max}$ | Maximum plasma Concentration |
| CrCL | Creatinine Clearance |
| $C_{ssavg}$ | Concentration at Steady State |
| DAAs | Direct-Acting Antiviral agents |
| DNA | deoxyribonucleic acid |
| EOT | End Pf Treatment |
| ERA | Environmental Risk Assessment |
| ESRD | End-Stage Renal Disease |
| FAS | Full Analysis Set |
| GCP | Good Clinical Practices |
| HCV | Hepatitis C Virus |
| HCV-RNA | Hepatitis C Viral Ribonucleic Acid |
| IFN | Interferon |
| LOCF | Last Observation Carried Forward |
| MAH | Marketing Authorisation Holder |
| mITT | Modified Intent to Treat |
| PegIFN | Peginterferon |
| PK | Pharmacokinetics |
| PR | Dtandard of care therapy |
| PRAC | Pharmacovigilance Risk Assessment Committee |
| PSUR | Periodic Safety Update Report |
| QD | Quaque Die (once daily) |
| RGT | Response-Guided Therapy |
| RNA | Ribonucleic Acid |
| SAE | Serious Adverse Event |
| SmPC | Summary of Product Characteristics |
| SVR | Sustained Virological Response |
| TID | Three times daily |
| $T_{max}$ | Time of Maximum concentration |
| TW | Treatment Week |

# 1. Background information on the procedure

## *1.1. Type II variation*

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme Limited submitted to the European Medicines Agency on 7 July 2014 an application for a variation.

This application concerns the following medicinal product:

| **Centrally authorised Medicinal product(s):**<br><br>**For presentations: See Annex A** | **International non-proprietary name** |
|---|---|
| Rebetol | ribavirin |

The following variation was requested:

| **Variation requested** | | **Type** | **Annexes affected** |
|---|---|---|---|
| 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 | Type II | I, II, IIIA and IIIB |

Change of the indication of Rebetol to reflect that ribavirin is indicated in the treatment of hepatitis C in combination with other medicinal products and to remove reference to the peginterferon used (2a or 2b) in line with the PRAC recommendation in the PSUR assessment (EMEA/H/C/PSUSA/000100007/201307). As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.7, 4.8, 4.9 and 5.1 of the SmPC are updated.

The variation proposed amendments to the Summary of Product Characteristics, Labelling, Annex II and Package Leaflet

***Information on paediatric requirements***

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision EMA/28/2009 on the granting of a class waiver.

***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.

***Scientific advice/Protocol assistance***

The applicant did not seek scientific advice/Protocol Assistance at the CHMP.

## *1.2. Steps taken for the assessment of the product*

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

Rapporteur: Joseph Emmerich Co-Rapporteur: N/A

| Timetable | Actual dates |
|---|---|
| Rapporteur's preliminary assessment report circulated on: | 16 September 2014 |
| Request for supplementary information and extension of timetable adopted by the CHMP on: | 23 October 2014 |
| MAH's responses submitted to the CHMP on: | 20 January 2015 |
| Rapporteur's preliminary assessment report on the MAH's responses circulated on: | 09 March 2015 |
| Rapporteur's updated assessment report on the MAH's responses circulated on: | 20 March 2015 |
| 2nd Request for supplementary information and extension of timetable adopted by the CHMP on: | 26 March 2015 |
| MAH's responses submitted to the CHMP on: | 24 April 2015 |
| Rapporteur's preliminary assessment report on the MAH's responses circulated on: | 05 June 2015 |
| Rapporteur's updated assessment report on the MAH's responses circulated on: | 19 June 2015 |
| 3rd Request for supplementary information and extension of timetable adopted by the CHMP on: | 25 June 2015 |
| MAH's responses submitted to the CHMP on: | 24 August 2015 |
| Rapporteur's preliminary assessment report on the MAH's responses circulated on: | 08 September 2015 |
| CHMP opinion: | 24 September 2015 |

# 2. Scientific discussion

## *2.1. Introduction*

Rebetol (ribavirin) is a synthetic nucleoside analogue that is used in the treatment of chronic hepatitis C (CHC) and is authorised for use in combination with peginterferon alfa-2b and boceprevir (tritherapy) and with interferon or peginterferon alfa-2b (bitherapy). Ribavirin monotherapy must not be used. The approved dosing of Rebetol is based on patient body weight. The following pharmaceutical forms are currently authorised for Rebetol: 200mg hard capsules and 40 mg/ml oral solution.

Currently, Rebetol 200 mg hard capsules is indicated for use in adults and children aged 3 years and older as bitherapy in combination with interferon (IFN) alfa-2b or peginterferon (PegIFN) alfa-2b for the treatment of CHC infection in patients not previously treated, without liver decompensation, with elevated alanine aminotransferase, who are positive for hepatitis C viral ribonucleic acid (HCV-RNA). It is also indicated in adults for the treatment of CHC infection in combination with peginterferon alfa-2b for naïve patients with compensated cirrhosis and/or clinically stable HIV co-infection and in previously treated patients.

Rebetol is also authorised as tritherapy in combination with boceprevir and peginterferon alfa-2b in the treatment of CHC genotype 1 infection in adult patients with compensated liver disease who were previously untreated or who have failed previous therapy.

Rebetol oral solution 40mg/ml is indicated as a bitherapy in a combination regimen with IFN alfa-2b or PegIFN alfa-2b, for the treatment of children 3 years of age and older and adolescents, who have CHC, were not previously treated, do not have liver decompensation, and are positive for HCV-RNA.

Ribavirin has shown *in vitro* activity against some ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) viruses. Antiviral activity is associated with the phosphorylated metabolites of ribavirin. Ribavirin is not effective when used alone for the treatment of CHC. However, when used in combination with IFN alfa or PegIFN alfa for the treatment of CHC, ribavirin has been shown to increase the efficacy of the IFN alfa or PegIFN alfa used alone.

After reviewing the combined Periodic Safety Update Report for ribavirin-containing medicines (EMEA/H/C/PSUSA/00010007/201307), the EMA Pharmacovigilance Risk Assessment Committee (PRAC) recommended on 6 February 2014 changes to the Rebetol product information, recommendations that were endorsed by the CHMP on 20 February 2014, who requested the MAH to implement them.

The request was the following:

Given the evolving treatment landscape, including IFN free regimens, the indication of Rebetol (currently confined to the combination with peginterferon alfa 2b needs to be revised. The MAHs should submit within three months a type II variation to update the respective Summary of Product Characteristics (SmPC) taking into account the following recommendations:

- to reflect in section 4.1 that ribavirin is indicated in the treatment of hepatitis C in combination with other medicinal products. Any reference to the peginterferon used (2a or 2b) should be deleted.
- to reflect in section 4.2, the posology recommended according to the regimens (use in combination with peginterferon alfa 2a, use in combination with peginterferon alfa 2b, use in combination with other antivirals)

- to revise the current recommendations on the use of ribavirin in patients with moderate to severe renal impairment including dialysis. An update of the SmPC should be proposed in the light of the available data (including literature data) in order to better help clinicians facing the need to adjust the dose of ribavirin in patients with renal impairment including ESRD. The current contra-indication of Rebetol in patients with clearance creatinine <50 ml/min is to be reconsidered.
- to revise the current contra-indication of ribavirin in patients with hepatic impairment/decompensation that was historically based on the safety profile of peginterferon alfa used in bitherapy with ribavirin.

Currently, most of the safety information stated in the Rebetol PI is related to its use in combination with pegIFN. Since the use of ribavirin in clinical practice is no longer confined to the co-administration with peginterferon, it was considered important to revise the safety sections of the Rebetol SmPC in order to focus on those safety issues which were specifically related to the use of ribavirin. It was also considered that other safety concerns more specifically related to its use in combination with peginterferon alfa (such as psychiatric disorders, growth inhibition in paediatric population) could be presented separately or with a cross reference with the respective PIs for pegIFN.

The MAH submitted on 7 July 2014 the present variation application to update the product information of Rebetol with regards to:

1. a more inclusive wording that encompasses the use of Rebetol in regimens containing peginterferon alfa-2a or in combination with direct-acting antiviral agents (DAAs);

2. revision of the current recommendations on the use of ribavirin in patients with moderate to severe renal impairment including dialysis;

3. revision of the current contraindication of ribavirin in patients with hepatic impairment / decompensation; and

4. revision of the safety sections of the SmPC in order to focus on safety issues specifically related to the use of ribavirin.

## *2.2. Non-clinical aspects*

No new nonclinical data have been submitted with this application, which was considered acceptable by the CHMP.

### 2.2.1. Ecotoxicity/environmental risk assessment

In accordance with the CHMP guidance EMEA/CHMP/SWP/4447/00 "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use", an evaluation of the environmental impact should be made if there is an increase in the environmental exposure.

The MAH did not provide an Environmental Risk Assessment (ERA) with this application since the maximal daily dose is not modified and the predicted environmental concentrations of ribavirin are not expected to increase as a result of this change of indication.

The CHMP discussed and agreed that the exposure to ribavirin was not expected to increase with the current change of the wording of the indication and that changes to the predicted environmental concentration subsequent to this change of indication were not foreseen.

Therefore, an ERA was not considered necessary by CHMP. Nevertheless, subsequent PSURs will monitor the exposure to Rebetol.

### 2.2.2. Discussion and conclusion on non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP. It was agreed that the change in the indication was not expected to lead to a significant increase in the environmental exposure consequent to the use of Rebetol and that an ERA was not needed at the time of the present application.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

***Good Clinical Practices (GCP)***

The MAH declared that the clinical trials submitted were performed in accordance with the GCP.

The MAH has provided a statement in which it declared that the clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

### 2.3.2. Pharmacokinetics

***Special populations***

- **Patients with hepatic impairment**

Possible pathways for ribavirin metabolism include reversible phosphorylation, and degradation via deribosylation and amide hydrolysis. Ribavirin metabolism is not mediated by liver cytochromes and hepatic impairment does not alter the pharmacokinetics (PK) ribavirin.

The effect on the hepatic function was evaluated in study C95_155 (a single dose (600 mg oral) PK study in patients with mild, moderate or severe hepatic dysfunction (Child-Pugh Classification A, B or C). This study was re-submitted by the MAH within this procedure, this time as part of a recent literature review conducted by the MAH. CHMP noted nevertheless that this study was previously assessed with the initial marketing authorisation of Rebetol.

**Title of the Study**

The single dose pharmacokinetics of ribavirin in subjects with chronic liver disease (Glue P. et al (2000)) (study C95_155).

**Objectives, study design, and methods**

The primary objective of this open label study was to describe the single dose pharmacokinetics of ribavirin in subjects with normal liver function and those with degrees of stable chronic liver disease. The study also assessed the safety and tolerability of ribavirin in this population.

23 subjects were enrolled, which received a single dose of 600 mg ribavirin: 6 healthy volunteers (with normal liver function) and 17 patients with liver impairment (5 mild, 7 moderate and 5 severe, which were Child-Pugh's group A, B, C respectively).

PK sampling and tolerability assessments were performed up to 168 hours post-dose. Pharmacokinetics sampling included: maximum plasma concentration ($C_{max}$), time of maximum concentration ($t_{max}$) and the area under the plasma concentration-time curve from time zero to last measurable concentration ($AUC_{0-tf}$).

**Results**

The mean values for $AUC_{0-tf}$ were not significantly different in subjects with mild, moderate or severe hepatic dysfunction (Child- Pugh Classification A, B, and C respectively) when compared to control subjects (Table 1 and Figure 1). The mean $C_{max}$ value increased with severity of hepatic dysfunction. It was two-fold greater in subjects with severe hepatic dysfunction (Child-Pugh group C) compared with control subjects. However, there was a considerable overlap in individual $C_{max}$ values among the four groups and the PK of the medicine is known to be highly variable (Figure 1).

There was no change in extent of absorption or renal clearance of ribavirin.

These results suggested that the major site of first pass elimination were probably the tissues of the gastrointestinal tract. Thus, hepatic dysfunction has no effect on the pharmacokinetics of ribavirin.

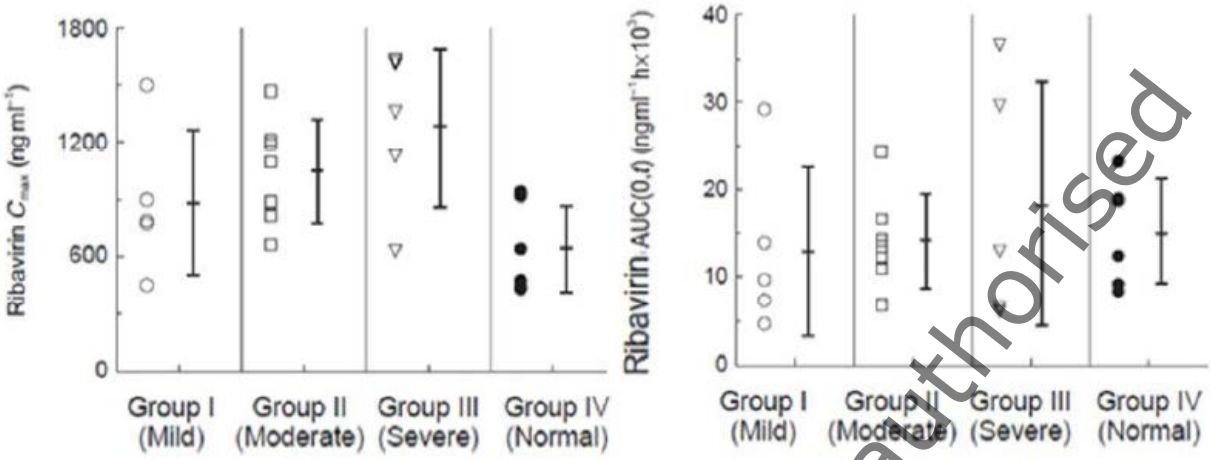
**Table 1.** Mean (%CV) Pharmacokinetic Parameters for Rebetol in Normal Controls and Patients with Hepatic Impairment

| | Controls | Child-Pugh A | Child-Pugh B | Child-Pugh C |
|---|---|---|---|---|
| n | 6 | 5 | 7 | 5 |
| Cmax (ng•ml-1) | 643 (37) | 886 (43) | 1048 (26) | 1273 (33) |
| Ratio; CI[a,b] | | 135%; 86-213 | 167%; 110-253 | 198%; 126-311 |
| tmax (h) | 1.33 (39) | 1.60 (56) | 1.29 (38) | 1.60 (34) |
| AUC(0-72 h) (ng•ml$^{-1}$ h) | 10927 (29) | 11284 (54) | 12274 (25) | 14454 (57) |
| AUC(tf) (ng•ml$^{-1}$ h) | 15162 (40) | 13046 (74) | 14184 (38) | 18392 (75) |
| Ratio; CI[a,b] | | 76%; 37-158 | 94%; 48-185 | 101%; 49-210 |

[a] Ratio = mean differences as percentage of control; 95% confidence intervals for ratio

[b] Ratio and confidence interval based on log-transformed data.

**Figure 1.** Individual Ribavirin Pharmacokinetic Parameters in Subjects with Normal Liver Function and with Various Degrees of Liver Impairment




The conclusion of the CHMP initial assessment for Rebetol was to include in section 5.2 of the Rebetol SmPC the following statement: "Single-dose pharmacokinetics of ribavirin in patients with mild, moderate or severe hepatic dysfunction (Child-Pugh Classification A, B or C) are similar to those of normal controls".

CHMP agreed that there are currently no additional pharmacokinetic data which would require a dose adjustment of ribavirin in patients with hepatic impairment.

It should be noted that the use of ribavirin and peginterferon alfa was previously contraindicated in patients with severe hepatic impairment or decompensated liver cirrhosis due to a lack of data from controlled clinical trials in this patient population and due to safety concerns associated with peginterferon alfa used in bi- and tri-therapy with ribavirin in those patients.

CHMP agreed that the existing contraindication was not applicable in interferon-free regimens. It has been acknowledged that experience on the use of ribavirin in patients with hepatic impairment has been gained from the recent DAA developments and some DAA are indicated in combination with ribavirin in patients with advanced liver disease. Published literature support the use of ribavirin in combination with DAA in patients with advanced liver disease.

Based on current scientific evidence, CHMP agreed to remove the contraindication for Rebetol in patients with severe hepatic impairment or decompensated cirrhosis.

- **Patients with renal impairment**

At the time of submission of this application, Rebetol was contraindicated in patients with moderate or severe renal impairment (i.e. creatinine clearance (CrCL) <50 mL/min), as there were no data available from dose ranging trials in this patient population.

## Supportive data

***Clinical Trials Conducted by MAH***

Two PK studies conducted in patients with renal impairment were also provided for assessment by the MAH.

**Study title**

Pharmacokinetics and safety of single-dose ribavirin in patients with chronic renal impairment

**Study design and methods**

This was an open-label, parallel-group, single-dose study to assess the PK parameters of ribavirin after administration of a 400mg oral dose in healthy adult subjects with normal renal function (control group with CrCl > 90 mL/min) and with varying degrees of renal impairment (between 60 and 10 mL/min).

Blood and urine samples were collected pre-dose and up to 168 hours post-dose for PK analyses.

**Results**

The mean $AUC_{tf}$ was three-fold greater in subjects with severe renal impairment (CrCL between 10 and 30 mL/min) compared with control subjects (CrCl > 90 mL/min). In subjects with moderate renal impairment (CrCL between 30 and 60 mL/min), $AUC_{tf}$ was two-fold greater compared with control subjects. The increased $AUC_{tf}$ appeared to be due to reduction of renal and non-renal clearance in these subjects. $C_{max}$ was also increased and the apparent clearance (CL/F), clearance ($CL_r$) and amount excreted values were reduced in subjects with renal impairment. The main finding of this study was that ribavirin exposure was significantly increased in patients with renal impairment.

**Study title**

Pharmacokinetics, safety, and tolerability of ribavirin in haemodialysis-dependent patients

**Study design and methods**

The study included six adult haemodialysis-dependent patients, not infected with HCV. Patients received a single oral 400 mg dose of ribavirin after an overnight fast. Fasting was maintained until 4 hours postpose, and haemodialysis session was performed between 6 and 10 hours post-dose.

Plasma and urinary concentrations of ribavirin were determined using validated high-performance liquid chromatography and tandem mass spectrometric methods.

**Results**

Ribavirin haemodialysis clearance ($CL_{hd}$ = 74.5 ml/min) in these patients was approximately 50% of the CLr measured in subjects with normal renal function (CLr = 129 mL/min). During a 4-hour dialysis session, the total amount of ribavirin removed was low (~2.4% of the dose).

Single oral doses of ribavirin 400 mg were safe and well tolerated in this population.

Urinary excretion of ribavirin over 48 hours was minimal (0.6 mg: approximately 0.14% of the dose).

The mean amount removed during the 4 hours haemodialysis session (9.6 mg) represented approximately 2.4% of the dose.

Ribavirin haemodialysis clearance ($CL_{hd}$ = 74.5 ml/min) represented approximately 50% of the renal clearance (CLr) measured in subjects with normal renal function (CLr=129 ml/min).

**Discussion**

The ribavirin principal route of elimination is renal excretion (for both the parent molecule and its metabolites). Both above mentioned studies showed that the pharmacokinetics of ribavirin is substantially altered in subjects with stable chronic renal impairment compared with subjects with normal renal function and in patients that are haemolysis dependent. Therefore, an adjusted dose recommendation for HCV-infected patients with chronic renal impairment was deemed necessary by CHMP.

The MAH has not conducted phase 3 efficacy clinical trials with ribavirin in subjects with CrCl < 50 mL/min.

***Literature review***

The MAH performed a literature review and the following clinical study by Brennan et al (2013) has been retrieved. In this publication, a population PK analysis was performed to propose dosing regimens for renally impaired patients.

**Title of the study**

Safety, Tolerability, and Pharmacokinetics of Ribavirin in Hepatitis C Virus-Infected Patients with Various Degrees of Renal Impairment.

**Study design and methods**

This was an open-label, non-randomised, parallel-group multicentre international study. The primary objective of the study was to evaluate the PK and safety profile of ribavirin plus peginterferon alfa in HCV infected adult patients with moderate (CrCL <30 to 50 ml/min) [group A], severe (CrCL <30ml/min) [group B] renal impairment or ESRD requiring haemodialysis [group C]. A total of 63 HCV-infected patients were enrolled, of whom 44 were evaluable for the PK analyses (Week 12).

All patients were administered peginterferon alfa-2a 180 µg once weekly except those with end-stage renal disease (ESRD) who received a reduced dose of 135 µg once weekly.

Ribavirin was administered as follows according to the renal impairment stage of the patient:

- 12 patients with normal renal function (CLCR >80 mL/min) were administered 1,000 or 1,200 mg of Ribavirin daily;
- 9 patients with moderate renal impairment (CLCR between 30 and 50 mL/min) were administered 600 mg of ribavirin daily;
- 10 patients with severe renal impairment (CLCR <30 mL/min) were administered 400 mg of ribavirin daily, and
- 13 patients with ESRD were administered 200 mg of ribavirin daily.

Serial PK ribavirin plasma samples were collected over 12 hours on Day 1 of Weeks 1 and 12. A non-compartmental PK analysis of the plasma ribavirin concentration was performed using WinNonlin (version 5.0.1). The analysis included 686 ribavirin plasma concentrations from the 63 subjects.

The calculated parameters were the $C_{max}$, CL/F and the area under the plasma concentration- time curve from 0 to time of interest (12 hours for ribavirin) after dosing ($AUC_{0-12h}$).

**Population PK analysis**

A population PK analysis was performed using non-linear randomised-effect modelling (NONMEN version VII, level 1.0) to describe the Ribavirin PK data and simulate alternate dosing regimen for patients with renal impairment that provided ribavirin exposure similar to the ones in patients with normal renal function.

The target ribavirin concentration for patients with renal impairment was defined as being within 20% of the average predicted Concentration at Steady State ($C_{ssavg}$) in patients with normal renal function from a previously developed population PK model receiving ribavirin doses of 1000 or 1200 mg daily based upon body weight. This was similar to the $C_{ssavg}$ (2338 ng/mL) for patients with normal renal function in the current study who were dosed with 800 to 1200 mg daily.

A covariate model of potential influential covariates (e.g. age, weight, sex, body mass index, etc.) was tested on apparent clearance (CL/F), apparent volumes of distribution (V2/F, V3/F), relative bioavailability and absorption-related parameters. Forward covariate selection was performed using selection criterion a P value < 0.05. Subsequently, backwards deletion was performed using a P value of < 0.01.

A predictive performance test was performed on the final model to compare the PK parameters ($AUC_{0-t}$ and $C_{max}$ after 12 weeks) derived by non-compartmental analysis with the model predictions.

The final model was used to simulate 100 new data sets based on the study patient's data.

**PK Results**

Non-compartmental analysis

In this study patients with ESRD dosed with 200 mg daily had a mean $AUC_{0-12h}$ that was 80% of the value in patients with normal renal function. At a 200 mg daily dose, ribavirin was well tolerated and generally safe in patients with ESRD, and dosage modification was relatively infrequent (22%).

Ribavirin was not effectively removed by haemodialysis due to its large volume of distribution.

Throughout the study the assigned ribavirin dose was reduced in 71% and 53% of patients with moderate or severe impairment, respectively, due to adverse events (AE), particularly anaemia. Despite dose reductions, patients with moderate and severe impairment had 36% and 25% higher plasma concentrations, respectively, compared to patients with normal renal function, as assessed by $AUC_{0-12h}$.

The authors noted that $AUC_{0-12h}$ and $C_{max}$ values reported for these two treatment groups were likely an underestimation of the anticipated steady-state values at the originally assigned ribavirin dose levels. Ribavirin exposure at Week 12 in these patients may not have reached steady-state because of extensive dose reduction. Thus, the authors concluded that ribavirin daily doses of 600 mg or 400 mg were too high for patients with moderate or severe impairment, respectively.

Population PK analysis and simulations

Given that the non-compartmental analysis was not appropriate in such situations to evaluate the impact of renal dysfunction, data was modelled using a population approach in which the change in the dosing regimen was incorporated on an individual basis.

A 2-compartment model with first-order elimination and parallel zero-and first – order absorption was constructed.PK modelling and simulation indicated that to achieve concentrations within 20% of the target concentration (2338 ng/mL) at steady state, the most appropriate ribavirin dose regimens were 200 mg or 400 mg alternating daily for patients with moderate renal impairment (30 – 50 ml/minute) and 200 mg daily for patients with severe renal impairment (<30 ml/minute) and for patients with ESRD receiving dialysis (Table 2).

**Table 2.** Dosage modification for renal impairment patients

| Creatinine Clearance (level of renal impairment) | Rebetol dose (daily) |
|---|---|
| 30 to 50 ml/min (moderate renal impairment) | Alternating doses, 200mg and 400mg every other day |
| Less than 30 ml/min (severe renal impairment) | 200 mg daily |

| Creatinine Clearance (level of renal impairment) | Rebetol dose (daily) |
|---|---|
| Haemodialysis (ESRD) | 200 mg daily |

The model was able to predict the values of $AUC_{0-12}$ and $C_{max}$ observed in the non-compartmental analysis.

Moreover, the MAH also provided a justification clarifying that the impact of renal dysfunction on the ribavirin exposure is similar regardless of the ribavirin medicinal product used and that the administration of Rebetol utilizing the above dosing regimen will provide adequate exposure of ribavirin.

**Renally Impaired Paediatric Patients**

No data are available to support a dose modification for paediatric patients with renal impairment. CHMP agreed to maintain the existing contraindication for paediatric patients with chronic renal failure, patients with creatinine clearance <50 ml/minute and/or on haemodialysis.

## 2.3.3. Discussion and conclusions on clinical pharmacology

Treatment with Rebetol in renally impaired patients (CrCl < 50 ml/min) was contraindicated until now, due to a lack of clinical data. Nevertheless, the need for treatment options in renally impaired HCV-infected patients (whose numbers are sizeable) has to be also recognised. Chronic hepatitis C may exacerbate renal disease, and among patients with ESRD undergoing haemodialysis, an estimated 14% or more are infected with HCV. The MAH was requested to revise the current SmPC recommendations on the use of ribavirin in patients with moderate to severe renal impairment including dialysis and to reconsider the current contraindication of Rebetol in patients with clearance creatinine <50 ml/min. In this context, the MAH provided PK studies conducted in patients with renal impairment.

As described in section 2.3.2 of this report, the PK parameters of ribavirin are importantly altered in subjects with renally impaired patients and CHMP agreed that the dose for HCV-infected patients with chronic renal impairment should be adjusted in the Rebetol SmPC.

The CHMP also agreed to remove the previously existing contraindication for adult patients with chronic renal failure, patients with CrCl <50 ml/min and /or on haemodialysis from the Rebetol SmPC.

Furthermore, modified dosing recommendations were added in the SmPC to better inform clinicians facing the need to adjust the dose of ribavirin in patients with renal impairment including ESRD (Table 2). These changes are consistent with the current therapeutic guidelines issued by relevant learned societies (e.g. AASLD, EASL).

Finally, CHMP agreed to maintain the contraindication for renally impaired paediatric patients in the Rebetol SmPC, due to the insufficient existing data to recommend dosing guidelines in these patients.

Following the PRAC/CHMP request to revise the current contraindication of ribavirin in patients with severe hepatic impairment or decompensated cirrhosis, the MAH presented the results of a PK study conducted in patients with hepatic dysfunction. This study showed that hepatic dysfunction has no significant effect on the PK parameters of ribavirin; therefore no dose adjustment of ribavirin in patients with hepatic impairment is deemed necessary. The existing contraindication, which was initially motivated by the co-administration with (peg)interferon alfa is not applicable in interferon free regimens and as a consequence it was removed from the Rebetol SmPC.

## *2.4. Clinical efficacy*

### 2.4.1. Main supportive studies

The MAH did not conduct any clinical trial that support the dosing of Rebetol with peginterferon alfa-2a. However, literature data support the fact that the various ribavirin-containing medicinal products have comparable pharmacokinetic profiles; therefore the available data on various ribavirin products can be also considered relevant for Rebetol.

The MAH submitted three MAH sponsored clinical trials including studies performed with ribavirin and peginterferon alfa 2a +/- boceprevir as DAA. In light of the above, the studies presented in the following table are considered relevant for the current application.

**Table 3.** Overview of the phase III studies submitted by the MAH to support this change of indication

| Trial ID | Phase | Country | Trial Title | Trial design | Dosing regimen | Trial population | Subject exposure |
|---|---|---|---|---|---|---|---|
| P03471<br><br>(Sec. 5.3.5.1 in EMEA/H/C/0 246/II/048) | 3b | USA | Comparison of PegIntron™ (SCH 54031; Peginterferon Alfa-2b) 1.5 µg/kg/wk Plus Rebetol™ (SCH 18908; Ribavirin) vs PegIntron 1.0 µg/kg/wk Plus Rebetol vs Pegasys™ (Peginterferon Alfa-2a) 180 µg/wk Plus Copegus™ (Ribavirin) in Previously Untreated Adult Subjects With Chronic Hepatitis C Infected With Genotype 1 | Randomized, parallel-group, multicenter, double-blinded for PEG2b dose, open label for PEG2a and ribavirin. | All arms: 48 week treatment with 24- week follow-up.<br>Arm 1: peginterferon alfa-2b 1.5 mg/kg/wk SC in combination with weight-based ribavirin 800 to 1400 mg/day PO (PEG2b 1.5/R).<br>Arm 2: peginterferon alfa-2b 1.0 mg/kg/wk SC in combination with weight-based ribavirin 800 to 1400 mg/day PO (PEG2b 1.0/R).<br>Arm 3: peginterferon alfa-2a 180 mg/wk SC plus weight-based ribavirin 1000 to 1200 mg/day PO (PEG2a/R). | 1833 males and 1237 females; ages 18-70. Previously untreated adult subjects with chronic hepatitis C infected with HCV genotype 1 | 3070 treated:<br>PEG2b 1.5/R: 1019<br>PEG2b 1.0/R: 1016<br>PEG2a/R: 1035 |

| Trial ID | Phase | Country | Trial Title | Trial design | Dosing regimen | Trial population | Subject exposure |
|---|---|---|---|---|---|---|---|
| P05101<br><br>(Sec. 5.3.5.1 in EMEA/H/C/0 246/WS/216) | 3 | Belgium, Canada, France, Germany, Italy, Puerto Rico, Spain, USA | A Phase 3 Safety and Efficacy Study of Boceprevir (SCH 503034) in Subjects With Chronic Hepatitis C Genotype 1 Who Failed Prior Treatment With Peginterferon/ Ribavirin (RESPOND-2) | Phase 3, randomized, parallel-group, multi-center study, double-blinded for BOC or placebo in combination with open-label PR. | Control:<br>Arm 1: PR for 4 weeks followed by placebo + PR for 44 weeks with 24 weeks post-treatment follow-up.<br>Experimental Therapy:<br>Arm 2: PR for 4 weeks followed by BOC 800 mg TID PO + PR for 32 weeks, then:<br>a. 36-week regimen: Subjects with undetectable HCV-RNA at TW 8 were to discontinue treatment at TW 36 and enter 36 weeks of post-treatment follow-up.<br>b. 48-week regimen: Subjects with detectable HCV-RNA at TW 8 were to be assigned an additional 12 weeks of therapy with placebo plus PR to complete a total of 48 weeks on treatment, followed by 24 weeks of post-treatment follow-up. (The switch from BOC to placebo occurred in a blinded fashion.)<br>Arm 3: PR for 4 weeks followed by BOC 800 mg TID PO + PR for 44 weeks, with 24 weeks post-treatment follow-up. | 269 males and 135 females; ages 26-74. Previous PEG/RBV treatment failures. | 403 subjects treated:<br>PR (Arm 1): 80;<br>BOC/PR36 or BOC/PR48 (Arm 2): 162;<br>BOC/PR48 (Arm 3): 161. |

| Trial ID | Phase | Country | Trial Title | Trial design | Dosing regimen | Trial population | Subject exposure |
|---|---|---|---|---|---|---|---|
| P05685<br><br>[Ref. 5.3.5.1: P05685] | 3 | Belgium, Canada, France, Italy, Germany, USA | 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 | Randomized, multicenter, double-blind, placebo-controlled. | Control:<br>Arm 1: peginterferon alfa 2a (PEG2a) 180 µg QW SC/ ribavirin (based on weight) for 4 weeks followed by placebo + PEG2a/ ribavirin for 44 weeks with 24 weeks post-treatment follow-up.<br>Experimental Therapy:<br>Arm 2: PEG2a/ribavirin for 4 weeks followed by BOC 800 mg TID PO + PEG2a/ ribavirin for 44 weeks with 24 weeks post-treatment follow-up. | 140 males, 61 females; ages 29-70. Previous PEG/RBV treatment failures. | PEG2a/R: 67<br>BOC/PEG2a/R: 134 |

**Study title**

Comparison of PegIntron 1.5µg/kg/wk plus Rebetol vs PegIntron 1µg/kg/wk plus Rebetol vs Pegasys 180µg/wk plus Copegus in previously untreated adult subjects with chronic hepatitis C infected with genotype 1 (IDEAL study (P04471)).

**Objective and endpoints**

The main objective of this study was to compare the safety and efficacy of the following three treatment regiments in previously untreated adult subjects with chronic hepatitis C infected with genotype 1:

- Arm 1: Peginterferon alfa-2b 1.5 µg /kg/week (PegIntron) plus ribavirin (Rebetol) at a dose of 800 to 1400 mg per day (QD) (PEG2b 1.5/R).
- Arm 2:Peginterferon alfa-2b 1.0 µg/kg/week (PegIntron) plus ribavirin (Rebetol) 800 to 1400 mg QD (PEG2b 1.0/R)
- Arm 3: Peginterferon alfa-2a 180 µg/week plus (Pegasys) ribavirin (Copegus) at a dose of 1000 to 1200 mg QD (PEG2a/R).

The primary endpoint variable was Sustained Virological Response (SVR) rate defined as the percentage of participants with undetectable HCV-RNA at the end of the 24-week post-treatment follow-up.

Comparison of proportions with SVR of arm 1 vs arm 2, and arm 1 vs arm 3 were defined as co-primary endpoints.

**Study design and methods**

This was a randomised, parallel-group multicentre trial conducted in the USA, in treatment-naive genotype 1 patients with chronic hepatitis C. Patients were randomised to three different treatment arms. In all arms, the pegylated interferon was combined with weight-based ribavirin as described above.

In the PegIFN 2b arms, ribavirin was dosed at 800 mg/day when body weight was 40-65 kg, 1000 mg/day if body weight > 65-85, 1200 mg/day if body weight > 85-105 and 1400 mg/day if body weight > 105 kg.

In the PegIFN 2a arm, patients with body weight < 75 kg received 1000 mg/day and those with body weight > 75 kg received 1200 mg.

The comparison between PegIFN 2b doses was double-blinded, whereas the assignment to PegIFN 2a or PegIFN 2b was open-label. This was due to the difference formulations of the peginterferon 2alfa (i.e. solution for Peginterferon alfa-2a versus lyophilized powder for Peginterferon alfa-2b).

Treatment duration was planned to 48 weeks, and stopping rules were applied in case of detectable HCV-RNA at 24 weeks, or detectable and less than > 2 $\log_{10}$ decline of HCV-RNA at week 12.

**Results**

A total of 3070 subjects in a 1:1:1 ratio to 48 weeks of treatment with one of three regimens were randomised and received at least one dose of study drug. The distribution was 1019 subjects in Arm 1 (PEG2b 1.5/R arm), 1016 subjects in Arm 2 (PEG2b 1.0/R) and 1035 subjects in Arm 3 (PEG2a/R arm).

The study has shown that each of the three treatment regimens resulted in similar SVR rates with numeric but not statistically significant differences observed between standard dose and low dose peginterferon alfa-2b and between standard dose peginterferon alfa-2b and peginterferon alfa-2a regimens. The SVR rates for the PEG2b 1.5/R and the PEG2b 1.0/R arms were 39.8 and 38%, respectively. The point estimate for the difference was 1.8 with a 95% CI between -2.3 and 6.0 (Table 4).

There were some limitations to data interpretation which were the following:

1. the initial ribavirin dose varied among patients,
2. the recommendations for ribavirin-dose reduction differed between the peginterferon alfa-2a and peginterferon alfa-2b groups and
3. the data may not be generalizable to regions outside the US or to other HCV genotypes.

**Table 4.** Sustained Virologic Response rates in the IDEAL study- bitherapy with ribavirin plus standard dose or low dose peginterferon alfa-2b or peginterferon alfa-2a

| | % of Subjects | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Arm 1 vs Arm 3 | | Arm 1 vs Arm 2 | | Arm 2 vs Arm 3 | |
| | PEG2b 1.5/R (Arm 1) | PEG2b 1.0/R (Arm 2) | PEG2a/R (Arm 3) | P-value | Odds ratio (95% CI)[a] | P-value | Odds ratio (95% CI)[a] | P-value | Odds ratio (95% CI)[a] |
| SVR[b] | 39.8% (406/ 1019) | 38.0% (386/ 1016) | 40.9% (423/ 1035) | 0.567 | 0.95 (0.79, 1.14) | 0.195 | 1.08 (0.90, 1.30) | 0.151 | 0.88 (0.73, 1.05) |

CI = confidence interval; PEG = peginterferon alfa; R = ribavirin; SVR = sustained virologic response.

a: The p-values and odds ratios are based on a logistic regression model that includes treatment and baseline stratification factors: viral load (≤600,000 IU/mL vs >600,000 IU/mL, measured by the sponsor's laboratory) and race (Black vs non-Black).

b: The primary efficacy analysis utilizing only the available Follow-up Week 24 data (ie, no carry-forward of FW 12 data for missing FW 24 data), resulted in similar trends in SVR rates: 36.1% (368/1019) in PEG2b 1.5/R vs 35.9% (365/1016) in PEG2b 1.0/R vs 38.5% (398/1035) in PEG2a/R, with nonsignificant P-values (CSR Sec. 14.2.1.1).

Reduction of ribavirin dose did not show to have a negative impact on SVR. Of note, the SVR rate was higher among patients who had the ribavirin dose reduced due to anaemia compared to those who received the standard dose.

**Study title**

A Phase 3 Safety and efficacy study of boceprevir (SCH 503034) in subjects with chronic hepatitis C Genotype 1 who failed prior treatment with peginterferon/ribavirin (RESPOND-2 study (P05101))

**Objectives and endpoints**

The primary objective was to compare the efficacy of two therapeutic regimens (i.e. 32 weeks and 44 weeks) of boceprevir 800 mg dosed orally three times daily in combination with the standard of care therapy (PR) to standard of care therapy (PR) alone in adult subjects with chronic hepatitis C HCV genotype 1 who failed previous treatment with a qualifying regimen of pegIFN/Ribavirin.

The standard of care therapy (PR) consisted of PEG2b 1.5 µg/kg subcutaneously once weekly plus weight-based dosing of ribavirin (600 mg/day to 1400 mg/day) dosed orally.

The primary efficacy endpoint was the achievement of SVR, defined as undetectable plasma HCV-RNA at follow-up week 24.

**Study design and methods**

This was a randomised, parallel-group, multi-centre study, double-blinded for boceprevir or placebo in combination with open-label PR, in adult subjects with chronic HCV genotype 1 who demonstrated interferon responsiveness but failed to achieve SVR on prior treatment with peginterferon/ribavirin.

Subjects were randomised to 1 of 3 treatment arms on Day 1 on a 1:2:2 ratio. At the time of randomisation, subjects were stratified based on response to their previous qualifying regimen (relapser vs non-responder) and by HCV subtype (1a vs 1b). A 12-week futility rule was followed for all arms, whereby all subjects with detectable HCV-RNA at Treatment Week (TW) 12 discontinued therapy and entered follow-up. Treatment failures in the PR control arm (Arm 1) were offered the opportunity to receive treatment with boceprevir plus PR (BOC/PR) via an access study (P05514) or to proceed to the follow-up phase of this study. Subjects in the Response-Guided Therapy (RGT) arm (Arm 2) and the BOC/PR48 arm (Arm 3) proceeded directly to the follow-up phase of this study. Sites and subjects remained blinded as to whether subjects had been in Arm 2 or Arm 3.

The primary efficacy endpoint (achievement of SVR) was analysed using the Full Analysis Set (FAS), which included all subjects who received at least one dose of any study drug (PEGIFN alfa 2b, ribavirin, or boceprevir/placebo).

It was summarised for each treatment arm using descriptive statistics (n, %). SVR rated were based on the last observation carried forward (LOCF) approach, in which the follow –up week 12 HCV-RNA results were carried forward for subjects with missing HCV-RNA value at and after follow –up week 24.

**Results**

*Patient disposition*

A total of 404 subjects were randomised. Of these, 403 subjects (Control [Arm 1], n=80; RGT [Arm 2], n=162; BOC/PR48 [Arm 3], n=161) received at least one dose of study medication (Full Analysis Set [FAS]), and 394 (Control, n=78; RGT, n=156; BOC/PR48, n=160) received at least one dose of boceprevir or placebo (Modified Intent to Treat [mITT]).

*Baseline characteristics*

In this study, 67% (269/404) of the randomized subjects were male, and 88% (355/404) were non-black. The mean age was 52.7 years (range, 26-74 years) and the mean weight was 85 kg. All subjects had genotype 1 (47% [189/403] subtype 1a, 44% [178/403] subtype 1b by TRUGENE assay), and 88% (353/403) had high viral load (>800,000 IU/mL), with a 6.63 mean $\log_{10}$ baseline viral load.

*Efficacy results*

The primary analysis showed that SVR rates in the boceprevir arms were significantly higher than in the control arm ($p<0.0001$). SVR rates in subjects who received boceprevir were 59% and 66% in the RGT and BOC/PR48 arms, respectively, compared to 21% in the control arm (Table 5). Even in subjects with < 1.0 log10 decrease in HCV-RNA at TW 4 (poorly IFN responsive), who comprised roughly one-third of the study population, SVR rates of 33-34% were observed in the boceprevir arms, compared with 0% in the control arm. Interferon responsive subjects achieved SVR rates of 73-79% with the 3-drug regimen.

The addition of boceprevir to PR standard of care substantially reduced relapse rates (15% and 12% in the RGT and BOC/PR48 arms, respectively, compared to 32% in the control arm), representing an important contribution to the treatment of HCV (table 5).

In early responders (undetectable HCV-RNA by TW 8), relapse rates remained low (approximately 10%) after only 36 weeks of BOC/PR therapy.

**Table 5.** Sustained Virologic Response, End of Treatment Response and Relapse Rates (FAS) Effect estimate per comparison in Study RESPOND-2 (P05101)

| | FAS | | |
|---|---|---|---|
| | Control | Experimental | |
| | Arm 1<br>PR48<br>n=80 | Arm 2<br>RGT<br>n=162 | Arm 3<br>BOC/PR48<br>n=161 |
| **EOT** (Undetectable HCV-RNA), n (%) | 25 (31.3) | 114 (70.4) | 124 (77.0) |
| **SVR**, n (%) | 17 (21.3) | 95 (58.6) | 107 (66.5) |
| ΔSVR' | -- | 37.4 | 45.2 |
| 95% CI for Δ | -- | (25.7, 49.1) | (33.7, 56.8) |
| P value | -- | <0.0001 | <0.0001 |
| Relapse, n/N (%) | 8/25 (32.0) | 17/111 (15.3) | 14/121 (11.6) |

Overall, this study has shown that both boceprevir regimens (RGT and BOC/PR48) significantly increased SVR rates over PR standard of care (59% and 66% vs 21%, respectively). No subgroup of subjects was identified for whom PR therapy was superior to triple therapy with boceprevir plus PR. In addition, the RGT arm offers shorter treatment duration while maintaining efficacy. Thirty-two weeks of boceprevir as an add-on to PR treatment is as efficacious as 44 weeks of triple therapy among subjects with detectable HCV-RNA at TW 8.

**Study title**

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 (study P05685)

**Objectives and endpoints**

The primary objective was to compare the efficacy of boceprevir in combination with PEGIFN-alfa 2a (PEG2a) plus ribavirin (PEG2a/R) to the same PEG2a/R regimen without boceprevir for 48 weeks in adult subjects with 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.

The primary efficacy endpoint was the achievement of SVR, defined as undetectable HCV-RNA at follow-up week 24, in all randomised patients receiving at least one dose of study medication (FAS).

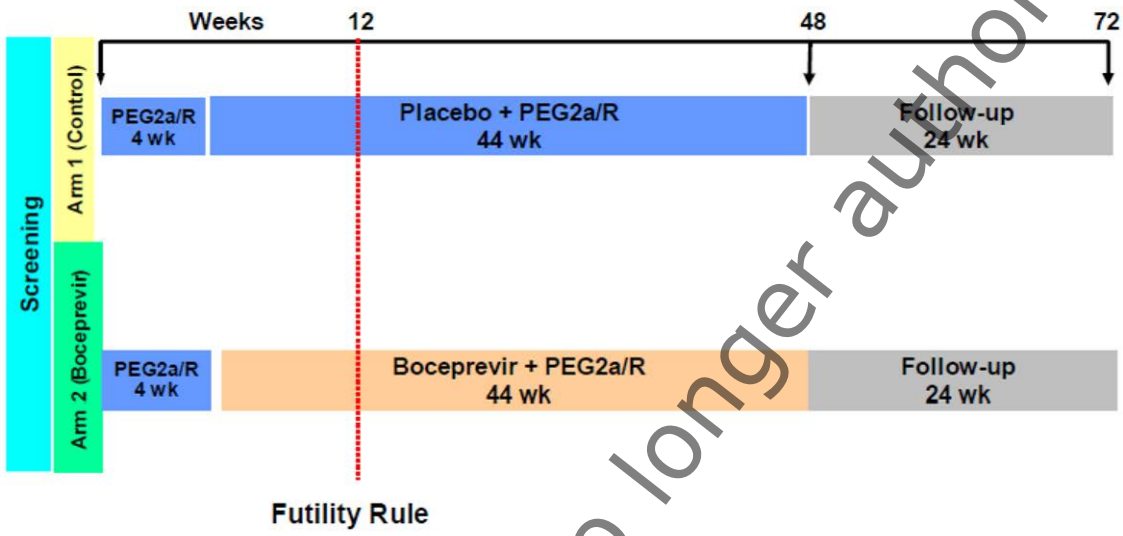
**Study design and methods**

This was a multicentre Phase 3 study, randomised (in a 1:2 ratio), 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.

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 HCV-RNA viral load $\geq$ 2 $\log_{10}$ by TW 12 or undetectable HCV-RNA at End of Treatment [EOT]) were selected for the study (Figure 2).

**Figure 2.** P05685 study design




**Results**

A total of 202 subjects were randomised in ratio of 2:1. 201 subjects received at least one dose of PEG2a/R, including 67 randomised to PEG2a/R control and 134 randomised to BOC/PEG2a/R.

*Baseline characteristics*

In this study, 70% (140/201) of the treated randomised 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.

Table 6 shows the efficacy outcomes (SVR rates) in the full analysis set, including all patients randomised and treated.

**Table 6.** Sustained Virologic Response, End of Treatment Response and Relapse Rates (FAS) effect estimate per comparison in Study P05685

| | 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) |

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.

Of note, SVR and relapse rates on the PegIFN alfa 2a plus ribavirin regimens (with or without boceprevir) were similar to those observed in the RESPOND-2 study with PegIFN alfa 2b plus ribavirin regiments in treatment-experienced patients with chronic HCV genotype 1.

## 2.4.2. Literature review

The MAH performed a literature review to support the revision of the indication. The following clinical studies published in the literature have been considered to be of particular relevance to support this application:

**Bitherapy**

**Adults**

In the study published by Rumi et al (Randomized study of peginterferon-alpha2a plus ribavirin vs peginterferon-alpha2b plus ribavirin in chronic hepatitis C. Gastroenterology. 2010 Jan;138(1):108-15) a direct comparison of Rebetol dosing with PegIFN alfa-2a and PegIFN alfa-2b was made.

Treatment-naïve patients with CHC were randomised in a 1:1 ratio after stratification for HCV genotype to receive either 1.5 µg/kg/week PegIFN alfa-2b plus Rebetol 800–1200 mg/day or 180 µg/week PegIFN alfa-2a plus Rebetol 800–1200 mg/day for 24 or 48 weeks according to HCV genotype. The study was powered to detect a difference of at least 10% in safety and efficacy of the two regimens.

Patient demographics and baseline disease characteristics, including cirrhosis, were similar for the 212 patients on PegIFN alfa-2a and the 219 patients on PegIFN alfa-2b. The two groups in the intent-to-treat population had similar rates of treatment-related serious adverse events (SAE) (1% vs 1%, respectively) and discontinuations for AEs (7% vs 6%, respectively). Overall, SVR rates were higher in patients treated with PegIFN alfa-2a compared with PegIFN alfa-2b (66% vs 54%, respectively, p=0.02), including the

combined 222 HCV GT1 and GT4 patients (48% vs 32%; p=0.04) and 143 HCV GT2 patients (96% vs 82%; p=0.01). PegIFN alfa-2a independently predicted SVR in a logistic regression analysis (odds ratio, 1.88; 95% confidence interval: 1.20–2.96).

Although the two regimens showed a similar safety profile, the PegIFN alfa-2a regimen yielded significantly higher SVR rates than PegIFNalfa-2b.

Table 7. Summary of trial of bitherapy with Rebetol plus peginterferon alfa -2a or peginterferon alfa-2b (Rumi et al)

| Study | Peg-IFN QW | REBETOL (mg/day) | HCV Genotype(s) | No. of Patients | SVR 24 | Safety |
|---|---|---|---|---|---|---|
| Rumi et al, 2010 [Ref. 5.4: 03TPK6] | 2a: 180 µg | 800-1200 | 1 | 91 | 48% (p=0.04) | No significant differences |
| | 2b: 1.5 µg/kg | 800-1200 | 1 | 87 | 32% | |
| | 2a: 180 µg | 800-1200 | 2 | 69 | 96% (p=0.01) | |
| | 2b: 1.5 µg/kg | 800-1200 | 2 | 74 | 88% | |
| | 2a: 180 µg | 800-1200 | 3 | 34 | 65% (p=0.09) | |
| | 2b: 1.5 µg/kg | 800-1200 | 3 | 32 | 69% | |
| | 2a: 180 µg | 800-1200 | 4 | 18 | Not available | |
| | 2b: 1.5 µg/kg | 800-1200 | 4 | 26 | Not available | |
| | 2a: 180 µg | 800-1200 | 1,2,3,4 | 212 (total) | 66% (p=0.02) | |
| | 2b: 1.5 µg/kg | 800-1200 | 1,2,3,4 | 219 (total) | 54% | |

The results of this direct comparison of ribavirin bitherapy regimens containing either PegIFN alfa-2a or PegIFN alfa-2b are consistent with conclusions reached in two meta-analyses of clinical trials conducted with unbranded ribavirin or with mixed regimens of branded ribavirin.

In a meta-analysis performed by Flori et al that included 11 randomised trials of peginterferon alfa and ribavirin (brand not specified), the SVR24 rate was significantly higher for patients treated with peginterferon alfa-2a than for those treated with PegIFN alfa-2b who had HCV genotypes 1 and 4 (odds ratio [OR] 1.45; 95% CI 1.09– 2.06; p = 0.013) and for patients with all genotypes combined (OR 1.34; 95% CI 1.05–1.72; p = 0.02). For patients with genotypes 2 and 3, the SVR24 was greater for treatment with PegIFN alfa-2a than with PegIFN alfa-2b, with the difference tending towards significance (OR 1.15; 95 % CI 0.98–1.35; p = 0.08). Publication bias was detected and was taken into account using appropriate statistical methods.

A more recently published meta-analysis performed by Hauser et al. on data from 12 randomised clinical trials of ribavirin bitherapy (brand not specified) showed that PegIFN alfa-2a significantly increased the number of patients who achieved SVR compared with PegIFNalfa-2b (1069/2099 (51%) versus 1327/3075 (43%); relative risk 1.12, 95% CI 1.06 to 1.18. Subgroup analyses based on risk of bias, viral genotype, and treatment history yielded similar results. Trial sequential analyses supported the results in patients with HCV genotype 1 or 4, but not in patients with genotype 2 or 3.

**Paediatric Patients**

Schwartz et al. (The combination of ribavirin and peginterferon is superior to peginterferon and placebo for children and adolescents with chronic hepatitis C. Gastroenterology. 2011 Feb;140 (2):450-458.e1) have shown the importance of the ribavirin administration for the virological response in a randomised trial that compared PegIFN alfa-2a plus ribavirin (Copegus 15 mg/kg orally in 2 doses daily) with PegIFN alfa-2a plus placebo in patients 5 to 17 years old with chronic hepatitis C.

Sustained virologic response was achieved in 53% of paediatric patients treated with PegIFN alfa-2a and ribavirin, compared with 21% of those who received PegIFN alfa-2a and placebo (P <0.001). A clinical trial conducted by the International Hepatitis C Paediatric Study Group evaluated PegIFN alfa-2a (100 µg/m$^2$ once weekly to a maximum of 180 µg) plus ribavirin (Copegus; 15 mg/kg/day to a maximum of

1200 mg) in treatment naïve children and adolescents ages 6-17 with CHC Eighty-nine percent of patients with HCV genotype 2 or 3 attained SVR on a 24-week regimen compared with 57% of patients with genotypes 1, 4, 5, or 6 on a 48-week regimen. Four additional paediatric trials with similar outcomes were reviewed by Hu et al.

Results are consistent with those reported in a paediatric study of PegIFN alfa-2b (60 µg/m$^2$/week) and Rebetol (15 mg/kg/day) in 107 children and adolescents ages 3-17 years paediatric (Wirth et al., High sustained virologic response rates in children with chronic hepatitis C receiving peginterferon alfa-2b plus ribavirin. J Hepatol. 2010 Apr; 52(4):501-7). SVR was documented in 53% of 72 patients with HCV genotype 1, in 93% of 30 patients with genotype 2 or 3, and in 80% of 5 patients with genotype 4. Treatment duration was 24 weeks for patients with genotypes 2 and 3 with low viral load (<600,000 IU/mL) and 48 weeks for patients with genotypes 1, 4, and 3 with high viral load (≥600,000 IU/mL).

**Tritherapy**

Marcellin et al. (Telaprevir is effective given every 8 or 12 hours with ribavirin and peginterferon alfa-2a or -2b to patients with chronic hepatitis C. Gastroenterology. 2011 Feb;140(2):459-468.e1) investigated the efficacy, safety, tolerability, and pharmacokinetics of telaprevir given every 8 hours or every 12 hours in combination with PegIFN alfa-2a or alfa-2b plus ribavirin to treatment-naïve patients infected with HCV genotype 1. The brand of ribavirin was not specified, but the dosing regimens were those approved for Copegus and Rebetol in combination with PegIFN alfa-2a and alfa-2b, respectively. A high proportion (>80%) of patients achieved SVR regardless of the telaprevir dosing frequency or type of PegIFN alfa used. A logistic regression model showed no significant difference in the percentage of patients achieving an SVR between the pooled PegIFN alfa-2a and PegIFN alfa-2b groups (P = 0.906; 95% CI for the difference, -10.8% to 12.1%).

A meta-analysis conducted by Sitole et al (Telaprevir versus boceprevir in chronic hepatitis C: a meta-analysis of data from phase II and III trials. Clin Ther. 2013). of 8 randomised, controlled trials compared SVR and drug-related AEs in 4144 treatment-naive and treatment-experienced patients with chronic HCV genotype 1 infection who were on 24- and 48-week regimens of telaprevir and boceprevir triple-therapy. All telaprevir regimens included PegIFN alfa-2a and Copegus whereas all boceprevir regimens included PegIFN alfa-2b and Rebetol.

The 48-week SVR rates in treatment-naive subjects were similar between telaprevir and boceprevir (OR = 0.82; 95% CI, 0.6 –1.11; P = 0.2). Telaprevir and boceprevir regimens also yielded similar rates of discontinuation due to adverse drug reactions (OR = 1.23; 95% CI, 0.95–1.6; P = 0.11).

## 2.4.3. Discussion and conclusions on the clinical efficacy

The MAH has re-submitted within this procedure the results of three phase 3 trials including studies performed with ribavirin and peginterferon alfa 2a +/- boceprevir as DAA, to support the proposed change in the indication. These studies are considered relevant, since it is agreed that various ribavirin-containing medicinal products have comparable pharmacokinetic profiles and CHMP acknowledged the literature data supporting this.

The IDEAL study (assessed by the CHMP in the procedure EMEA/H/C/000246/II/48) has shown comparable safety and efficacy for regimens of PegIFN alfa-2b plus ribavirin (Rebetol) and PegIFN alfa-2a plus ribavirin (Copegus).

The RESPOND-2 study (P05101) (assessed by CHMP in the procedure EMEA/H/C/000246/WS/216) supported the extension of indication of ribavirin to tritherapy with PegIFN alfa 2b and boceprevir. The results of this study showed that the addition of boceprevir to the standard of care represented a

substantial advance in the treatment of CHC (HCV genotype 1). Both boceprevir regimens have shown significant improvement in SVR rates when added to PR for 36 or 48 weeks of treatment in all subject groups, regardless of demographic or baseline disease characteristics. RGT with boceprevir has also shown an advantage over fixed-duration BOC/PR48 by offering a decreased length of therapy to 36 weeks without compromising efficacy.

Study P05685 was conducted by the MAH to confirm the efficacy benefits of boceprevir when administered in combination with other marketed pegylated interferon products PegIFN alfa-2a and ribavirin (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 as effective as the use of the same medicines with PegIFN alfa-2b.

Therefore, clinical trials conducted by the MAH have shown similar efficacy for a regimen of boceprevir and ribavirin in combination with either PegIFN alfa-2a or alfa-2b.

In addition, the MAH submitted the results of the literature review conducted to support the revision of the indication.

Among the submitted evidence, one study (Rumi et al) performed a direct comparison of Rebetol dosed with PegIFN alfa-2a and PegIFN alfa-2b; the study results supported the safety and effectiveness of Rebetol in both regimens in adults.

For paediatric patients, the MAH has not generated data that support the dosing of Rebetol with PegIFN alfa-2a. However, published data support the safety and effectiveness of ribavirin in combination with either PegIFN alfa-2a or alfa-2b in paediatric patients.

Overall, as far as the comparable PK profiles between the various ribavirin containing medicinal products is admitted, both peginterferon alfa (2a and 2b) could theoretically be used with any ribavirin medicinal product provided that the posology of ribavirin is tailored to the associated peginterferon alfa.

Moreover, clinical experience has been gained over time for combination with ribavirin outside the unique bitherapy with peginterferon alfa.

Safety and effectiveness of ribavirin in triple therapy regimens with PegIFN alfa and the first generation of DAA agents NS3/4A protease inhibitors (boceprevir and telaprevir) is also supported by data published in the literature. Moreover, the current treatment guidelines recommend the use of ribavirin in various combinations, including with newest DAAs. Of note, the current versions of both the EASL and ASSLD Hepatitis C guidelines recommend the use of Ribavirin with the newly approved DAAs in interferon free-regimens. The recommended ribavirin dose is < 75kg = 1000mg and > 75kg= 1200mg.

Overall, the CHMP considered that the results of the submitted clinical trials together with the literature data provided were in accordance with the current treatment recommendations of the learned societies and agreed to update the Rebetol PI accordingly.

## *2.5. Clinical safety*

## Safety summary of the supportive studies

### Study P04471 (IDEAL study)

Similar safety profiles were observed for the PegIFN alfa-2a and alfa-2b containing regimens; however, higher rates of dose adjustments and discontinuation due to low neutrophil counts were seen in the PegIFN alfa-2a arm.

The safety profile of PegIFN alfa 2b and PegIFN–alfa 2a when used in combination with ribavirin was consistent in this study with the existing ribavirin product information; no new or unexpected AEs were observed. As already mentioned, the study drug discontinuation rate was higher in the PegIFN alfa-2b1.5 µg/kg arm than in the PegIFN alfa2b1.0 µg/kg arm (12.7 vs. 9.6%). The frequency of SAE was similar: 8.6% vs. 9.3%. There was however a higher rate of anaemia and neutropenia in the 1.5 µg/kg arm as compared to the 1.0µg/kg arm, as expected.

**Study P05101 (RESPOND-2)**

Boceprevir did not appear to add any treatment –limiting toxicity when used in combination with standard of care therapy in subjects treated for up to 48 weeks.

The safety profile of 36 weeks of RGT was similar to continued triple therapy until TW 48, with the exception of a small increase in dose modifications (39% TW 36 RGT vs 33% BOC/PR48).

RGT demonstrated an advantage over 48 weeks of triple therapy, with respect to over a rate of SAEs, discontinuations due to AEs (in subjects with and without erythropoietin use), and transfusions.

SAEs (10-14% experimental vs 5% control), discontinuation (8-12% vs 3%), and dose modifications due to AEs (29-33% vs 14%) occurred with greater frequency in the boceprevir arms compared with the control arm.

No novel AEs were observed in the boceprevir arms. Anaemia occurred more frequently on boceprevir treatment, but was managed with ribavirin dose reduction and/or erythropoietin use. Furthermore, the presence of anaemia and concomitant erythropoietin use were associated with higher SVR rates.

Dysgeusia was also increased in the boceprevir arms, but was not treatment-limiting. Rash/skin eruption AEs were also increased in the boceprevir arms, but did not appear to limit the use of boceprevir; there were no SAEs or discontinuations due to rash. Importantly, there was no evidence of rash syndromes such as toxic epidermal necrolysis or Stevens-Johnson syndrome. Overall, boceprevir was well tolerated.

**Study P05685**

No novel AEs were reported. The most common AEs were those previously reported with PegIFN alfa-2a+ribavirin therapy, such as, e.g., fatigue, myalgia, influenza-like symptoms, and cytopenias. Treatment-emergent and treatment-related AEs reported more frequently in the boceprevir-containing arm compared with the control arm (≥ 10% difference) were blood and lymphatic system disorders, including anaemia, neutropenia, and leukopenia; rash; myalgia; and gastrointestinal disorders, including dysgeusia, nausea, diarrhoea, and vomiting.

SAEs 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 + PegIFN alfa-2a+ribavirin arm.

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 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 PegIFN alfa-2b and ribavirin. Thus, overall, the main adverse effect burden associated with the use of boceprevir is due to the marked increase of anaemia as compared to the already significant rate of anemia with PegIFN +ribavirin.

The risk of neutropenia (including grade3/4) was markedly increased when boceprevir was combined to PegIFN- alfa 2a than when combined with alfa 2b.

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 anaemia in boceprevir-treated subjects compared with control subjects (50% vs 33%, respectively), none of the anaemia AEs was considered serious, and only one resulted in drug discontinuation.

## Safety in special populations

### Patients with renal impairment

As already mentioned, a single-dose (400 mg oral) pharmacokinetic study was conducted by the MAH in patients with chronic renal impairment. Vital signs were measured at screening, immediately prior to dosing (0 hours) and at regular intervals until 168 hours post-dose.

The safety and tolerability results were acceptable in all subjects.

The results of a safety, tolerability, and PK study in HCV-infected patients with various degrees of renal impairment (Brennan et al (2013)) were also submitted.

A complete physical examination, including vital signs at screening and at study completion was performed. Clinical laboratory tests were also performed throughout the study. AEs were assessed at weeks 1,2,3,5,8,10 and 12 and at the follow-up examination at week 13.

Almost all patients in each of the 4 treatment groups reported ≥ 1 AE, and most patients had ≥ 1 AE that was considered by the investigator that could be related to the studied drug. The most frequently reported AE were those known to be associated with ribavirin and PegIFN alfa 2a, including fatigue, anaemia, headache, nausea, pyrexia, diarrheal, chills and arthralgia.

Patients in the severe renal impairment group had a greater incidence of severe or SAEs, ribavirin dosage adjustments or discontinuations, and laboratory abnormalities leading to discontinuation compared to the other 3 treatment groups.

The most common SAEs were anaemia (1 moderate impairment group patient and 2 patients with severe renal impairment) and mental status change (reported in 2 patients with severe renal impairment). No AEs were considered to be life threatening were observed in any patient.

Ribavirin was poorly tolerated in patients with renal impairment and throughout the study the assigned ribavirin dose was reduced in 71% and 53% of patients with moderate or severe impairment, respectively, due to AE, particularly anaemia.

The 3 most frequently reported laboratory abnormalities potentially related to ribavirin dose modification in patients with severe or moderate renal impairment were haemoglobin concentration of 10 g/dl or a decrease from baseline in haemoglobin concentration of 3 g/dl (43% to 47%), followed by abnormal white blood cells (36% to 41%) and platelet counts (24% to 29%).

### Patients with hepatic impairment

A single dose PK study of ribavirin in subjects with chronic liver disease (Glue P, et al. (2000)) was submitted. This study included measurements of vital signs, drawing of safety laboratory tests and recording of AEs.

There were no changes in clinical relevance in any laboratory parameters during or at completion of the study. ARs were reported by 2 /23 subjects (9%), erythema and abdominal pain. Both AEs were of mild severity and were considered unrelated to the study drug.

### 2.5.1. Discussion and conclusion on clinical safety

CHMP noted that the results of the submitted studies showed that the PK parameters of ribavirin were similar in subjects with mild, moderate, or severe hepatic dysfunction (Child-Pugh Classification A, B, or C) and in subjects with normal hepatic function. Moreover, in patients with moderate to severe renal impairment the data submitted by the MAH (Brennan et al (2013)) required an update of the dosing recommendation.

The CHMP agreed that there was a need to update the safety data in the Rebetol SmPC (for further details refer to section 2.7).

CHMP also noted that the safety results of the above mentioned three studies submitted in support of this change of indication have been assessed by the CHMP in previous regulatory procedures and the benefit–risk balance of the combination of ribavirin with PegIFN alfa-2a and with boceprevir was positive.

### 2.5.2. PSUR cycle

The PSUR cycle is maintained, as per the existing annex II.

## *2.6. Risk management plan*

The RMP is not updated with this variation.

## *2.7. Update of the Product information*

Sections 4.1, 4.2, 4.3, 4.4, 4.7, 4.8, 4.9 and 5.1 of the Rebetol SmPC have been updated. The Package Leaflet and Labelling are updated accordingly. For further details please consult the approved updated product information.

In particular several contraindications, warnings and undesirable effects (in sections 4.3, 4.4 and 4.8 of the product information respectively) related exclusively to peginterferon alfa 2b have been removed from the product information. CHMP agreed nevertheless that adverse reactions reported during clinical trials of Rebetol will continue to be listed in section 4.8 of the SmPC as they were reported for regimens with peginterferon alfa-2b or peginterferon alfa-2b.

Changes were also made to the PI to bring it in line with the current Agency QRD template, SmPC guideline and other relevant guideline(s).

# 3. Benefit-Risk Balance

### Benefits

#### Beneficial effects

Ribavirin in combination with peginterferon alfa-2b or -2a has shown to increase SVR compared with peginterferon monotherapy, particularly in the difficult-to-treat chronic hepatitis C genotype 1 subjects.

In 2011, the approval of first generation DAA agents NS3/4A protease inhibitors (e.g., telaprevir or boceprevir) in combination with peginterferon alfa 2a or 2b and ribavirin has established a new standard of care for patients with chronic hepatitis C genotype 1 infection (naïve and previously treated).

Recently, outstanding efficacy with improved safety profile has been documented with newly approved DAAs in interferon-free regimen, leading to a shift towards use of these DAA combination as standard of care for patients with chronic hepatitis C.

Ribavirin remains recommended in combination with some DAAs in order to maximise the probability of SVR. This is the case of patients with advanced liver disease in whom it might be the last course before decompensation or in patients with chronic hepatitis C genotype 3 infection for whom no very potent drugs against this genotype are currently approved.

Overall, the evidence from published literature and clinical trial data supports the efficacy of Rebetol in various combinations with peginterferon, but also with DAAs.

#### Uncertainty in the knowledge about the beneficial effects

So far, the use of ribavirin in paediatric patients is confined to the co-administration with peginterferon alfa. However, clinical development is ongoing and the therapeutic management of paediatric patients will likely be aligned to that in adults with notably involvement of ribavirin in some circumstances.

### Risks

#### Unfavourable effects

The safety profile of ribavirin in combination with peginterferon is overall well-established. The important safety issues associated with the ribavirin use are the haematological disorders, mainly haemolytic anaemia. Indeed, a decrease in haemoglobin levels to <10g/dl was observed frequently in adult patients treated with Rebetol in combination with peginterferon alfa 2b.

Although less pronounced when ribavirin is used in combination with DAA (i.e. outside the concomitant myelosupressive effects of interferon), haemolytic anaemia and related-AE remain notable aspects when using ribavirin in combination with DAAs.

Anaemia associated with ribavirin may result in deterioration of the cardiac function or in exacerbation of the symptoms of coronary disease. This led to a contraindication for use in patients with a history of severe pre-existing cardiac disease and to a warning when administering ribavirin to patients with pre-existing cardiac disease. The majority of haematological abnormalities could be managed by dose reduction. A close monitoring is nevertheless recommended in the SmPC.

Another important safety concern for ribavirin therapy is the significant teratogenic and/or embryocidal potential that have been seen in studies conducted in animal species. The use of ribavirin is contraindicated during pregnancy due to the teratogenic potential of ribavirin identified in the non-clinical

studies. Furthermore, extreme care is recommended in the SmPC to avoid pregnancy in female patients and in partners of male patients taking ribavirin.

***Benefit-Risk Balance***

**Discussion on the Benefit-Risk Balance**

Before the start of this application, Rebetol was only indicated in combination with peginterferon alfa 2b and not with peginterferon alfa 2a. However, other ribavirin-containing medicinal products were indicated in combination with peginterferon alfa 2a. In addition, a different posology of ribavirin was recommended, based on the type of interferon alfa with which ribavirin was intended to be used (i.e. 800 mg – 1400 mg when ribavirin is used with peginterferon alfa 2b and 800 mg or 1000 - 1200 mg when ribavirin is used with peginterferon alfa 2a).

The CHMP agreed that ribavirin should no longer be confined to the use in combination with peginterferon alfa 2b in adult and paediatric patients. It was decided to update the currently approved wording of the Rebetol indication to one that would encompass the use of Rebetol within other therapeutic regimens (e.g. containing peginterferon alfa-2a or in combination with DAAs). The approved indication is now in line with the most recent CHMP decisions regarding the indications granted for medicinal products for the treatment of chronic hepatitis C.

The current contraindications for Rebetol in patients with severe hepatic impairment or decompensated cirrhosis that were motivated by the use of ribavirin in combination with peginterferon have been removed. The current contraindication in patients with renal impairment has been removed and a change in dosage recommendations for patients with renal impairment has also been implemented. Finally, the safety sections of the SmPC have been updated and the safety issues that were not relevant for interferon-free regimens were removed.

Consequently, the Rebetol PI is now brought in line with the therapeutic armamentarium and with current clinical practice.

The CHMP agreed that, based on the data that were submitted and assessed, the benefit-risk of Rebetol in the approved indication is positive.

# 4. Recommendations

***Outcome***

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

| Variation(s) accepted | | Type | Annex affected |
|---|---|---|---|
| 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 | I, II, IIIA and IIIB |

Change of the indication of Rebetol to reflect that ribavirin is indicated in the treatment of hepatitis C in combination with other medicinal products and to remove reference to the peginterferon used (2a or 2b)

in line with the PRAC recommendation in the PSUR assessment (EMEA/H/C/PSUSA/000100007/201307). As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.7, 4.8, 4.9 and 5.1 of the SmPC are updated.

The variation proposed amendments to the Summary of Product Characteristics, Labelling, Annex II and Package Leaflet

***Conditions and requirements of the marketing authorisation***

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and published on the European medicines web-portal.

***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.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, 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.