London, 4 October 2007
Product name: **Rebetol**
Procedure No. EMEA/H/637/II/35

SCIENTIFIC DISCUSSION

I. SCIENTIFIC DISCUSSION

1.1 Introduction

Rebetol is indicated for the treatment of chronic hepatitis C and must only be used as part of a combination regimen with peginterferon alfa-2b (adults) or interferon alfa-2b (adults, children (3 years of age or older).

This combination is indicated in naïve patients as well as for the treatment of adult patients with chronic hepatitis C who have previously responded (with normalisation of Alanine transaminase (ALT) at the end of treatment) to interferon alpha monotherapy but who have subsequently relapsed.

The spontaneous remission rate in chronic hepatitis C is very low and there are currently no licensed alternative treatment options to alfa interferon and ribavirin in the treatment of chronic hepatitis C.

This variation concerns a revision of section 4.1, 4.2 and 5.1 of the summary of product characteristics to include the retreatment of patients who have failed prior therapy with alfa-interferon (pegylated or nonpegylated) and ribavirin. A new maximum ribavirin dose of 1,400 mg for patients over 105 kg of weight is also proposed.

Data from the EPIC (Evaluation of PegIntron in Control of Hepatitis) studies program is submitted in support of this variation. The EPIC studies program consists of three clinical trials in patients with chronic hepatitis C with at least moderate fibrosis who have failed prior therapy with alpha interferon (including peginterferon alfa) and ribavirin. Protocol P02370 assesses sustained viral response (SVR), P02570 assesses whether low dose peginterferon alfa-2b (0.5 mcg/kg/w.) can slow progression of fibrosis and P02569 whether this therapy delays progression to end-stage liver disease in patients with cirrhosis. In this submission data from study P02370 is presented.

The EPIC program was subject to advice from the CHMP in September 2002 and the studies programme was accepted, including the single arm design of study P02370, with some caveats related to the assessment of safety.

No formal interim analysis was planned, but data were available for review on an ongoing basis. Data from the analysis of October 2003 were made public at the European Association for the Study of the Liver (EASL) annual meeting in April 2005. In November 2005, data were also presented to FDA and the EU Rapporteur (Sweden). It was accepted that an interim analysis based on all subjects enrolled by 1 April 2004, the first cohort, could be submitted as a basis for a label change. This manner of proceeding; repeat analyses, making study data public, followed by a formal interim analysis and a regulatory submission, is ill suited to control for the overall type-1 error. Nevertheless, as data were already made public and appeared convincingly far from the predetermined cut-off for a meaningful clinical effect, the submission strategy was accepted by the CHMP.

Further to the submission of this variation in September 2006 the Marketing Authorisation Holder (MAH) informed the CHMP in February 2007 that in some instances the hepatitis C virus ribonucleic acid (HCV-RNA) assays conducted in the company's laboratories (in-house Polymerase Chain Reaction (PCR) assay) to quantitatively assess HCV-RNA from subjects samples in this clinical trial had underreported the levels of HCV-RNA as evidence by the under recovery of the positive control.

A corrective action plan was developed by the MAH that included the development of new and revised procedures with additional assay and laboratory controls to ensure confidence in the robustness of the assay and retesting of the impacted samples. The retested sample results were submitted to the CHMP for assessment and had no meaningful impact on the study results.

The data presented in this report constitutes the retested sample data.

1.2 Clinical Efficacy

The main study submitted in support of this variation is study P02370 which is presented and evaluated hereafter. Study P02370 assessed SVR in patients treated for hepatitis C with peginterferon alfa 2b plus Rebetol who failed to respond to previous combination therapy (any interferon treatment in combination with repairing). Data from two further studies has been submitted in support of the safety profile associated with retreatment of previous nonresponders and is discussed in Section 3.3 'Clinical Safety' of this report. These two trials are the registration trial C/I98-580 in treatment naive patients and study P02314, an investigator-initiated study performed to support Rebetol weight-based dosing in the United States.

Study P0230 Objectives
Primary: to estimate SVR after treatment with peginterferon alfa 2b 1.5 mcg/kg/w and ribavirin 800 – 1400 mg/d for 48 weeks. SVR was defined as undetectable plasma HCV RNA at the end of 24 weeks of follow-up.

Secondary: the identification of non-responders to study therapy for inclusion in studies P02570 and P02569.

The hypothesis to be tested was that the SVR in non-responders and relapse patients is higher than 10%.

Design
Single arm, multicenter (132, 107 non-US sites) study in patients with chronic hepatitis C who failed to respond or relapsed after treatment with combination therapy (any interferon and ribavirin). Patients with undetectable viral load at week 12 continued on therapy for a total of 48 weeks then entered a 24-week follow up period (no treatment); subjects who were HCV RNA positive at Treatment Week 12 (TW12) were to be discontinued from this trial and enrolled in a maintenance therapy trial.

There were deviations from the protocol for subjects with detectable HCV RNA at treatment week 12. Some of these subjects were allowed to continue treatment with peginterferon alfa-2b plus ribavirin in study P02370:

Prior to November 2003 subjects with HCV RNA level decreased ≥2 log10 were given deviations to continue.
November 2003 to October 2004 subjects with HCV RNA level of ≤750 IU/ml were given deviations to continue.

Study population
Adults (18-65 years of age) with chronic hepatitis C, regardless of HCV genotype, with moderate to advanced hepatic fibrosis (METAVIR F2, F3, or F4) who failed previous therapy with alfa- interferon plus ribavirin therapy were eligible. Cirrhotic subjects must have been modified Child-Pugh Class A.

The estimated number of patients to be recruited was 2200. This submission is based on the "first cohort" in study P02370 (n=1354).

Statistical methods
The primary efficacy endpoint, SVR rate, was summarised using descriptive statistics (N, %) along with the 99% confidence intervals (based on the normal approximation to the binomial distribution). The SVR rates in the key subgroups were summarised using descriptive statistics (N, %) with 95% confidence intervals.

Baseline Characteristics

The vast majority of patients had genotype 1 disease. About 3 out of 4 patients had received prior therapy with non-pegylated interferon and about 2 out of 3 patients were classified as non-responders to prior therapy. There was a large number of patients with cirrhosis (METAVIR F4). Degree of fibrosis correlates with age, otherwise there were no major differences in baseline characteristics comparing different METAVIR fibrosis groups

Results

Table 1 shows the virologic response rates. In the full study population, the lower 99% CI margin for SVR is close to 20%, i.e. reassuringly far from the hypothesis set out to be tested (SVR >10%).

Table 1 Virologic response rates

	Cohort 1 Efficacy Population (n=1336)	
Time Point	Virologic Response % (Number of Subjects)	99% CI %
Treatment Week 12	37.4 (499/1336)	33.9, 40.8
Treatment Week 24	42.1 (563/1336)[b]	38.7, 45.6
End of Treatment	41.4 (553/1336)	37.9, 44.9
SVR[a]	22.7 (303/1336)	19.7, 25.6

CI=confidence interval; EOT=end of treatment; SVR=sustained virologic response.

a: Primary endpoint.

b: TW24 was not considered a key time point; therefore, no impacted samples were reassayed. The results depicted represent the original assay values for this time point.

The stability of study data over time are illustrated as follows in table 2:

Table 2 Sustained Virologic Response by Order of Enrolment

	Cohort 1 Efficacy Population (n=1336)	
Subcohort Enrolled in	SVR (%)	95% CI
First 500	21.8	(18.2, 25.4)
501-1000	21.8	(18.2, 25.4)
1001-1336	25.3	(20.6, 29.9)

SVR=sustained virologic response; CI=confidence interval. Taking protocol-specified dose modifications and early discontinuations into account, 1075/1336 subjects were adherent to the peginterferon alfa-2b dosage, 1089/1336 to the ribavirin dosage, and 1029/1336 to both drugs.

As shown in Table 3 in patients with a viral log reduction of ≥2, altogether 153 out of 293 patients continued combination therapy and the sustained response rate in this group was 11.8% (95% CI 7; 17%).

In patients with less pronounced reduction in viral load only 55/457 continued combination therapy. No patients with SVR were seen in this group. A similar pattern was seen in relation to absolute viral load as shown in table 4.

Table 3: Predictability of SVR by week 12 response

Protocol No. P02370

	Cohort 1 Efficacy Population (n=1336)		Subjects Who Did Not Enroll in a Maintenance Protocol (n=786)	
	SVR % (Number of Subjects)	95% CI %	SVR % (Number of Subjects)	95% CI %
Response at TW 12				
Negative	56.5 (282/499)	52.2, 60.9	56.6 (282/498)	52.3, 61.0
Positive with ≥2 log_{10} drop	6.1 (18/293)	3.4, 8.9	11.8 (18/153)	6.7, 16.9
Positive with <2 log_{10} drop	0 (0/457)	Not calculated	0 (0/55[a])	Not calculated
Missing	3.4 (3/87)[b]	0, 7.3	3.8 (3/80)	0, 7.9

SVR=sustained virologic response; CI=confidence interval; TW=Treatment Week.
a: Eight of these 55 subjects continued in study P02370 beyond TW 22.
b: Includes 84 subjects with missing viral load at TW 12, as well as 3 subjects with missing baseline viral load and positive HCV-RNA at TW 12.

Table 4 Sustained Virologic Response by HCV-RNA Level at Treatment Week 12

HCV RNA at TW 12 (IU/ml)	Cohort 1 Efficacy Population (n=1336) SVR % (Number of Subjects)	Subjects Who Did Not Enroll in a Maintenance Protocol (n=786) SVR % (Number of Subjects)
>750	0 (0/593)	0 (0/96)
>500 – 750	3.7 (1/27)	6.7 (1/15)
>250 – 500	6.3 (2/32)	11.8 (2/17)
125 – 250	6.1 (2/33)	8.0 (2/25)
<LLD	52.0 (295/567)	53.3 (295/553)
<LLD, signal detected	19.1 (13/68)	23.6 (13/55)
<LLD, signal not detected	56.5 (282/499)	56.6 (282/498)
Missing	3.6 (3/84)	3.8 (3/80)

HCV RNA=hepatitis C virus ribonucleic acid; LLD=lower limit of detection; TW=Treatment Week; SVR=sustained virologic response.

In patients infected with HCV genotype 1 and cirrhosis, the SVR rate is low (44/451), but these patients have a poor prognosis and a cure rate of close to 10% is of clinical relevance.

The sustained response rates for patients in study P02370 summarised by prior therapy (non-pegylated interferon/ribavirin vs pegylated interferon/ribavirin) versus prior response (non-responder vs relapser), genotype, fibrosis and baseline viral load are shown in Table 5. The pattern of SVR in this population of non responders/relapsers is similar compared with treatment naïve patients as regards the influence of genotype, viral load and METAVIR score. The SVR rate is lower in previous non-responders compared with patients with relapse. Similarly the SVR appears higher in patients previously treated with non-pegylated interferon.

Table 5:P02370 Sustained Virologic Response (SVR) by Prior Therapy

	IFN/Ribavirin		PegIFN/Ribavirin	
	SVR % (n)	99% CI	SVR % (n)	99% CI
Overall	24.8 (255/1030)	21.3, 28.2	16.1 (48/299)	10.6, 21.5
Prior Response				
Relapse	44.6 (95/213)	35.8, 53.4	35.7 (40/112)	24.1, 47.4
Genotypes 1/4	33.8 (52/154)	24.0, 43.6	28.9 (24/83)	16.1, 41.7
Genotypes 2/3	73.2 (41/56)	58.0, 88.5	55.2 (16/29)	
NR	17.4 (117/673)	13.6, 21.1	4.1 (7/172)	0.2, 8.0
Genotypes 1/4	12.7 (75/592)	9.1, 16.2	3.8 (6/160)	0, 7.6
Genotypes 2/3	51.3 (40/78)	36.7, 65.9	10 (1/10)	
Genotype				
1	16.7 (138/825)	13.4, 20.1	11.5 (28/243)	6.2, 16.8
2	63.6 (21/33)	42.1, 85.2	40 (4/10)	
3	61.7 (82/133)	50.8, 72.5	44.8 (13/29)	
4	31.3 (10/32)	10.1, 52.4	20 (3/15)	
1/4	17.3 (148/857)	13.9, 20.6	12.0 (31/258)	6.8, 17.2
2/3	62.0 (103/166)	52.3, 71.7	43.6 (17/39)	23.1, 64.0
METAVIR Fibrosis score				
F2	31.8 (92/289)	24.8, 38.9	22.7 (15/66)	9.4, 36.0
F3	26.6 (86/323)	20.3, 33.0	17.4 (16/92)	7.2, 27.6
F4	18.5 (77/416)	13.6, 23.4	12.1 (17/141)	5.0, 19.1
Baseline Viral Load				
HVL (≥600,000 IU/mL)	20.6 (128/622)	16.4, 24.8	8.9 (17/192)	3.6, 14.1
LVL (<600,00 IU/mL)	31.3 (127/406)	25.4, 37.2	28.6 (30/105)	17.2, 39.9

Table 6 summarises SVR with HCV RNA below the Limit of Detection (LLD) of 125 IU/ml at TW 12. The subjects are categorised as follows:

1) below the limits of detection: includes all subjects (i.e. also patients with signal detected) with viral load below the limits of detection

or

2) below the limits of detection, signal detected: includes all subjects with viral load below the limits of detection for whom a signal was detected

The overall sustained response rate in patients previously treated with interferon/ribavirin and viral load below LLD but signal detected is thus 18% versus 61% in those with viral load below LLD no signal detected (for peginterferon alfa-2b/ribavirin, corresponding figures were 21% versus 51%).

Table 6 Rates of Response to Retreatment in Prior Treatment Failures with HCV RNA Below the Limit of Detection at TW 12

	IFN/Ribavirin			PegIFN/Ribavirin		
	SVR of Subjects With HCV RNA below **LLD/signal detected** at TW12 % (n/N)	SVR- of all Subjects with HCV RNA **below LLD/all at TW12** % (n/N)	99% CI	SVR of Subjects With HCV RNA **below LLD/signal detected** at TW12 % (n/N)	SVR of all Subjects with HCV **RNA below LLD/all at** TW12 % (n/N)	99% CI
Overall SVR (regardless of previous treatment)	52.0 (295/567) 99% CI=46.6, 57.4					
Overall	18.4 (9/49)	54.6 (247/452)	48.6, 60.7	21.1 (4/19)	42.5 (48/113)	30.5, 54.5
Prior Response						
Relapse	30.8 (4/13)	57.2 (91/159)	47.1, 67.3	27.3 (3/11)	50.0 (40/80)	35.6, 64.4
Genotypes 1/4	25.0 (3/12)	45.8 (49/107)	33.4, 58.2	30.0 (3/10)	43.6 (24/55)	26.4, 60.9
Genotypes 2/3	100 (1/1)	80 (40/50)	65.4, 94.6	0 (0/1)	64.0(16/25)	
NR	16.1 (5/31)	51.3 (114/222)	42.7, 60.0	16.7 (1/6)	25.0 (7/28)	
Genotypes 1/4	17.9 (5/28)	45.1 (73/162)	35.0, 55.1	16.7 (1/6)	26.1(6/23)	
Genotypes 2/3	0 (0/3)	69.0 (40/58)	53.3, 84.6		20 (1/5)	
Genotype						
1	16.7 (7/42)	44.8 (133/297)	37.3, 52.2	23.5 (4/17)	37.8 (28/74)	23.3, 52.4
2		77.8 (21/27)			66.7 (4/6)	
3	20 (1/5)	72.7 (80/110)	61.8, 83.7	0 (0/1)	54.2 (13/24)	
4	100 (1/1)	76.9 (10/13)		0 (0/1)	33.3 (3/9)	
1/4	18.6 (8/43)	46.1 (143/310)	38.8, 53.4	22.2 (4/18)	37.3 (31/83)	23.7, 51.0
2/3	20 (1/5)	73.7 (101/137)	64.0, 83.4		56.7 (17/30)	33.4, 80.0
METAVIR Fibrosis score						
F2	33.3 (3/9)	63.0 (87/138)	52.5,	50.0 (3/6)	60 (15/25)	

			73.6			
F3	18.8 (3/16)	59.0 (85/144)	48.5, 69.6	0 (0/3)	45.7 (16/35)	24.0, 67.4
F4	12.5 (3/24)	44.4 (75/169)	34.5, 54.2	10.0 (1/10)	32.1 (17/53)	15.6, 48.6
Baseline Viral Load						
HVL (≥600,000 IU/mL)	14.8 (4/27)	52.1(122/234)	43.7, 60.5	10.0 (1/10)	32.7 (17/52)	15.9, 49.4
LVL (<600,000 IU/mL)	23.8(5/21)	57.6 (125/217)	49.0, 66.2	33.3 (3/9)	50.0 (30/60)	33.4, 66.6

NR: Non-responder- defined as serum/plasma HCV-RNA positive at the end of a minimum of 12 weeks of treatment.
Serum HCV RNA is measured with a research-based quantitative polymerase chain reaction assay by a central laboratory.
[i] 1) below the limits of detection: includes all subjects with viral load below the limits of detection or 2) below the limits of detection/signal detected: includes all subjects with viral load below the limits of detection for whom a signal was detected

Discussion on Clinical Efficacy

This study demonstrated an overall SVR rate of around 20%. The pattern of SVR in the population of non responders/relapsers is similar compared with treatment naïve patients as regards the influence of genotype, viral load and METAVIR score. The SVR rate is as expected lower in previous non-responders compared with patients with relapse. Similarly the SVR appears higher in patients previously treated with non-pegylated interferon. This was confirmed in a multivariate analysis and is reflected in the SPC.

For patients with undetectable HCV viral load at week 12, only two predictors of SVR were identified in the multivariate analysis; genotype and METAVIR score. The SVR in week 12 responders, according to genotype are outlined below:

genotype	***SVR in week 12 responders***
1	48%
2	74
3	72
4	60

Overall approximately 37 % of patients had undetectable plasma HCV-RNA levels at Week 12 of therapy. In this subgroup, there was a 57 % (282/499) sustained virological response rate.

In patients with detectable HCV-RNA week 12, other factors in addition to quantitative viral response are likely to have influenced the decision to continue or not on combination therapy. Therefore outcome in patients who continued combination therapy probably overestimates the benefit of continued therapy. This, however, is not self evident as, for example, a high fibrosis score could be viewed as an incitement to continue combination therapy, e.g. in patient with a low viral load or viral log reduction of ≥2, even if a positive outcome was considered less likely.

Overall it is agreed that week 12 data are pivotal for the decision whether to continue or not on combination therapy and information has been provided in the SPC.

The SVR rates in the SPC refer to "below LLD, no signal detected". The CHMP considered whether SVR in patients close to detectability, i.e "LLD, signal detected", should be mentioned in the SPC. The overall SVR in patients previously treated with interferon/ribavirin and peginterferon/ribavirin viral load below LLD but signal detected is 18% and 21% respectively. However "LLD, signal detected" is assay dependent and thus not interpretable by assays other than the in house assay of the Marketing Authorisation Holder. As such this information has not been included in the SPC.

1.3 Clinical Safety

In order to assess the safety profile associated with retreatment of previous nonresponders, in addition to data from study P02370, data from treatment-naïve subjects enrolled in the registration trial C/I98-580 and data from Study P02314, an investigator-initiated study performed to support Rebetol weight-based dosing in the United States were taken into consideration.

Patient Exposure
There were 1341 subjects in the Safety Population of study P02370 all of whom received treatment. Because of the study design the percentage of subjects receiving treatment decreased from 93% (1243 subjects) at TW 18 to 50% (669 subjects) at TW 24. Forty-five percent of the subjects (598/1341) received 48 weeks of treatment.

Adverse events
To assess the safety profile associated with retreatment of previous nonresponders, the Adverse Events (AE) profile for subjects enrolled in Study P02370 (prior nonresponders) was compared with the AE profile of treatment-naïve subjects enrolled in the registration trial C/I98-580. Common AE occurring during the first 18 weeks of treatment in each trial were compared.

Patients in study P02370 generally experienced individual AEs with a lower frequency. This is likely due to a variety of factors including the exclusion of subjects with a history of moderate or severe depression and subjects with intolerance to ribavirin/interferon based on their prior treatment experience. Additionally, subjects who experienced significant AEs with prior treatment may have chosen to not be retreated. Likewise investigators may have chosen not to retreat such subjects even if the subjects were willing to be retreated.

Overall the pattern of AEs was qualitatively as expected and there were no new safety issues.

Serious adverse events and deaths
There was one death on therapy. This was a 66 year old man who entered coma due to a cerebral haemorrhage on day 30 of therapy. This was reported as unlikely to be related. Cerebral haemorrhage is a listed event and was much discussed in relation to the Japanese experience with alpha interferons.

The incidence of serious adverse events was similar to the incidence reported in treatment naïve patients. In F2 patients 7%, F3 9% and F4 10%. One patient underwent liver transplantation, one developed oesophageal varices and there were three reports of liver malignancies. The most frequently reported SAEs were pneumonia (8), neutropenia (5), “chest pain” (5) and suicidal ideations (5). The 8 cases of “pneumonia” included two cases of lobar pneumonia and 6 not further specified.

Severe AEs were reported in 22% of subjects. Thrombocytopenia (2%) and neutropenia (7%) were overall more commonly seen in this population compared with treatment naïve.

Drug Discontinuations and modifications
Dose modifications were undertaken in a total of 30% of subjects; in most cases due to haematotoxicity, but asthenia was the cause in 2% of patients. The pattern was similar with respect to discontinuations; altogether 7% (n=89) discontinued, among them there were cases of depression (n=6), influenza like illness (n=5) and fatigue (n=5).

Table 7: dose modifications and Discontinuations Due to Haematologic Adverse Events by Hepatic Fibrosis Stage

	Cohort 1 Safety Population (n=1341)							
	Number (%) of Subjects							
	F2 (n=356)		F3 (n=417)		F4 (n=564)		All[a] (n=1341)	
Dose Modifications[b]								
Anemia	30	(8)	40	(10)	58	(10)	129	(10)
Neutropenia	26	(7)	31	(7)	57	(10)	114	(9)
Leukopenia	8	(2)	4	(1)	7	(1)	19	(1)
Thrombocytopenia	0		7	(2)	28	(5)	35	(3)
Discontinuations[c]								
Anemia	2	(1)	0		3	(1)	5	(<1)
Neutropenia	1	(<1)	3	(1)	4	(1)	8	(1)
Thrombocytopenia	0		1	(<1)	4	(1)	5	(<1)

a: Includes 2 subjects with METAVIR fibrosis score of F1 and 2 subjects with missing fibrosis scores.

b: Excluding subjects who later discontinued.

c: There were no discontinuations due to leukopenia.

The most obvious F-score related difference in event rates was thrombocytopenia and this is expected (Table 7).

Overall, affective disorders were less commonly reported in this treatment-experienced patient population.

Safety data for new maximum dose 1400mg

In study P02370, 82 subjects in cohort 1 received the 1400 mg dose of ribavirin. There was no meaningful difference in the rate of treatment discontinuation, overall adverse events, or serious adverse events in subjects receiving the 1400 mg dose in comparison to those receiving the 800 mg, 1000 mg, or 1200 mg doses (see Table 8). The only adverse event that appeared to occur at a higher rate in the 1400 mg group was vomiting (18% vs. 6%, 10% , and 8% for the 3 other groups, respectively), however none were serious adverse events and there was no meaningful difference in the incidence of vomiting in the F4 subjects compared to the F2/3 subjects.

Table 8 Discontinuation, Adverse Events and Serious Adverse Events by Rebetol Dose

	Rebetol 800 mg/day	Rebetol 1000 mg/day	Rebetol 1200 mg/day	Rebetol 1400 mg/day
Discontinued*	57%	58%	53%	49%
D/C for AE	6%	6%	7%	10%
Adverse Event	96%	97%	98%	96%
SAE	4%	9%	8%	10%

*Includes subjects who discontinued due do treatment failure as per protocol design

In addition to the data from study P02370, data on an additional 292 subjects who received the 1400 mg dose of ribavirin in study P02314 were considered. Study P02314 is an investigator-initiated study performed to support Rebetol weight-based dosing in the United States.

Taking into account data from P02314 and P02370 there are no clinically relevant safety differences related to the use of ribavirin 1400 mg in patients weighing more than 105 kg.

Discussion Clinical Safety
Overall the pattern of AEs was qualitatively as expected and there were no new safety issues. There was one death on therapy. This was reported as unlikely to be related.

The incidence of serious adverse events was similar to the incidence reported in treatment naïve patients. Severe AEs were reported in 22% of subjects. Thrombocytopenia (2%) and neutropenia (7%) were overall more commonly seen in this population compared with treatment naïve.

Regarding the new maximum dose of 1400mg, 82 subjects in study P02370, in cohort 1 received the 1400 mg dose of ribavirin. There was no meaningful difference in the rate of treatment discontinuation, overall adverse events, or serious adverse events in subjects receiving the 1400 mg dose in comparison to those receiving the 800 mg, 1000 mg, or 1200 mg doses. The only adverse event that appeared to occur at a higher rate in the 1400 mg group was vomiting however none were serious adverse events and there was no meaningful difference in the incidence of vomiting in the F4 subjects compared to the F2/3 subjects.

In addition to the data from study P02370, data on an additional 292 subjects who received the 1400 mg dose of ribavirin in study P02314 were considered. Overall, no clinically relevant safety differences related to the use of ribavirin 1400 mg in patients weighing more than 105 kg were identified.

1.4 Risk management

The CHMP agreed that a EU-Risk management plan would not be required for Rebetol for the extension of indication of the treatment of patients who failed previous treatment with interferon alpha (pegylated or nonpegylated) and ribavirin combination therapy.

1.5 Overall conclusion and Benefit-risk assessment

This submission is based on an interim analysis of an ongoing single-arm trial. Study outcome in altogether 1354 patients with prior non-response or relapse after treatment with (any) alpha interferon plus ribavirin for chronic hepatitis C were detailed in this interim report.

The spontaneous remission rate in chronic hepatitis C is very low. All patients included in the study had fibrosis and about 40% cirrhosis, i.e. a poor long-term prognosis. Therefore a sustained viral response rate about 20% as demonstrated in this submission convincingly demonstrates efficacy. There are currently no licensed alternative treatment options to (peg)interferon plus ribavirin in the treatment of chronic hepatitis C.

Efficacy results however differ significantly with regard to the mode of prior treatment failure ("relapse" versus "nonresponder") and with regard to the previous therapy regimen. Nonresponder patients whose previous combination therapy included nonpegylated interferon/ribavirin were more likely to respond to treatment than patients who had previously received pegylated interferon/ribavirin (17% vs. 4%). The low response rate in prior non-responders to the same therapy is expected. Nevertheless, "near response" to prior therapy and, e.g. a short duration of prior therapy would be a reason to try to induce sustained response in a patient with poor prognosis due to fibrosis/cirrhosis, not least as there are no alternative curative therapies currently available and that viral response at week 12 can be used to identify patients with an increased likelihood to become sustained responders.

Probably due to selection based on prior tolerance to interferon plus ribavirin therapy, the overall incidence of treatment-related adverse reactions was lower than in treatment naïve patients. In patients with cirrhosis a higher incidence of haematotoxicity was reported as expected. There were no unexpected findings. Overall there are no clinically relevant safety differences related to the use of ribavirin 1400 mg in patients weighing more than 105 kg, and the 1400 mg dose is accepted in these patients.

Despite the well-known tolerability and safety concerns related to treatment with interferon plus ribavirin for one year, the benefit–risk balance of Rebetol in the treatment of hepatitis C patients who have failed previous treatment with interferon alfa (pegylated or non-pegylated) and ribavarin combination is considered favourable, especially as viral response at week 12 can be used to identify patients with an increased likelihood to become sustained responders.

The MAH has committed to provide the final study report of P02370 to the CHMP by May 2008.