European Medicines Agency

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ASSESSMENT REPORT
FOR
Rebetol

International non-proprietary name/Common name:
ribavirin

Procedure No: EMEA/H/C/246/II/48

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

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LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine transaminase
BMI	body mass index
BSA	Body Surface Area
CHC	chronic hepatitis C
CHMP	Committee for Human Medicinal Products
EOT	End of Therapy
FDA	Food and Drug Administration
HCC	Hepatocellular carcinoma
HCV	hepatitis C virus
IFN	interferon
NIH	National Institutes of Health
NNT	number needed to treat
NPV	negative predictive value
PPV	positive predictive value
PEG2a	peginterferon alfa-2a (Pegasys)
PEG2b	peginterferon alfa-2b (PegIntron/ViraferonPeg)
RBV	ribavirin
RNA	ribonucleic acid
SAE	Serious Adverse event
sc	subcutaneous
SVR	Sustained Virological response
ULN	Upper limit normal

I. SCIENTIFIC DISCUSSION

I.1 Clinical aspects

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), and adolescents). Rebetol monotherapy must not be used.

The approved dose of peginterferon alfa2b (PEG2b) is 1.5 µg/kg. To date the efficacy of the 1.0 µg/kg dose and the 1.5 µg/kg dose in combination with ribavirin has not been compared. The study "IDEAL" (P03471) was therefore designed, in accordance with a post-approval commitment to the FDA, to compare the safety and efficacy of the two PEG2b dosing regimens. IDEAL also included the use of an active comparator, peginterferon alfa-2a (PEG2a) 180 µg/week plus weight-based ribavirin to allow for the evaluation of comparative safety and efficacy of the peginterferon alfa-2b/ribavirin (PEG2b/R) and PEG2a/R treatment regimens.

The IDEAL study (P03471) supports a therapeutic extension of indication to include treatment of patients with compensated cirrhosis. On the basis of the IDEAL study results the MAH proposes to maintain the approved dose of peginterferon alfa2b (PEG2b) as 1.5 µg/kg. A change in the scheme for dose reduction of peginterferon alfa-2b in case of adverse effects and a change in the weight-based dosing algorithm for Rebetol are also proposed. The MAH also proposed an increase in the dose of Rebetol in the 81-85 kg weight category across all genotypes.

I.2 Scientific Overview and discussion

Study design

IDEAL 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:

- Peginterferon alfa-2b 1.5 µg /kg/week plus ribavirin (PEG2b 1.5/R).
- Peginterferon alfa-2b 1.0 µg/kg/week plus ribavirin (PEG2b 1.0/R)
- Peginterferon alfa-2a 180 µg/week plus ribavirin (PEG2a/R).

In all arms, the pegylated interferon was combined with weight-based ribavirin. The dosing algorithm for ribavirin, however, was different between arms, reflecting the different posologies for ribavirin co-treatment in the PegIntron and Pegasys SPCs:

- In the PEG2b arms, ribavirin was dosed at 800 mg/day when body weight (BW) was 40-65kg, 1000 mg/day if BW >65-85, 1200 mg/day if BW >85-105 and 1400 mg/day if BW >105kg.
- In the PEG2a arm, patients with BW < 75 kg received 1000 mg/day and those with BW >75 kg received 1200 mg.

The predefined algorithms for ribavirin dose modification in case of anaemia differed between arms:

- In the PEG2b arm, the ribavirin dose was to be decreased stepwise by 200 mg (400 mg if initial dose 1400 mg), and again by 200 mg if necessary.
- In the PEG2a arm, the dose was to be decreased to 600 mg regardless of initial dose.

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 log10 decline of HCV-RNA at week 12.
The comparison between PEG2b doses was double-blinded, whereas the assignment to PEG2a or PEG2b was open-label.

Endpoints

- The primary endpoint variable was SVR (sustained virological response = undectectable HCV-RNA 24 weeks post treatment completion).
- Comparison of proportions with SVR of arm 1 vs arm 2, and arm 1 vs arm 3 were defined as co-primary endpoints.
- Patients were stratified as to race (black vs non-black) and baseline HCV-RNA (≤600 000 vs >600 000 IU/mL). Differential responses in these strata were predefined secondary endpoints.

Power considerations

The comparison between the two PEG2b was designed to have an 80% power to detect a 6.5% difference in response rate, given a one-sided test, on the assumption of a greater efficacy of the higher dose, for an alpha of 0.025. The comparison between PEG2b1.5/R and PEG2a/R had 80% power to detect a 7% difference in response rate, at a two-sided alpha of 0.025.

Results

Patient disposition

A total of 3070 subjects (1019 in the PEG2b 1.5/R arm, 1016 in the PEG2b 1.0/R arm, and 1035 in the PEG2a/R arm) were randomised and received at least one dose of study drug.

Baseline characteristics

The study population consisted of mostly male (60%), Caucasian subjects, over 40 years old, with 82% having a high viral load (>600,000 IU/mL). Most subjects had METAVIR F0/1/2 scores, and 11% of each arm had bridging fibrosis/cirrhosis.

I.3 Clinical Efficacy

Primary endpoint

The study demonstrated that each of the three treatment regimens results in similar SVR rates (Table 1) that did not differ significantly. The response 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 of -2.3 - +6.0.

Table 1: Sustained Virologic Response rates in IDEAL comparator groups
Protocol No. P03471

	% of Subjects								
	PEG2b 1.5/R (Arm 1) (n=1019)	PEG2b 1.0/R (Arm 2) (n=1016)	PEG2a/R (Arm 3) (n=1035)	Arm 1 vs Arm 3		Arm 1 vs Arm 2		Arm 2 vs 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; PEG2b 1.5/R = peginterferon alfa-2b 1.5 µg/kg/wk plus ribavirin; PEG2b 1.0/R = peginterferon alfa-2b 1.0 µg/kg/wk plus ribavirin; PEG2a/R = peginterferon alfa-2a 180 µg/wk plus 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 SP laboratory) and race (Black vs non-Black).

b: The primary efficacy analysis utilizing only the available FW 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.

Table 2 shows the probability of response in the different treatment arms by baseline demographic and disease characteristics.

Table 2 Sustained Virologic Response by Baseline Demographic and Disease Characteristics
Protocol No. P03471

	Number (%) of Subjects		
	PEG2b 1.5/R (n=1019)	PEG2b 1.0/R (n=1016)	PEG2a/R (n=1035)
Gender			
Female	44.3% (180/406)	35.9% (147/409)	41.9% (177/422)
Male	36.9% (226/613)	39.4% (239/607)	40.1% (246/613)
Age (years)			
≤40	52.9% (74/140)	46.8% (72/154)	55.8% (91/163)
>40	37.8% (332/879)	36.4% (314/862)	38.1% (332/872)
Race			
Caucasian	43.6% (319/732)	43.6% (316/724)	44.2% (324/733)
Black	23.0% (42/183)	16.6% (31/187)	26.0% (52/200)
Hispanic	39.2% (31/79)	29.4% (20/68)	43.9% (29/66)
Asian	70.0% (7/10)	61.9% (13/21)	50.0% (10/20)
Other	46.7% (7/15)	37.5% (6/16)	50.0% (8/16)
Baseline Stratification Factors[a]			
Black	23.0% (42/183)	16.6% (31/187)	26.0% (52/200)
≤600,000 IU/mL	29.3% (27/92)	21.0% (21/100)	35.2% (37/105)
>600,000 IU/mL	16.5% (15/91)	11.5% (10/87)	15.8% (15/95)
Non-Black	43.5% (364/836)	42.8% (355/829)	44.4% (371/835)
≤600,000 IU/mL	49.0% (190/388)	47.7% (184/386)	52.0% (205/394)
>600,000 IU/mL	38.8% (174/448)	38.6% (171/443)	37.6% (166/441)
Body Weight (kg)			
40 to 65	45.8% (65/142)	37.1% (52/140)	43.1% (69/160)
>65 to <75	36.7% (55/150)	40.0% (66/165)	41.1% (72/175)
75 to 85	36.4% (99/272)	37.2% (93/250)	45.6% (123/270)
>85 to 105	40.8% (142/348)	36.6% (140/383)	36.3% (117/322)
>105 to 125	42.1% (45/107)	44.9% (35/78)	38.9% (42/108)
Years since Exposure			
≤Baseline Median of 24.8 years	40.7% (207/509)	41.6% (213/512)	42.8% (221/516)
>Baseline Median of 24.8 years	39.0% (199/510)	34.3% (173/504)	38.9% (202/519)
Baseline HCV-RNA Viral Load[b]			
≤600,000 IU/mL	60.7% (111/183)	58.6% (109/186)	65.6% (120/183)
>600,000 IU/mL	35.3% (295/836)	33.4% (277/830)	35.6% (303/852)
Baseline METAVIR Fibrosis Score			
F0	52.6% (10/19)	33.3% (4/12)	82.4% (14/17)
F1	44.0% (306/696)	39.3% (276/703)	43.8% (306/698)
F2	32.5% (50/154)	36.9% (55/149)	38.1% (56/147)
F3	34.0% (17/50)	29.7% (11/37)	31.6% (12/38)
F4	9.8% (6/61)	30.0% (21/70)	19.4% (14/72)
F0/1/2	42.1% (366/869)	38.8% (335/864)	43.6% (376/862)
F3/4	20.7% (23/111)	29.9% (32/107)	23.6% (26/110)

The PEG2b 1.5/R arm showed a higher proportion of SVR among black patients, compared with the PEG2b 1.0/R arm (23 vs 16.6%). This difference was discernable regardless of baseline HCV-RNA. In the subgroup with high baseline viral load (> 600 000 IU/mL), the probability of SVR was roughly similar (35.3 vs 33.4%; difference 1.9%; 95% CI -3.1 - +6%). Among non-black patients, the probability of SVR in patients with high baseline viral load was similar between arms (38.8 vs 38.6%).

In subjects with cirrhosis (METAVIR F4), SVR rates for PEG2b 1.5/R was strikingly lower than for PEG2b 1.0/R (9.8 vs 30%).

Ribavirin dose and probability of SVR
Table 3 shows SVR rates by assigned ribavirin dose. The large difference in SVR rates between the PEG2b arms and the PEG2a arm in the 80-85 kg stratum, where the formers received 1000 mg/day and the latter 1200 mg/day, is notable.

Table 3 Sustained Virologic Response Rates by Assigned Ribavirin Dose
Protocol No. P03471

Body Weight (kg)	% (Number) of Subjects					
	PEG2b 1.5/R (n=1019)		PEG2b 1.0/R (n=1016)		PEG2a/R (n=1035)	
	R (mg/day)	SVR	R (mg/day)	SVR	R (mg/day)	SVR
40 to 65	800	45.8% (65/142)	800	37.1% (52/140)	1000	43.1% (69/160)
>65 to <75	1000	36.7% (55/150)	1000	40.0% (66/165)	1000	41.1% (72/175)
75 to 85	1000	36.4% (99/272)	1000	37.2% (93/250)	1200	45.6% (123/270)
75 to 80	1000	41.9% (62/148)	1000	45.1% (64/142)	1200	47.6% (69/145)
>80 to 85	1000	29.8% (37/124)	1000	26.9% (29/108)	1200	43.2% (54/125)
>85 to 105	1200	40.8% (142/348)	1200	36.6% (140/383)	1200	36.3% (117/322)
>105	1400	42.1% (45/107)	1400	44.9% (35/78)	1200	38.9% (42/108)

Bold = higher dose of ribavirin in PEG2a arm.

Italics = higher dose of ribavirin in PEG2b arms.

Normal text = equivalent ribavirin dosing in PEG2b and PEG2a arms.

PEG2b 1.5/R = peginterferon alfa-2b 1.5 µg/kg/wk plus ribavirin; PEG2b 1.0/R = peginterferon alfa-2b 1.0 µg/kg/wk plus ribavirin; PEG2a/R = peginterferon alfa-2a 180 µg/wk plus ribavirin; SVR = sustained virologic rate.

Table 4 demonstrates the overall trend towards a higher response rates with higher doses of ribavirin per body weight.

Table 4 Sustained Virologic Response Rates by Assigned Ribavirin Dose in Milligrams per Kilograms
Protocol No. P03471

Ribavirin Dose (mg/kg)	% (Number) of Subjects		
	PEG2b 1.5/R (n=1019)	PEG2b 1.0/R (n=1016)	PEG2a/R (n=1035)
9 to 11	-	-	38.4% (28/73)
>11 to 13	37.2% (215/578)	35.9% (204/568)	35.6% (73/205)
>13 to 15	43.2% (174/403)	39.6% (160/404)	42.1% (190/451)
>15 to 17	42.9% (15/35)	51.3% (20/39)	40.8% (97/238)
>17	66.7% (2/3)	40.0% 2/5	51.5% (35/68)

PEG2b 1.5/R = peginterferon alfa-2b 1.5 µg/kg/wk plus ribavirin; PEG2b 1.0/R = peginterferon alfa-2b 1.0 µg/kg/wk plus ribavirin; PEG2a/R = peginterferon alfa-2a 180 µg/wk plus ribavirin

Predictability of Response

Table 5 summarizes the sustained response rates in subjects achieving HCV negativity at TW 4 (rapid virologic response; RVR) and TW 12 (early virologic response; EVR)

As shown in previous studies with interferon and ribavirin, early negativity is an important predictor for achieving a SVR. Subjects who achieve HCV negativity by TW 4 (rapid virologic response) have a high probability of being sustained responders (high PPV). As shown in Table 5, subjects with an

undetectable HCV-RNA level at TW 4 who were treated with PEG2b 1.5 µg/kg/wk (92.2%) had the highest response, followed by subjects treated with PEG2b 1.0 µg/kg/wk (87.3%) or PEG2a (79.7%). Consistent with the higher relapse rate observed with PEG2a/R, the PPV was lower in the PEG2a/R arm than in the PEG2b/R arms.

Among those subjects who had detectable HCV-RNA at TW 12 and met the criteria of ≥2-log decrease, reassessment at TW 24 allowed for good predictability in the two PEG2b groups (44.6%/48.7%). Predictability for the PEG2b/R arms was better than for the PEG2a/R arm.

Table 5: Positive Predictive Values at TW 4 and TW 12
Protocol No. P03471

	% (Number) of Subjects					
	PEG2b 1.5/R		PEG2b 1.0/R		PEG2a/R	
Visit	PPV	95% CI	PPV	95% CI	PPV	95% CI
Undetectable at TW 2	95.6 (43/45)	N/A	90.5 (38/42)	N/A	84.1 (37/44)	N/A
Rapid Virologic Response: Undetectable at TW 4[a]	92.2 (107/116)	87.4, 97.1	87.3 (69/79)	80.0, 94.7	79.7 (98/123)	72.6, 86.8
Complete Early Virologic Response: Undetectable at TW 12[b]	80.6 (328/407)	76.7, 84.4	82.8 (303/366)	78.9, 86.7	73.8 (344/466)	69.8, 77.8
Partial Early Virologic Response: ≥2 log reduction and Detectable at TW 12 and Undetectable at TW 24	44.6 (70/157)	36.8, 52.4	48.7 (75/154)	40.8, 56.6	34.2 (66/193)	27.5, 40.9

CI = confidence interval; FW = Follow-up Week; N/A = not available; PPV = positive predictive value; PEG2b 1.5/R = peginterferon alfa-2b 1.5 µg/kg/wk plus ribavirin; PEG2b 1.0/R = peginterferon alfa-2b 1.0 µg/kg/wk plus ribavirin; PEG2a/R = peginterferon alfa-2a 180 µg/wk plus ribavirin; TW = Treatment Week.

Note: TW 4 and TW 12 HCV-RNA results are independent of one another.

a: Sensitivity Analysis Week 4 PPV : Subjects with missing data at FW 24 were included in the analysis if TW 4 and TW 24 were undetectable: PPVs at TW 4 are 94%, 91%, and 89% for PEG2b 1.5/R, PEG2b 1.0/R, PEG2a/R, respectively.

b: Sensitivity Analysis Week 12 PPV : Subjects with missing data at FW 24 were included in the analysis if TW 12 and TW 48 were undetectable: PPVs at TW 12 are 82%, 84%, and 76% for PEG2b 1.5/R, PEG2b 1.0/R, PEG2a/R.

The negative predictive value (NPV) is defined as the probability of not achieving SVR given that a subject did not achieve undetectable HCV-RNA at a specific time point. The decrease in HCV-RNA levels at TW 4 is highly sensitive and specific in identifying those subjects who are unlikely to achieve SVR. In this study, a failure to achieve a 1-log decrease in HCV-RNA level at TW 4 was associated with a 95% to 97% probability that the subject would fail to respond to treatment (Table 6). Subjects with greater decreases in viral load had a better chance of achieving SVR.

Table 6: Negative Predictive Value at TW 4
Protocol No. P03471

	% (Number) of Subjects		
Visit	PEG2b 1.5/R	PEG2b 1.0/R	PEG2a/R
TW 4			
Detectable with <1 log Reduction in HCV-RNA	95.5% (210/220)	96.7% (294/304)	95.1% (215/226)
Detectable with <2 log Reduction in HCV-RNA	86.8% (402/463)	86.3% (477/553)	83.0% (380/458)
Detectable with <3 log Reduction in HCV-RNA	77.0% (471/612)	77.1% (543/04)	75.6% (466/616)

PEG2b 1.5/R = peginterferon alfa-2b 1.5 µg/kg/wk plus ribavirin; PEG2b 1.0/R = peginterferon alfa-2b 1.0 µg/kg/wk plus ribavirin; PEG2a/R = peginterferon alfa-2a 180 µg/wk plus ribavirin; TW = treatment week.

Discussion Efficacy

The presently approved dose of PEG2b is 1.5 µg/kg. The IDEAL study tested the superiority hypothesis that a higher end of treatment rate seen in monotherapy phase 3 trials for the 1.5 µg/kg dose as compared to the 1.0 µg/kg would translate into a higher rate of the clinically relevant SVR for the 1.5 µg/kg compared to 1.0 µg/kg, when combined with ribavirin. The IDEAL study did not deliver evidence in support of this hypothesis. The overall SVR rates for PEG2b 1.5 and 1.0 µg/kg/week were similar (40% and 38%, respectively).

Regarding the extension to include patients with compensated cirrhosis, 11 % of patients in the IDEAL study had bridging fibrosis/cirrhosis, approximately 35 % had a normal baseline ALT. It should be noted that the IDEAL study was not designed to evaluate treatment of subjects with normal ALT level. However the results according to baseline ALT appeared to be comparable between the three treatment arms with somewhat higher SVR rates for patients with elevated ALT at baseline. Therefore the extension of indication is considered approvable. Overall the addition of patients with cirrhosis is sufficiently substantiated by the IDEAL study.

Subgroups of patients with HCV known to have a lower likelihood of successful treatment outcome include those with genotype 1, high baseline HCV-RNA, black race and/or cirrhosis. In patients with baseline HCV-RNA >600 000 there was however no significant difference in the SVR rate between doses in the IDEAL study, and point estimates are roughly similar (35.3 vs. 33.4%; difference 1.9%; 95% CI -3.1 - +6%). This equivalence of effect is supported by data from the dose-ranging monotherapy study [1], where the SVR rates for PEG2b 1.5 and PEG2b 1.0 were similar regardless of baseline HCV-RNA.

In black patients there was a non-significant trend towards a higher SVR rate in patients treated with PEG2b1.5/R compared to PEG2b1.0/R (23.0 vs. 16.6%). These results imply that the exposure-response relation of peginterferons may be different in this population. The fact that similar rates of dose modifications and discontinuations due to neutropenia are seen regardless of race, despite lower baseline neutrophil counts in black, may corroborate this implication.
A number of studies have established that African-Americans (AA) are less responsive to interferon therapy than Caucasians and that higher initial doses of interferon in difficult to treat patients have limited effect in increasing SVR. This suggests that increasing interferon doses for African-Americans will have led to only a small improvement in SVR, especially in contrast to using a protease inhibitor as a third therapeutic agent. As such no change in the posology for black patients has been recommended.

Importantly, in patients with cirrhosis (METAVIR F4; n = 61 and 70), there was a striking and statistically significant difference in SVR rates, to the advantage of the lower PEG2b 1.0/R arm on the PEG2b 1.5/R arm (30.0 vs. 9.8%; difference 20.2%, 95% CI 7-33%). In the broader category of patients with fibrosis or cirrhosis (F3/F4; n = 111 and 107), point estimates were also clearly, and almost statistically significantly, in favour of the lower dose (29.9 vs. 20.7%; difference 9.2%; 95% CI 20.7 - -2.3).

The CHMP considered whether a lower starting dose could be considered for cirrhotic patients who may have lower haematological reserve and could potentially tolerate higher total regimen when receiving a lower PEG2b dose. However the CHMP agreed that the IDEAL study is not robust enough to demonstrate this taking into account that the conclusion are based on a subgroup analysis from a failing global analysis and this subgroup represents around 7% of the whole population of the study. There are also critical imbalances in favour of the PEG2b lower dose, including factors potentially influencing the treatment response (i.e. VL>600K, black). An unexpected sharp decrease in the response rate between F3 and F4 was also noted in the PEG2b 1.5/R (from 34% to 9.8%). Furthermore the difference between both treatment arms in favour of the PEG2b 1.0 µg/kg dose is already observed at week 2 suggests a sampling bias more than a true difference due to a differential tolerance. Finally the higher rate of EPO in the PEG2b 1.0 µg/kg allowing a higher dose ribavirin might in part explain the better response rate in the PEG2b 1.0 µg/kg arm.

As such the CHMP agreed that the higher dose (1. 5 µg/kg) should be used for patients with cirrhosis.

Taking into account the higher response rates with higher doses of ribavirin per body weight the CHMP accepted the proposed change in ribavirin dose from 1000 mg to 1200 mg (or 14-15 mg/kg) in patients with a body weight of 81-85 kg and Genotype 1. There were concerns that the higher ribavirin dose might have an impact on adherence and thus SVR rates. However data provided by the MAH did not show a falling adherence rate within the range of mg/kg in question for the proposed change in posology.

The MAH also proposed an increased ribavirin dose from 1000 to 1200 mg in Genotype 2 and 3 patients in the 81-85 kg stratum, although IDEAL exclusively studied patients with Genotype 1. The CHMP had concerns that putative gain in efficacy with the increased dose is at best marginal in these genotypes, and would mainly cause an increased rate of anaemia. Taking this into account the CHMP considered that the posology for ribavirin when treating with peginterferon alfa-2b might be harmonised with the flat dosing of ribavirin that is used when co-treating with peginterferon alfa-2a.

The only randomised comparison between a flat dose of 800 mg and a weight based regimen (800-1400 mg/day) for PEG2b 1.5 µg/kg is the WIN-R [2] study, in which there was no genotype restriction. In a subgroup of 1500 patients with Genotype 2/3, point estimates for SVR in the weight-based and flat dose arms were 61.8% and 59.5% respectively, a non significant difference. Of note, the WIN-R study had a rather high rate of missing data, as reflected by the relatively low point estimates.

The 800 mg flat dose posology for ribavirin in Genotype 2/3 is mainly based on a phase III clinical trial published by Hadziyannis et al [3]. In this study, including over 1000 patients of whom approximately 500 patients had Genotype 2/3, an 800 mg flat dose of ribavirin was compared to a higher, weight based ribavirin dose regimen (1000/1200 mg below/above 75 kg), both in combination with PEG2a. The study, which had a factorial design, also compared 24 versus 48 weeks of therapy. There was no evidence of an increased efficacy in patients with Genotype 2/3 given the higher, weight based dose, point estimates for SVR rates being very similar at around 80%. Data from this study also show a higher rate of serious adverse events and anaemia with the higher, weight-based dose.

Overall the available randomised evidence with PEG2a or PEG2b fail to support any clinically significant efficacy advantage of a higher dose of ribavirin. Available observational evidence including suboptimal interferon regimens such as IntronA or peginterferon alfa-2b dosed at 0.5 µg/kg imply that there may be a lower response rate in very heavy individuals (>110 kg), where effects of dose and baseline factors could hardly confidently be separated by multiple regression approaches. Importantly the ribavirin exposure response relationship when co-treating with standard interferon is not relevant to the question at hand. With regards to safety, the two studies comparing flat dose and weight based ribavirin treatment have, as is expected, shown a greater degree of anemia in patients treated with the higher dosed weight based ribavirin algorithms. Taking into account the lack of supportive evidence for weight based ribavirin dosing the CHMP requested the MAH to provide a rational for the differing dosing recommendations between the different peginterferons.

The MAH provided a putative rational as to why data from studies with PEG2a in Genotype 2/3 might not be applicable to PEG2b. Importantly the size and position of the PEG molecule used for PEG2b and PEG2a differ significantly in their respective physical-chemical characteristics. Of note it also results in loss of *in vitro* biological activity. The antiviral activity of PEG2b is approximately 28% of the interferon alfa-2b core protein while the antiviral activity of PEG2a ranges between 1% to 7% of the antiviral activity of the interferon alfa-2a core protein. It has also been demonstrated that the size and position of the PEG moiety on the interferon alpha molecule markedly affects its specific activity, presumably by stearic hindrance imposed upon the peptide by the addition of a larger PEG molecule.
Silva et al [4] compared pharmacokinetics and assessed mRNA expression of selected interferon-induced RNA gene transcripts for the two pegylated interferons (PEG2b and PEG2a). In this trial (COMPARE), 26 Genotype 1 patients received PEG2b (1.5 µg/kg/week) or PEG2a (180 µg/week) monotherapy for 4 weeks followed by 4 weeks with the addition of ribavirin (~13 mg/kg/day).

Overall there is a much greater protein exposure with the larger PEG2a at the recommended dose which, in part, reflects the lower specific activity of the molecule thus requiring more product to achieve optimal antiviral activity. Despite the greater exposure with PEG2a, there was consistently greater up-regulation of RNA transcripts in patients treated with PEG2b compared with patients treated with PEG2a for the majority of the interferon-response genes investigated. Similarly, with a greater up-regulation in interferon response genes, PEG2b demonstrated significantly greater antiviral activity vs. PEG2a at week one, with greater maximum antiviral activity (P<0.001) and greater cumulative antiviral activity (P=0.017); the slope of the viral load reduction for Peg2b was greater over the eight-week study duration (P<0.002). In addition, 72% percent of patients in the PEG2b arm achieved at least a 2.0 log10 reduction in viral load as compared to 44% of patients in the PEG2a arm during the study (p=0.09). The mean maximum and time-weighted decreases in log10 viral load were significantly greater with PEG2b than PEG2a on Week 1 and Week 4. These results show that the viral kinetics are very different for both of these interferons with apparent periods of viral replication with PEG2b versus PEG2a. This may also affect the mechanism by which the pegylated interferons interact with ribavirin. Thus, the two molecules, while each exerting interferon antiviral activity, do so in a very different manner, and it cannot be assumed that the ribavirin interaction at a given dose will be the same.

The CHMP considered that it is questionable whether these differences in PK/PD really imply that the need of ribavirin dosing is actually higher for PEG2b in Genotype 2/3, given that the total viral load decline over time in this cited study was greater with PEG2b than with PEG2a and that ribavirin has virtually no direct effect on HCV viral load [5]. Overall however the CHMP acknowledged that the MAH has provided an argument that data generated with PEG2a might not be applicable to PEG2b, due to the clear differences in the PK/PD relation between these two drugs. As such the CHMP agreed to maintain weight base dosing for ribavirin in combination with PEG2b and therefore agreed to the dose increase of ribavirin in Genotype 2 and 3 patients weighing 81-85 kg.

Regarding the predictive value of response at treatment week 4 and 12 and their usefulness in clinical practice for the management of HCV-infected patients, this has been increasingly highlighted in the recent years. Some data suggest that rapid and early virological response to treatment (at treatment week 4 (TW 4) and 12 (TW 12)) rather than genotype might be better factor to guide optimal treatment duration (24 weeks, 48 weeks or longer treatment duration). In the IDEAL study a null response (defined as less than 1 log decline in HCV RNA from baseline) at TW4 was found to be a strong predictor of lack of response and is a relevant early stopping rule. Furthermore among those subjects who had detectable HCV-RNA at TW12 and met the criteria of ≥2-log decrease, reassessment at TW24 allowed for good predictability in the two PEG2b groups (44.6%/48.7%). Rebetol and PegIntron SPC have been revised in order to include these observations on predictiveness, in order to better guide physicians in their clinical decision making.

I.4 Clinical Safety

Patient exposure
3070 patients received at least one dose of study medication. Approximately half of the subjects (54% and 49%) received 48 weeks of PEG2b 1.5/R andPEG2b 1.0/R treatment. 61% of the subjects in the PEG2a/R arm received 48 weeks of treatment.

Adverse events
The incidence of treatment related AEs were similar in the PEG2b 1.5 arm compared with the PEG2b 1.0 arm. AEs in which the difference was ≥3% in incidence between the PEG2b 1.5 and PEG2b 1.0 treatment arms are shown in Table 7.

Table 7: Treatment-related treatment-emergent AEs (≥ 3% difference between Peg2b 1.5 vs 1.0 arms)

	Peg2b 1.5/RBV	Peg2b 1.0/RBV	Peg2a/RBV
Blood and lymphatic system disorders	499 (49)	413 (41)	540 (52)
Anaemia	343 (34)	293 (29)	348 (34)
Neutropenia	263 (26)	188 (19)	325 (31)
Gastrointestinal Disorders	630 (62)	583 (57)	577 (56)
Nausea	412 (40)	357 (35)	351 (34)
General Disorders and Administration Site Conditions	917 (90)	933 (92)	892 (86)
Chills	397 (39)	362 (36)	241 (23)
Pyrexia	352 (35)	323 (32)	219 (21)
Investigations	225 (22)	183 (18)	189 (18)
Weight decreased	135 (13)	100 (10)	100 (10)
Metabolism and Nutrition Disorders	340 (33)	284 (28)	252 (24)
Anorexia	121 (12)	95 (9)	75 (7)
Decreased appetite	182 (18)	156 (15)	141 (14)
Musculoskeletal and Connective Tissue Disorders	473 (46)	505 (50)	467 (45)
Nervous System Disorders	664 (65)	626 (62)	601 (58)
Psychiatric Disorders	588 (58)	561 (55)	587 (57)
Depression	254 (25)	192 (19)	209 (20)
Suicidal ideation*	8 (1)	9 (1)	6 (1)
Suicide attempt*	0	0	2 (<1)
Skin and Subcutaneous Tissue Disorders	592 (58)	547 (54)	617 (60)
Alopecia	232 (23)	205 (20)	176 (17)

*Note: Suicidal ideation and suicide attempt are shown, but do not reflect a ≥3% difference in incidence between the Peg2b 1.5 vs 1.0 treatment arms.

The higher rates of anaemia and neutropenia in the 1.5 µg/kg arm as compared to the 1.0 µg/kg arm is noted and expected. The study drug discontinuation rate was higher in the 1.5µg/kg arm than in the 1.0µg/kg arm (12.7 vs. 9.6%). The frequency of SAE was similar: 8.6% vs. 9.3%.

The incidence of treatment-related, treatment-emergent depression was 6% higher in the PEG2b 1.5 treatment arm compared with the PEG2b 1.0 treatment arm, although the more severe outcomes of suicidal ideation and suicide attempt were similar among the three arms of the study. The incidences of psychiatric disorders were similar among the treatment arms (58% in the PEG2b 1.5 arm and 55% in the PEG2b 1.0 arm).

Deaths
Twelve subjects died during this study: 5 subjects in the PEG2b 1.5/R arm, 1 in the PEG2b 1.0/R arm, and 6 in the PEG2a/R arm. One of these events, a completed suicide in the PEG2b 1.5/R was judged by the investigator as possibly related to the treatment.

Discontinuation
AEs led to study drug discontinuation in 12.7% of subjects in the PEG2b 1.5/R arm, 9.6% in the PEG2b 1.0/R arm, and 13.0% in the PEG2a/R arm. The difference in discontinuation rates between PEG2b 1.5/R and PEG2b 1.0/R was statistically significant (3%; 95% CI 0.2-5.7%).

Dose modification
The proportion of subjects (excluding those who discontinued) that required dose modifications of PEG2b where 25% in the PEG2b 1.5/R and 17% in the PEG2b 1.0/R. The percentages of patients reporting typical peginterferon side effects were higher in the PEG2b 1.5/R arm compared to the PEG2b 1.0/R: Pyrexia/Chills 51 vs 47%, Neutropenia/leukopenia 27 vs 20%, depression 25 vs 19%.

Proposed change in the scheme of dose reduction for PegIntron and Rebetol in case of adverse effects.

The MAH proposed a new dose-reduction schedule for PegIntron of 1.5→1.0→0.5 µg/kg, in case of adverse events. Presently, the SPC for PegIntron states that the PegIntron dose be reduced to one-half if WBC count falls below $1.5*10^9$/L, if neutrophils falls below $0.75*10^9$/L or if the platelet count falls below $50*10^9$/L (and that PegIntron be discontinued if these levels fall below $1*10^9$/L, $0.5*10^9$/L and $25*10^9$/L, respectively). A large proportion of patients randomised to 1.5 µg/kg, who had a one step dose reduction, did not require a second dose reduction, maintaining a high exposure. This dose reduction schedule appears justified as the 1.5 µg/kg starting dose has been endorsed. However, the dose reduction scheme did not prevent a significantly higher number of discontinuations in patients randomised to the higher dose: 12.7% of subjects discontinued treatment in the PEG2b 1.5/R arm, compared to 9.6% in the PEG2b 1.0/R arm, and 13.0% in the PEG2a/R arm. The difference in discontinuation rates between PEG2b 1.5/R and PEG2b 1.0/R was 3%; 95% CI 0.2-5.7%.

Table 8: Summary of dose modification steps due to adverse events

P03471
All Treated Subjects

Summary Of Peginterferon Dose Modification Steps For Dose Modifications Due To An Adverse Event
Excluding Subjects Who Discontinued Treatment Due to an Adverse Event

Category #	Peg2b 1.5/R n=1019		Peg2b 1.0/R n=1016		Peg2a/R n=1035	
First Dose Reduction As Per Protocol	164	(16)	117	(12)	152	(15)
Second Dose Reduction As Per Protocol	43	(4)	23	(2)	68	(7)
Dose Interrupted	44	(4)	27	(3)	43	(4)

The MAH also proposed a change to the algorithm for dose adjustment of Rebetol in case of anaemia to be modified in accordance with that used in the PEG2b1.5/R and PEG2b1.0/R arms of the IDEAL study. In the PEG2b arm, the ribavirin dose was decreased stepwise by 200 mg (400 mg if initial dose 1400 mg), and again 200 mg if necessary. This strategy was also used in the WIN-R study [2]. The dose modification algorithm has been extensively evaluated, and is in line with available evidence that maintaining a high ribavirin exposure is important for the optimisation of the likelihood of SVR.

Discussion Clinical Safety

The safety profile of PEG2b and PEG2a when used in combination with ribavirin in this study is consistent with that in the respective current product information; no new or unexpected AEs were observed. The study drug discontinuation rate was higher in the PEG2b 1.5 µg/kg arm than in the PEG2b 1.0 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 anemia and neutropenia in the 1.5 µg/kg arm as compared to the 1.0µg/kg arm which is as expected.

The proportion of patients with moderate to severe depressive symptoms, as defined by the Center for Epidemiologic Studies Depression Scale (CES-D) Data, was compared for the two PegIntron doses (32% in the PEG2b 1.5 arm and 29.4% in the PEG2b 1.0 arm). From a clinical perspective the difference of 2.6% is not meaningful, although due to the large sample size of the study the difference is statistically significant. Study sites were notified in case of critical values of CES-D assessment and patients were to be assessed and managed clinically according to a pre specified plan at site.

The CES-D evaluation was included in the IDEAL study to determine if a patient self-administered assessment could provide, in addition to physician assessment, an indicator of development of psychiatric adverse events. The CES-D scores during the study did not predict the most severe psychiatric outcomes and cannot therefore supersede a physician's clinical assessment. In an attempt to determine the physician utility of the CES-D and the potential to use baseline CES-D scores to

predict the likelihood of a particular patient developing a psychiatric adverse event(s), further analyses are being performed by the MAH.

The new dose-reduction schedule for PegIntron of 1.5→1.0→0.5 μg/kg, and the stepwise dose reduction of 200 mg (400 mg if initial dose 1400 mg), and again 200 mg of ribavirin if necessary in case of adverse events is accepted. This dose reduction schedule of PegIntron appears justified also taking into account that the 1.5 μg/kg starting dose has been endorsed The dose modification algorithm for ribavirin has been extensively evaluated, and is in line with available evidence that maintaining a high ribavirin exposure is important for the optimisation of the likelihood of SVR.

Risk management

The CHMP agreed that a EU - Risk management plan would not be required for the extension of indication in for the target population of patients with compensated cirrhosis.

II. BENEFIT-RISK ASSESSMENT AND CONCLUSION

The IDEAL study did not demonstrate any overall difference in efficacy between the doses investigated. No major safety disadvantage of the higher dose has emerged. Furthermore for many Caucasians the higher dose is likely to be more efficacious. Therefore 1.5 μg/kg remains the recommended dose in the overall population.

Regarding the extension to include patients with compensated cirrhosis, 11 % of patients in the IDEAL study had bridging fibrosis/cirrhosis, approximately 35 % had a normal baseline ALT. It should be noted that the IDEAL study was not designed to evaluate treatment of subjects with normal ALT level. However the results according to baseline ALT appeared to be comparable between the three treatment arms with somewhat higher SVR rates for patients with elevated ALT at baseline. Therefore the extension of indication is considered approvable. Overall the addition of patients with compensated cirrhosis is sufficiently substantiated by the IDEAL study.

The CHMP considered whether a lower starting dose could be recommended for cirrhotic patients who may have lower haematological reserve and could potentially tolerate higher total regimen when receiving a lower PEG2b dose. However the CHMP agreed that the study is not robust enough to demonstrate this and thus agreed to maintain the 1.5 μg/kg posology in this subgroup.

In black patients there was a non-significant trend towards a higher SVR rate in patients treated with PEG2b 1.5/R compared to PEG2b 1.0/R A number of studies have established that African-Americans (AA) are less responsive to interferon therapy than Caucasians and that higher initial doses of interferon in difficult to treat patients have limited effect in increasing SVR. This suggests that increasing interferon doses for African-Americans will have led to only a small improvement in SVR, especially in contrast to using a protease inhibitor as a third therapeutic agent. As such no change in the posology for black patients has been made.

Concerning the weight based dosing of Rebetol, PK/PD data give a putative pharmacologic rationale for why data from studies with PEG2a in Genotype 2/3 might not be applicable to PEG2b. Discounting the Hadziyannis study, the evidence base for a flat dose is considerably weakened. There is clearly more experience with weight based regimens when co-treating with PEG2b, though the relative merit of this remains undecided. The generalisation of the suggested dose increase is not mandated by data, but there are no prohibitive safety concerns. From a practical point of view, two very similar posologies for Genotype 1 and 2/3 should be avoided. Finally, the putative benefit of harmonised ribavirin dosing between peginterferons in Genotype 2/3 would depend on this being implemented also outside EU. As this presently does not appear feasible, the main argument for pursuing harmonised dosing falls Therefore, the generalisation of the dose increase to all genotypes is recommended.

Overall the risk benefit balance of peginterferon alfa-2b is considered positive taking into account the changes implemented to reflect the results of the IDEAL study.

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