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/49

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
PEG2b	peginterferon alfa-2b (PegIntron/ViraferonPeg)
RBV	ribavirin
RNA	ribonucleic acid
SAE	Serious Adverse event
sc	subcutaneous
SAG	Scientific Advice Group
SVR	Sustained Virological response
TSH	Thyroid Stimulating Hormone
ULN	Upper limit normal

I. SCIENTIFIC DISCUSSION

I.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 or interferon alfa-2b. Rebetol monotherapy must not be used.

The MAH applies to extend the therapeutic indication of pegylated interferon alfa-2b in combination with Rebetol capsules or oral solution (ribavirin) to the paediatric patients with chronic hepatitis C.
A Type II variation application has been submitted in parallel for both PegIntron/ViraferonPeg and Rebetol.

To support this variation the MAH submitted one pivotal study (P02538) evaluating the safety and efficacy of peginterferon alfa-2b plus ribavirin in the treatment of Chronic Hepatitis C (CHC). There is a planned 5 year long- term follow-up portion of the study.

I.2 Scientific overview and Discussion

Hepatitis C is a milder disease in children than in adults with a less frequent and a slower progression. Severe hepatitis and cirrhosis are very infrequent complications (2-4%) in childhood up to 20 years post infection in the absence of associated conditions (polytransfusion infection, chemotherapy, HIV or Hepatitis B Virus (HBV) co-infection) [1,6]. Chronic infection is asymptomatic in most cases, with minimal histological lesions in 80% cases, as assessed when analysing results of biopsies from 300 children aged 6-10 yrs with a chronic hepatitis C since 3-7 yrs. Significant fibrosis was present in 15% cases, cirrhosis in < 4% [2.3.4.5].

Fibrosis progression, histological score, alanine transaminase (ALT) levels and viral load were lower in children when compared to adults over a 10 years period [6] Hepatocellular carcinoma as the result of CHC is extremely rare in childhood, and only a few cases have been reported.

Even though important inter-individual variations exist, and severe evolution may be observed in childhood, some data demonstrate an overall mild pathology in children, with a low rate of complications in the adult age in the absence of alcohol consumption and of another hepatic disease.

With regards to treatment, for adults the goal of therapy is to avoid progression towards the life threatening conditions that are cirrhosis and Hepatocellular Carcinoma (HCC). In adults, the standard of care is treatment of patients at risk of progression or of "easy-to-treat" patients (genotypes 2/3 without co-factors), with the combination of ribavirin and pegylated interferon. In the difficult-to-treat G1 patients, the efficacy of pegylated INF plus ribavirin provided an approximately 10% increase in the rate of sustained responders when compared to the combination with standard interferon.

Regarding treatment in children, due to the relatively slow progression of the disease, the potential for spontaneous clearance of the infection (in approximately 20% of cases and up to 45%) and the typically asymptomatic or mild nature of the disease, it is mostly considered that treatment could be deferred to adulthood or initiated only in the presence of progressing disease. The National Institute of Health (NIH) consensus conference for the management of hepatitis C confirmed the most frequent "wait and see" strategy towards management of CHC in children.

There is to date no clear international consensus for the treatment of children and treatment seems restricted to children with rapidly progressive disease (most often polytransfused, receiving chemotherapy or HIV/HBV co-infected), and treatment strategy is assessed on a case by case basis.

In January 2005, interferon alfa-2b and ribavirin were granted an extension of indication for use in children from 3 years with chronic hepatitis C. The clinical development consisted of 4 open studies with only 1 phase III study (P00321) in 70 paediatric subjects aged 3 through 16 years. During the assessment of the dossier several safety concerns were identified, in particular growth retardation and psychiatric disorders since a higher rate of suicidal attempt/ideation compared to adult patients was reported. Of note, the impact of growth was principally marked by a decrease in linear growth and weight gain. These data were later substantiated by data from 97 children enrolled in the long-term pediatric study P01906 showing that twenty (21 %) of 97 children had a > 15 percentile decrease in height percentile, of whom 10 of the 20 children had a > 30 percentile decrease in their height percentile from the start of treatment to the end of long-term follow-up (up to 5 years) raising a concern towards potential non reversibility of the growth inhibition.

Although pegylated interferon is considered to have a clear therapeutic advantage over standard interferon in terms of efficacy (like for adults) the safety signal of non reversible growth inhibition identified with standard interferon raise the same safety concern on the use of the pegylated bitherapy in childhood.

Taking into account the safety concerns of bitherapy in children the CHMP agreed that the Scientific Advisory Group should be requested to consider when treatment of Hepatitis C should be initiated in childhood, the safety profile of bitherapy in children and the place of bitherapy with standard interferon as compared to bitherapy with pegylated interferon. The list of Questions to the SAG was adopted in March 2009. The SAG meeting was held in May 2009.

Overall the SAG experts were not reassured that there is no irreversible growth retardation associated with the bitherapy.

Regarding treatment initiation in children, the SAG concluded that early fibrosis is a criterion for treatment initiation. Due to the high response rates of around 90% in patients with genotypes 2 and 3, as well as considering the potentially shorter treatment duration of 6 months, initiation of treatment in this population could also be considered. However, there was a mixed view amongst SAG experts whether in this case it might be more appropriate to defer treatment given the safety issues as well as the fact that treatment in (early) adulthood would also lead to similar response rates. For genotypes 1 and 4 the potential risks together with the lower response rates and the longer treatment period required made the SAG experts only recommended closer monitoring, i.e. every 3-5 years. The recommendation was that treatment initiation should only occur in case of early fibrosis.

The SAG experts agreed that treatment can be initiated after the pubertal growth spurt as the risk of growth retardation is no longer of clinical relevance. This recommendation can be given irrespective of genotype and the presence of early fibrosis as the treatment responses in children with genotypes 1 and 4 are superior to those in adults.

The pubertal period should be avoided for treatment. Whether there is an option for treatment prior to pubertal period cannot be concluded due to the lack of sufficient data in final growth outcomes in younger children.

The SAG experts agreed that adequate warnings in the Summary of Product Characteristics (SPC)/ Package Leaflet (PL) are an important element to highlight that the risk of irreversible growth inhibition cannot be excluded; the proposed wording was not discussed further.

However, the SAG experts felt strongly that it needs to be ensured that information about the safety risk "growth retardation" is provided to parents and – as appropriate – to the concerned child upfront in the consenting process prior to treatment initiation. It is acknowledged that parents have a particular role in the treatment decision in this case, and might request treatment if deferral is recommended, hence full information is a pre-requisite.

Regarding the place of bitherapy with standard interferon as compared to bitherapy with pegylated interferon there is higher response rates, shorter treatment duration for genotype 2 and 3 and once weekly dosing regimen versus 3 times a week for standard interferon. As such, the SAG experts felt confident that pegylated interferon would replace standard interferon in medical practice provided a license for the use of pegylated interferon in children was granted.

I.3 Non clinical aspects

No non clinical pharmacology, pharmacokinetics and toxicology studies have been submitted by the MAH in support of this extension of indication. However ribavirin juvenile toxicology studies have been performed post approval of the paediatric indication of interferon alfa-2b plus ribavirin. In order to better appreciate the potential impact of the ribavirin safety profile in children, and in particular the potential impact of ribavirin to affect growth, the MAH committed to conduct a dose range-finding study to define a maximum tolerated dose for ribavirin in rat pups and a juvenile toxicity study to assess effects on growth, skeletal formation, and reproductive development and function. Assessment of these studies led to the update of the Rebetol SPC to draw the attention of prescribers to these non animal data in line with the concern raised in clinic. (Commission Decision 04/01/2007).

As for standard interferon, no juvenile study has been conducted with peginterferon alfa-2b due to feasibility issue (antibodies development in chronic treatment).

Environmental risk assessment

No data were submitted by the MAH as regards the environmental risk assessment. As the PEC surface water for the active ingredient peginterferon alfa-2b is clearly below the action limit of 0.01 µg/l no further action is required and the environmental risk assessment can be stopped in Phase I.

The MAH has not performed an octanol-water partition coefficient study with peginterferon alfa-2b and requested a waiver to perform this test given the nature of peginterferon alfa-2b, which is a polyethylene glycol-modified derivative of IntronA (human recombinant interferon alfa-2b). Proteins are polar, water-soluble compounds. Even if the log K_{ow} has not been calculated, it can be assumed that it is below the trigger value of 4.5.

I.4 Clinical aspects

In support of this extension of indication of the combination peginterferon alfa-2b/Ribavirin to children and adolescents 3 years of age and older, the MAH submitted study P02538 (n=107). The primary objectives of this study was to assess the efficacy, safety, tolerability and pharmacokinetics of peginterferon alfa-2b 60µg/m^2 once weekly plus ribavirin 15 mg/kg/day in paediatric subjects with CHC.

I.4.1 Pharmacokinetic

The secondary objective of study P02538 was to measure the multiple-dose pharmacokinetics of PEG2b and ribavirin in paediatric subjects with CHC in order to develop population pharmacokinetic models to describe PEG2b and ribavirin disposition in HCV-infected paediatric subjects and to evaluate the effect of covariates on PEG2b and ribavirin pharmacokinetics.

Twenty one subjects were enrolled in the pharmacokinetic group (PK subjects) and had intensive blood sample collections at Weeks 1, 4, and 8. The other 86 subjects (Profile Pharmacokinetic Group, PPK subjects) had sparse blood sample collections at treatment weeks (TW) 4, 6, 12, 24, 30, and 48 for profile pharmacokinetics.

A nonlinear mixed effect modelling approach was used to analyse the ribavirin and PegIntron data. The primary objective of the PPK analysis was to estimate exposure of peginterferon in the paediatric population receiving 60µg/m^2/week. On the basis of the model, it was shown that exposure to peginterferon in children was 58% higher than observed in adults dosed with 1.5 µg/kg/week. However no particular signal was raised towards a worsening of the haematologic or psychiatric adverse events as compared to adults in relation to this over-exposure. Furthermore, the proposed 1.5µg/kg dose was considered acceptable as it allows an enhancement of the response rate as compared to standard IFN.

I.4.2 Clinical pharmacology

The dose of Rebetol and PegIntron selected for study P02538 are PegIntron 60 µg/m^2 once weekly (QW) plus Rebetol 15 mg/kg/day (in two divided doses).

The dose of PegIntron to be used for this clinical study, 60 µg/m^2 QW, is approximately equivalent to the dose licensed for adults in the US and the EU based on calculated conversion to body surface area (1.5µg/kg/week). A Body Surface Area (BSA)-based dosing of pegylated interferon was chosen by the MAH since judged appropriate to adjust the dose in paediatric patients on the basis of a similar mean BSA-normalised apparent clearance across the different paediatric age groups. No comparison with clearance from adults was nevertheless provided.

A dose ranging pharmacokinetic/pharmacodynamic (PK/PD) study (P00018 cohort 1) identified the 15mg/kg dose as the optimal dosage of ribavirin in children. This dose was further evaluated in clinical phase II (P000018 cohort 2) and III (P00321) in combination with IntronA.

I.4.3 Clinical efficacy

The clinical study, P02538, is provided as a pivotal study to support the efficacy and safety of combination therapy pegylated interferon alfa-2b plus RBV in patients 3 years of age and older. The study is presented hereafter:

Title
Part 1: Assessment of the Safety, Efficacy, Tolerability, and Pharmacokinetics of Peginterferon Alfa-2b Plus Ribavirin in Pediatric Patients With Chronic Hepatitis C

Study design
Phase 3/1B, open-label, global, multicenter study in paediatric patients who were all treated with PEG2b plus ribavirin for up to 48 weeks and followed for an additional 24 weeks post-treatment. Subjects with Genotype 1, 4, 5, 6, or high-viral-load (≥600,000 IU/mL) Genotype 3 whose Treatment Week (TW) 12 HCV-RNA levels were above the lower limit of quantitation (LLQ) and had dropped <2 log10 as compared to baseline values were to discontinue treatment at TW 18 and proceed to follow-up, unless the principal investigator discussed and obtained approval from the sponsor's project physician prior to the continuation of therapy beyond TW 18. Subjects who had TW 12 HCV-RNA levels that were below LLQ were to continue therapy to 48 weeks. Subjects whose TW 12 HCV-RNA levels were above LLQ and had dropped ≥2 log10 as compared to baseline values were to continue therapy and be reassessed at TW 24. If the TW 24 HCV RNA levels remained above LLQ, these subjects were to discontinue therapy at TW 30 and proceed to follow-up. Subjects with HCV Genotype 2 or low-viral-load (<600,000 IU/mL) and Genotype 3 were to receive 24 weeks of treatment plus 24 weeks of follow-up.

Subjects who were treated with at least one dose of PEG2b and ribavirin and who completed the 24-week post-treatment follow-up were eligible for enrollment in the 5-year long-term follow-up portion of the study.

Objectives
The primary objective of this study was to assess the safety, efficacy, and tolerability of the combination of PEG2b 60 µg/m^2 QW plus ribavirin 15 mg/kg/day in paediatric subjects with CHC. The secondary objective was to measure the multiple-dose pharmacokinetics of PEG2b and ribavirin in paediatric subjects with CHC. There is a planned 5 year long- term follow-up portion of the study.

Study Participants
Planned enrolment was for 100 paediatric subjects with CHC. 107 subjects, including 67 aged 3-11 years and 40 aged 12- 17 years were enrolled and treated.

Eligible subjects were male and female children and adolescents, 3 through 17 years of age, weighing ≤90 kg, who had a diagnosis of CHC documented by a positive anti-HCV or HCV-RNA for at least 6 months prior to screening, with a liver biopsy (historical or pretreatment) showing evidence of fibrosis and/or inflammatory activity. A liver biopsy waiver was possible for children 3-11 years old with an elevated ALT within 1 year prior to the Screening 1 visit.

Patients were excluded from entry if having serum ALT level >10 times ULN, evidence of decompensated liver disease, known coinfection with either HIV or HBV, insulin-dependent diabetes mellitus or poorly controlled noninsulin dependent diabetes mellitus, pre-existing psychiatric condition, including but not limited to moderate to severe depression, or a history of severe psychiatric disorder, such as psychosis, suicidal ideation and/or suicidal attempt.

Treatments
PEG2b, 60 µg/m2 QW; Administered by SC injection Ribavirin; 15 mg/kg/day in two divided doses for up to 48 weeks (the maximum dose of ribavirin was not to exceed 1200 mg/day); Administered PO with food.

Efficacy Analyses
The primary efficacy variable is the proportion of subjects with sustained virologic response (SVR) at 24 weeks following the end of treatment. For the primary efficacy analysis, any subject with undetectable HCV RNA level at the Follow-Up Week 24 visit was considered a sustained virologic responder. Additional, "carry-forward", efficacy analyses were conducted in subjects with undetectable HCV RNA level at the Follow-Up Week 12 visit and missing data for Follow-Up Week 24 were also considered to be sustained responders and were summarised by age group. The proportion of sustained virologic

responders was estimated using the normal approximation to the binomial. Ninety-five percent confidence intervals of the proportion of sustained virologic responders were computed for each of the two age groups (3-11 years old and 12-17 years old).

Plasma HCV-RNA assay

The MAH informed the CHMP in February 2007 that in some instances the 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 substantial proportion of samples were impacted in study P02538 (23%). 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. All but 11 samples in study P02538 were retested. Among the 11 subjects with insufficient plasma available to be retested, it is noteworthy that under-reporting of HCV RNA due to assay problem led to inadequate management in 3 patients (early stopping rule was mistakenly not applied). SVR was however achieved in one of these patients. The data presented in this report constitutes the retested sample data.

Results

Patient disposition

One hundred seven subjects were enrolled. Patient disposition was as follows and presented in table 1 below:

	Number (%) of Subjects								
	Subjects Assigned 24-week Treatment			Subjects Assigned 48-week Treatment			All Subjects		
	Subject Age (years)			Subject Age (years)			Subject Age (years)		
	3-11	12-17	All	3-11	12-17	All	3-11	12-17	All
Treatment Phase									
Enrolled	13 (100)	14 (100)	27 (100)	54 (100)	26 (100)	80 (100)	67 (100)	40 (100)	107 (100)
Discontinued Treatment Phase	0	0	0	19 (35)	10 (38)	29 (36)	19 (28)	10 (25)	29 (27)
Adverse Event	-	-	-	0	1 (4)	1 (1)	0	1 (3)	1 (1)
Treatment Failure	-	-	-	17 (31)	9 (35)	26 (33)	17 (25)	9 (23)	26 (24)
Subject did not wish to continue, reasons unrelated	-	-	-	2 (4)	0	2 (3)	2 (3)	0	2 (2)
Completed Treatment Phase	13 (100)	14 (100)	27 (100)	35 (65)	16 (62)	51 (64)	48 (72)	30 (75)	78 (73)
Follow-up Phase									
Entered Follow-up	13 (100)	14 (100)	27 (100)	53 (98)	26 (100)	79 (99)	66 (99)	40 (100)	106 (99)
Completed Follow-up	13 (100)	14 (100)	27 (100)	53 (98)	26 (100)	79 (99)	66 (99)	40 (100)	106 (99)
Never Entered Follow-up	-	-	-	1	0	1	1	0	1

All patients in the 24-weeks treatment arm (n=27) completed the treatment phase. On the contrary, only 64% (51/80) of patients in the 48-week treatment arm (equally shared between the 2 age groups) completed treatment phase due to a high rate of treatment failure. Indeed, contrarily to the 24-week treatment group, stopping rule (at TW 12 and TW24) were applied for subjects assigned to the 48-week treatment group (i.e. for G 1, 4, 5, or 6 or high-viral-load G3)

Baseline characteristics

Paediatric patients included in this study had similar demographic characteristics to children that were included in the paediatric study using IntronA and RBV (P00321) although study P02538 included more Caucasians (89% vs 80%) and patients were a little younger in this study (median age: 9 vs 10.5). Subjects weighting less than 47kg were to receive RBV oral solution. As a consequence, 94% (63/67) of younger children (3-11 years old) received oral solution and 78% (31/40) of adolescents (12-17 years old) received RBV capsule. 63% of paediatric patients included in this study were aged 3-11 years, of which most

(67%) were aged from 6-<12 years. Similarly, in the previous paediatric study with IntronA plus RBV 67% of children were aged from 3-12, most of then being aged from 7-12 (64%).

In line with epidemiological data, vertical transmission was the primary mode of contamination in the study patients (70%). Median year since exposure was 8 years. In this study, 67% of patients were infected with genotype G1 (74% of patients had G1 in P00321). In study P02538, the more difficult to treat patients, i.e. G1 patients with high viral load, account for 29% of the study population. G2/3 account for 28% of patients (of which 1/3 having high viral load G3).As a consequence of the problem of HCV-RNA under-reporting, 7 patients with G3 and high viral load (HVL) were mistakenly assigned to receive 24 weeks of treatment instead of 48 weeks.

Pre-therapy biopsies (performed at an unspecified time) were available for 99% of subjects. Twelve percent of patients had no fibrosis and the large majority of patients (82%) had minimal fibrosis (F1). Furthermore, most of the subjects had mild (44%) or moderate (30%) liver inflammation with only 18% having severe inflammatory activity. No patients had cirrhosis in this study. Biopsy results were similar between both age groups. Median ALT was 0.87 ULN in this study and 59% of patients had normal ALT level at baseline. Overall, a large proportion of patients treated with peginterferon alfa-2b plus RBV in this study had only minimal hepatic disease. This is in line with the previous paediatric study with IntronA plus RBV.

Efficacy results

The primary analysis was to include all subjects who were assigned a subject number. The secondary analysis was to include all subjects who received at least one dose of study medication. Since all subjects who were assigned a subject number received at least one dose of study medication, the secondary efficacy analysis (All Treated population) is identical to the Intent-to-Treat population.

Primary endpoints: SVR rates
Overall, 64.5% (69/107) of the subjects achieved SVR. When carry-forward analysis was used, the SVR rates were similar (65.4% [70/107]), since only one additional subject with Genotype 1 (who had a rapid virologic response and remained negative from TW 4 to FW 12) was considered a sustained "carry forward" responder.

Table 2 Carry-forward Sustained Virologic Response Rates by Genotype, Age Group, and Assigned Treatment Duration

	Subjects Aged 3 to 11 yr n=67				Subjects Aged 12 to 17 yr n=40				All Subjects n=107			
	24 Weeks		48 Weeks		24 Weeks		48 Weeks		24 Weeks		48 Weeks	
	Virologic Response		Virologic Response		Virologic Response		Virologic Response		Virologic Response		Virologic Response	
	n[a]	(%)	n[a]	(%)	n[a]	(%)	n[a]	(%)	n[a]	(%)	n[a]	(%)
Genotype												
All	12/13	(92.3)	29/54	(53.7)	14/14	(100)	15/26	(57.7)[b]	26/27	(96.3)	44/80	(55.0)[d]
1	-	-	24/47	(51.1)	-	-	14/25	(56.0)[c]	-	-	38/72	(52.8)[e]
2	5/6	(83.3)	-	-	9/9	(100)	-	-	14/15	(93.3)	-	-
3	7/7	(100)	2/3	(66.7)	5/5	(100)	-	-	12/12	(100)	2/3	(66.7)
4	-	-	3/4	(75.0)	-	-	1/1	(100)	-	-	4/5	(80.0)

b: SVR rate at Follow-up Week 24, n = 14/26 (53.8%).
c: SVR rate at Follow-up Week 24, n = 13/25 (52.0%).
d: SVR rate at Follow-up Week 24, n = 43/80 (53.8%).
e: SVR rate at Follow-up Week 24, n = 37/72 (51.4%).

SVR rate were 72.5% in subjects aged 12 to 17 years and 61.2% in subjects ages 3 to 11 years. However, when response rate is analyzed by genotype, no significant difference between both age groups is noticed. These results highlight the fact that the genotype but not the age drives the response to bitherapy. In G1

patients, SVR rate was 52.8% after 48-w treatment, which is substantially higher than the response rate previously reported in G1 paediatric patients that received 48 weeks of IntronA plus RBV therapy in the pivotal study P00321 (36%). Although less striking, combination therapy with pegylated interferon plus RBV enhances response rate when compared to combination therapy with standard interferon (93.3% vs 82%).

Relapse rates

Subjects who had undetectable HCV-RNA at the last treatment visit and detectable HCV-RNA at the last follow-up visit were considered relapsers. Among the 75 subjects who had undetectable HCV RNA at the end of study treatment, 5 relapsed (all had detectable HCV RNA at FU Week 4). Therefore, the overall relapse rate in the study was 6.7%. All 5 relapsers were female patients with G1. All had fibrosis grade F1. Of note, 4 /5 had >80% adherence to ribavirin, PegIntron and treatment duration. Due to the small number of relapsers, relationship between relapse rate and baseline characteristics are difficult to assess. However, no relationship was apparent between relapse rate and baseline viral load, age or weight/Body Mass Index (BMI)/ Body Surface Area (BSA).

SVR by Baseline Demographics and Disease Characteristics

Sustained virologic response by baseline demographic data and disease characteristics is presented in the table 3 below:

	HCV Genotype 1 n=72		HCV Genotype 2 n=15		HCV Genotype 3 n=15		HCV Genotype 4 n=5	
	Virologic Response		Virologic Response		Virologic Response		Virologic Response	
	n[a]	(%)	n[a]	(%)	n[a]	(%)	n[a]	(%)
Overall Response	38/72	(52.8)	14/15	(93.3)	14/15	(93.3)	4/5	(80)
Sex								
Female	22/39	(56.4)	9/9	(100)	3/4	(75.0)	3/4	(75.0)
Male	16/33	(48.5)	5/6	(83.3)	11/11	(100)	1/1	(100)
Age								
3-11 years	24/47	(51.1)	5/6	(83.3)	9/10	(90.0)	3/4	(75.0)
12-17 years	14/25	(56.0)	9/9	(100)	5/5	(100)	1/1	(100)
Race								
Asian	1/4	(25.0)	1/1	(100)	2/2	(100)	-	-
Black	0/1	-	-	-	-	-	-	-
Multiracial	2/3	(66.7)	-	-	1/1	(100)	-	-
White	35/64	(54.7)	13/14	(92.9)	11/12	(91.7)	4/5	(80.0)
Source of Exposure								
Other	4/5	(80.0)	-	-	2/3	(66.7)	-	-
Parenteral	1/1	(100)	2/2	(100)	2/2	(100)	-	-
Sporadic	4/10	(40.0)	-	-	2/2	(100)	-	-
Transfusion	3/4	(75.0)	2/2	(100)	-	-	1/1	(100)
Vertical Trans	26/52	(50.0)	10/11	(90.9)	8/8	(100)	3/4	(75.0)
Baseline Viral Load								
<600,000 IU/mL	28/39	(71.8)	10/11	(90.9)	5/5	(100)	3/3	(100)
≥600,000 IU/mL	9/31	(29.0)	4/4	(100)	9/9	(100)	0/1	(0)
Missing	1/2	(50.0)	-	-	0/1	(0)	1/1	(100)
Ribavirin Form								
Capsules	15/22	(68.2)	9/9	(100)	3/3	(100)	1/1	(100)
Oral Solution	23/50	(46.0)	5/6	(83.3)	11/12	(91.7)	3/4	(75.0)

The SVR rate in subjects with HCV Genotype 1 was much higher in subjects with a baseline low viral load (<600,000 IU/ml) (71.8%) than in subjects with a baseline high viral load (≥600,000 IU/ml) (29%). Similarly, an additional analysis showed that the SVR rate in G1 subjects with baseline viral load <400,000 IU/ml was notably higher than in subjects with baseline HCV-RNA ≥ 400,000 IU/ml (82.8% [24/29] vs 32.6% [14/43] including 2 subjects with missing baseline results).

Furthermore, subjects with HCV Genotype 1 who took ribavirin capsules had a higher SVR rate compared with those who took oral solution (68.2% [15/22] vs. 46.0% [23/50], respectively).

In addition, predictors of SVR were assessed using logistic regression analysis in logistic regression models. HCV genotype, viral load and ribavirin form remain predictor of the response rate in multivariate analysis as shown in table 4 below:

Effect	Odds Ratio	95% CI	P-Value
Univariate Logistic Regression Analysis			
HCV Genotype			0.0088
Genotype (1 vs other)	0.105	0.029, 0.379	0.0005
Log baseline Viral Load	0.421	0.229, 0.774	0.0054
≥800,000 IU/mL vs <800,000 IU/mL	0.250	0.105, 0.592	0.0016
Age	1.074	0.970, 1.190	0.1679
Baseline Weight (kg)	1.021	0.998, 1.046	0.0777
Gender (male vs female)	0.941	0.424, 2.090	0.8820
Race[a]			0.9425
Years Since Exposure	1.013	0.914, 1.124	0.8020
Source of Exposure[a]			0.6100
Metavir Fibrosis Score	0.591	0.215, 1.621	0.3068
Metavir Activity Score	0.897	0.557, 1.444	0.6535
Steatosis	0.372	0.173, 0.801	0.0115
Steatosis ≤5% vs >5%	1.941	0.262, 14.389	0.5164
Treatment Duration Assignment	0.047	0.006, 0.363	0.0034
PEG2b Dose ($\mu g/m^2$)	1.937	0.789, 4.754	0.1492
Ribavirin Dose (mg/kg)	0.825	0.449, 1.516	0.5354
Ribavirin Dose Form (dosing solution vs capsules)	0.350	0.135, 0.906	0.0306
Multivariate Linear Regression Analysis			
Baseline Viral Load (<800,000 vs ≥800,000)	0.201	0.071, 0.568	0.0025
HCV Genotype 1 vs Others	0.035	0.006, 0.212	0.0003
Steatosis (pretreatment score)	0.182	0.063, 0.526	0.0016
Ribavirin Form (dosing solution vs capsules)	0.208	0.060, 0.713	0.0125

Positive and Negative Predictive Values for SVR

Similarly to adults, TW12 and TW4 response were highly predictive of treatment response in G1 patient. In these difficult to treat patients, a SVR rate as high as 88.9% was reported in G1 paediatric patients who exhibited undetectable HCV RNA at TW4. However, only 9/72 G1 patients achieved this early endpoint. A larger proportion of G1 patients achieved TW12 undetectability (60%). In this subgroup, SVR was 83.7%.

For Genotypes 2, 3, and 4, the majority of subjects (29/35) attained EVR and SVR. In this group, the response rate was also high (2/2) in subjects who became negative later in the study.

Due to protocol-defined stopping rules, subject with < 2 log drop at TW12 as compared to baseline were to discontinue treatment at TW18. Therefore, the negative predictive value of TW12 response is not available for pegylated interferon plus RBV combination therapy in children. By extrapolation from the NVP of TW12 response observed with standard interferon plus RBV in children, it is proposed to recommend treatment discontinuation in G1 (and G4) patients if their TW12 HCV RNA dropped <2log10 compared to pre-treatment value or if they have detectable HCV RNA at TW24.

ALT response

Overall, normalisation of ALT occurred in 77.3% (34/44) of subjects who had elevated ALT at baseline. The ALT normalisation was mostly associated with SVR (79.4% [27/34]). Seven subjects demonstrated ALT normalization without having attained SVR.

Effect of adherence on SVR
Subjects were considered adherent to the assigned treatment regimen if they received at least 80% of both PEG2b and ribavirin doses (according to the assigned dosing regimen) for at least 80% of treatment duration. If the subject's dose was reduced by the investigator according to protocol-specified criteria and the subject dosed according to the instructions given by the investigator, then the subject was considered compliant with his/her drug therapy but non-adherent to the therapy.

Per the predefined criterion, 71% (76/107) of subjects were considered at least 80% adherent to initially-assigned doses and duration. Many subjects were considered non adherent due to the protocol-specified early discontinuation requirement for poor virologic response (treatment failure).

Treatment adherence was similar in both age groups.

To further assess the effect of adherence on the SVR rate in this study, 26 subjects who discontinued treatment early (had <80% of planned duration of therapy), were excluded from the analysis. The remaining 81 subjects were at least 80% adherent to treatment duration. The dosing adherence of these subjects was very high; thus a comparison based on dose adherence is not meaningful because of the high proportion of subjects who received at least 80% of PEG2b and ribavirin doses (93.8%; 76/81).

Of note the 4 patients who had < 80% adherence for Peginterferon and/or ribavirin dose nevertheless achieved SVR in this study. Adherence was similar for ribavirin in both age groups, suggesting patients were similarly adherent to ribavirin oral solution and capsule.

Discussion on the Clinical Efficacy

Overall, the efficacy results from study P02538 show that, similarly to adults, use of combination therapy with pegylated interferon compared to combination therapy with standard interferon results in an enhanced response rate. An approximate 17% gain is obtained in children infected with G1 (achieving a 53% SVR) and approx 14% for children infected with G2/3 (achieving a 93% SVR). This gain appears more marked as compared to adults (respectively of approx 9% and 3%). Furthermore, the levels of SVR achieved with PegIFN plus ribavirin is higher in children as compared to adults (G1: around 50% vs 40%; G2/3: around 90% vs 80%). No difference in treatment response rate was observed between both age groups (3-11 and 12-17 years of age).

Similarly to adults, high baseline viral load in G1 patients was associated with a poor response to treatment. Forty- eight week treatment with pegylated interferon plus RBV in G1 patients having low viral load defined as HCV RNA < 400 000 IU/ml allows to achieve response rate as high as 82.8%, which is close to the response rate obtained in G2/3 patients. Of note, baseline viral load does not influence response rate in genotype 2 and 3 patients.

In adult studies, it was shown that 41% of G1 patient with baseline low viral load (<600 000 IU/ml) may achieve RVR, allowing for a SVR rate of 92% with an as short as 24 weeks treatment duration. The MAH did not explore different treatment durations for paediatric Genotype 1 patients in study P02538. However, the MAH considered that extrapolation from adult data is acceptable given that children have been shown to have a better response to bitherapy. It is noteworthy that in practice the reduction of treatment duration might have to be discussed only in a marginal subgroup of paediatric patients given that, as illustrated in study P02538, only 15% of G1 children with LVL achieved RVR. In order to better appreciate to whether reduction of treatment duration might be proposed, the CHMP requested that any differences in the proportion of G1 patients achieving 4 weeks RVR between adults and paediatric patients be discussed as this might represent a difference in the kinetics of viral load decrease/clearance making the 4 weeks RVR less predictable in children than in adults. The MAH has committed to provide a response to this issue as a follow up commitment.

Due to protocol-defined stopping rules, subject with < 2 log drop at TW12 as compared to baseline were to discontinue treatment at TW18. Therefore, the negative predictive value of TW12 response is not available for pegylated interferon plus RBV therapy. However, by extrapolation from the NVP of TW12 response observed with standard interferon plus RBV in paediatric patients, it is proposed to recommend treatment discontinuation in G1 (and G4) patients if their TW12 HCV RNA dropped <2log10 compared to pre-treatment value or if they have detectable HCV RNA at TW24.

Lower response rates were consistently reported in patients treated with oral solution in each genotype group with a marked difference in G1 patients: 68.2% of G1 patients that received RBV capsule had SVR versus 46% of G1 patients that received RBV oral solution. Furthermore the pharmaceutical form of ribavirin was found to be predictive of treatment response in univariate and multivariate logistic regression analysis.

The CHMP requested the MAH to provide reassurance as regards the comparability of exposure between children dosed with the ribavirin capsule and the oral solution. The MAH provided a limited PK assessment with data available from 5 children dosed with the capsule and 11 children dosed with the oral solution. No significant difference in exposure was found between both formulations. Nevertheless, it is noteworthy that SVR rates in children dosed with the oral solution was consistently lower than SVR rates in the capsule group. The MAH considered this is due to an artefact of the small sample size. The difference in SVR seems striking in G1 children with HVL (SVR capsule: 56% vs SVR solution: 18%). According to the MAH this difference is driven by the unexplained poor response rate observed in the HVL youngest children (3-5 years) where only 1 out of 8 patients achieved SVR. If not explained by a difference in the PK parameters in relation to the formulation, the lower response rate levels observed in young children as compared to adolescents in this study might be explained by a difference in the likelihood of response between both patient populations, related or non related to the disease, such as difference in tolerance, or in compliance (driven by the acceptability of the oral solution).However based on the available data the CHMP concluded that it is unlikely that tolerability/acceptability issue has driven the virological failure in children treated with the oral solution.

In order to better address this issue the MAH has committed to perform a bioequivalence study of the oral solution in relation to the capsules. An initial proposal has been made that raised some comments from the CHMP. The MAH will revise the protocol in the frame of a follow up measure and specify the timelines for study initiation and completion.

I.4.4 Clinical Safety

Patient exposure
All safety assessments were based on data from all 107 enrolled subjects. All 27 subjects who were assigned to 24 weeks of treatment (HCV Genotype 2 and low viral load HCV Genotype 3) completed the treatment with a mean treatment duration of 169 days. Sixty-four percent (51/80) of subjects who were assigned to 48 weeks of treatment (HCV Genotype 1, 4, and high viral load HCV Genotype 3) completed the treatment, and 29 subjects discontinued the treatment mostly due to poor response to the treatment (90%, 26/29), according to discontinuation stopping rules defined in the study protocol, with a mean treatment duration of 273 days. Only one subject discontinued due to an adverse event (AE). The overall mean treatment duration was 247 (SD: 92) days in this study.

Overall safety profile
The overall safety profile of the PEG2b plus ribavirin observed in this paediatric study is consistent with that observed in previous adult clinical studies and also in the paediatric population treated with interferon alfa-2b plus ribavirin. No new safety issues were identified in this study. All patients experienced AEs in this study. However, very few patients presented serious AEs and only 1 discontinued the study from AEs. Furthermore, a slightly lower rate of dose modification due to AE was reported in this study when compared to previous paediatric studies with interferon alfa-2b plus RBV.

Table 5 Summary of safety

	Subjects Aged 3 -11 yr (n=67)		Subjects Aged 12 -17 yr (n=40)		All Subjects (n=107)	
	n	(%)	n	(%)	n	(%)
Subjects reporting any AE	67	(100)	40	(100)	107	(100)
SAEs	0	-	3	(8)	3	(3)
Discontinuations due to AE	0	-	1	(3)	1	(1)
Dose modification due to AE	13	(19)	14	(35)	27	(25)

AE = adverse event; SAE = serious adverse event; yr = year

Common treatment-emergent AEs

The frequency and pattern of treatment-emergent adverse events are overall consistent with what has been reported in adults treated with peginterferon alfa-2b and ribavirin. As previously noted in paediatric studies with interferon alfa-2b plus ribavirin, injection site disorders, pyrexia, anorexia, abdominal pain and vomiting were reported more frequently in children compared to adult patients. Furthermore, nervousness was also more frequently reported (8%) in this study.

The safety profile of peginterferon plus ribavirin combination in children is also similar to that reported with interferon alfa-2b plus RBV combination in this population, with the exception of a lower rate of psychiatric adverse events reported in pegylated interferon plus RBV treated children.

It is noteworthy that vomiting was reported in 48% of children aged 3-11 years but in 24% of children aged 12-17 years. Notably, a large majority of cases were reported in the first 12 weeks of treatment. However, surprisingly, no difference in compliance between both ribavirin formulations was reported in this study.

Treatment-related AEs

The most prevalent treatment-related AEs in all subjects were pyrexia (80%), headache (62%), neutropenia (33%), fatigue (30%), anorexia (29%), injection-site erythema (29%) and vomiting (27%):

Severe adverse events (SAEs)

The majority of treatment-related AEs reported in this study were mild or moderate in severity. Severe AEs were reported in 8% (9/107) of all subjects: 10% (7/67) of subjects aged 3 to 11 years and 5% (2/40) of subjects aged 12 to 17 years, as shown in table 10.

Table 6 Severe adverse events

	Number (%) of Subjects					
	Subjects Aged 3 to 11 yr n=67		Subjects Aged 12 to 17 yr n=40		All Subjects n=107	
Subjects Reporting Any Severe AE	7	(10)	2	(5)	9	(8)
Pyrexia	3	(4)	1	(3)	4	(4)
Injection Site Pain	1	(1)	0	-	1	(1)
ALT Increased	1	(1)	0	-	1	(1)
Pain in Extremity	1	(1)	0	-	1	(1)
Headache	1	(1)	0	-	1	(1)
Neutropenia	0	-	1	(3)	1	(1)

AE = adverse event; ALT = alanine aminotransferase; yr = years; "-" = not applicable.

Serious adverse events

Serious AEs were reported in 3 subjects in the 12 to 17 years of age group; these events were considered by the investigator to be unlikely related to study drugs.

Discontinuation of Study and Dose Modification Due to Adverse Events

Adverse event leading to discontinuation: thrombocytopenia led to discontinuation of study medication in one subject in the group 12 to 17 years of age (platelet count = 45 x 109/l) at Week 42, considered resolved on Day 298). This subject attained SVR.

Adverse event leading to dose modification: reductions in the dose of one or both study medications were permitted if necessary for the management of AEs. While at the first reduced dose level, the subject was to return for assessment at a minimum of every 2 weeks until the AE resolved or the subject was stable. If further dose reduction was required, the second level of dose reduction was to be utilized. Reduced doses of PEG2b and ribavirin are summarised in table 7 below:

Table 7 Reduced dose of PEG2b and ribavirin

	Protocol Dose	First Reduced Dose	Second Reduced Dose
PEG2b	60 µg/m^2 QW	40 µg/m^2 QW	20 µg/m^2 QW
Ribavirin	15 mg/kg/day (half administered AM, half PM)	12 mg/kg/day (half administered AM, half PM)	8 mg/kg/day (half administered AM, half PM)

A total of 27 (25%) subjects modified their dose. The AEs that most commonly led to dose modifications included anaemia (7%, 7/107) neutropenia (12%, 13/107) and weight loss (10%, 11/107). Dose modifications were more common in 12- to 17-year-old subjects (35%, 14/40) than in 3- to 11-year-old subjects (19%, 13/67). Neutropenia (neutrophil count <0.75 x 109/l) was the most common AE that led to PEG2b dose modification. Anaemia (haemoglobin <10 g/dl) and weight loss were the most common AEs that led to ribavirin dose modifications.

Dose-modification rate in this study was close to that observed in paediatric interferon alfa-2b plus ribavirin studies, in which 31% (37/118) of subjects experienced dose modification and 6% (8/118) were discontinued due to AE. Fewer paediatric subjects needed dose modifications compared with adult subjects receiving similar treatment. 43.3% (441/1019) of adult patients that received PegIntron 1.5µg/kg+RBV (1000-1200mg/d) in the IDEAL study had dose reductions and 12.7% (129/1019) were discontinued due to AE.

Clinical laboratory findings
Most of the changes in laboratory values with PEG2b plus ribavirin therapy were mild or moderate, as classified by modified WHO criteria. Grade 3 decreases in neutrophil count occurred in 13% (8/107) of subjects and Grade 4 decreases in neutrophil count occurred in 3% (3/107) of subjects. Occurrence of Grade 3/4 neutropenia did not correlate with occurrence of infectious disorders. Grade 3 thrombocytopenia was reported for one subject in the 12- to 17-year-old group, which resulted in the only discontinuation of study treatment due to an AE. Grade 2 anaemia occurred in 2% (2/107) of subjects, the remaining cases were all grade 1. The events of anaemia were managed through dose reductions. No subject received growth factor (eg, erythropoietin) or required blood transfusion, and no subject discontinued treatment because of anaemia.

Haematologic AEs were more common in 12- to 17-year-old subjects than in 3- to 11-year-old subjects, possibly due to a better compensatory bone marrow function in 3- to 11-year-old subjects. Furthermore, Grade 3 ALT elevation was reported in 3% (3/107) of subjects.

Laboratory abnormalities occurred with a similar frequency in children treated with pegylated interferon alfa-2b plus RBV when compared to children treated with standard interferon alfa-2b plus RBV. A better haematological tolerance seems to be observed in children, notably as regards the rate of anaemia (38% of grade 1 anaemia and 15% of grade 2 anaemia were reported in the IDEAL study).

Adverse events associated with endocrine function (including Thyroid related disorders)
There were no cases of diabetes. Treatment-emergent abnormalities in fasting glucose level were mild and transient in nature and included fasting glucose values slightly below or above normal reference range.

Hypothyroidism was reported in three female subjects (3%, 3/107). Five subjects, all females, received levothyroxine treatment for hypothyroidism or elevated TSH.

TSH abnormalities at one or more visits during the treatment period, occurred in 23% (25/107) of subjects: 28% (19/67) of subjects 3 to 11 years old and 15% (6/40) of subjects 12 to 17 years old. Most of these abnormalities (92%, 23/25) were TSH elevations above normal range; 16 subjects had only mild TSH elevations (<10 mIU/L).

Elevation of TSH occurred earlier in treatment in the younger children (3-11 years old) than in adolescents (12-17 years old): elevated TSH was reported for five (8%) subjects at TW 12 and nine (16%) subjects at TW 24, in contrast to the older group, in which only one (3%) subject had elevated TSH before TW 40. Female subjects were more likely to have clinical or subclinical hypothyroidism on PEG2b treatment compared with male subjects. At least one elevated TSH value was reported in 32% (18/56) of female subjects and in 10% (5/52) of male subjects.

Three female subjects had elevated TSH at the end of the follow-up period (FW 24) and stayed on levothyroxine. Subjects are being followed for thyroid problems for an additional 5 years in the long-term follow-up study.

Overall the incidence of thyroid disorders in this study were similar to that reported in previous paediatric studies with interferon alfa-2b plus RBV (hypothyroidism was reported in 4%) and to that reported in adults (hypothyroidism was reported in 5% of patients treated with PEG2B 1.5µg/kg/week plusRBV in the IDEAL study).

Psychiatric Adverse events
Twenty-eight percent (30/107) of subjects had at least one adverse event that is categorized under the body system/organ class of "psychiatric disorders." Psychiatric disorders were less frequent in subjects aged 12 to 17 years (18%; 7/40) as compared to subjects aged 3 to 11 years (34%, 23/67). All AEs within the psychiatric disorder category were deemed mild or moderate in severity, and none met the criteria for an SAE. No subjects were discontinued or had dose modifications because of psychiatric AEs. No subject received antidepressants in this study.

Body height and weight assessments
Height and weight were measured at baseline and at the end of treatment and follow-up periods to assess the effect of the study medications on growth. Each subject's available height and weight data were converted to an age- and sex specific percentile for the baseline, end of treatment, and end of follow-up time points. Percentile assignments were made using the 2000 standard growth charts developed by the Centres for Disease Control.

Height

The mean change in height percentile from baseline to the end of treatment was -10.85 for subjects 3 to 11 years old and -2.5 for subjects 12 to 17 years old. The mean change in height percentiles from the end of treatment to the end of follow-up was 2.03 for subjects 3 to 11 years old and -0.42 for subjects 12 to 17 years old**.** The mean last height percentile in the follow-up period (44.25) was slightly below the median.

Table 8 presents the distribution of patients who had a > 15 percentile decrease in height percentile among the 107 patients enrolled. In study P02538, 20% (21/107) of patients had >15 -<30 percentile decreases in height between Baseline and End of 24 weeks follow-up and 2% (2/107) had > 30 percentile decreases in height: 21/107 (20%) had >15 percentiles decreases in height from baseline to EOT of which 7 (6.5% of total population) had >30 percentiles decreases.

Table 8 Decrease in height percentiles by All subjects

Decrease in Height Percentiles by All Subjects n (%)

	From Baseline to End of Treatment		End of Treatment to End of Follow-Up		From Baseline to End of Follow-Up	
	< 48 weeks of Treatment*	48 weeks of Treatment	< 48 weeks of Treatment*	48 weeks of Treatment	< 48 weeks of Treatment	48 weeks of Treatment
	N=52	N=55	N=52	N=55	N=52	N=55
>15- ≤30	1/52 (2%)	13/55(24%)	2/52 (4%)	0/55 (0%)	4/52 (8%)	17/55(31%)
>30	1/52 (2%)	6/55 (11%)	0/52 (0%)	0/55 (0%)	0/52 (0%)	2/55 (4%)
All >15	2/52 (4%)	19/55(35%)	2/52 (4%)	0/55 (0%)	4/52 (8%)	19/55(35%)

* Subjects with <167 days of treatment with mean duration of 155 days

For this subpopulation, Table 8 shows height percentile change for baseline to end of treatment, end of treatment to end of 24 week follow-up, and baseline to end of 24 week follow-up. Of the patients receiving the longer duration of therapy, 31% (17/55) had a height percentile decrease to between 15 and 30 percentiles. In the shorter duration group, 8% (4/52) had a height percentile decrease of between 15 and 30 percentiles. A greater than 30 percentile decrease in height percentile was reported in 0 subjects in the shorter treatment group and 4% (2/55) of the subjects in the longer treatment group.

Weight

The mean change in weight percentile from baseline to the end of treatment was -17.06 for subjects 3 to 11 years old and -12.8 for subjects 12 to 17 years old. The mean change in weight percentile from the end of treatment to the end of follow-up was 12.68 for subjects 3 to 11 years old and 11.63 for subjects 12 to 17 years old. These data suggest that there was a compensatory, catch-up weight gain for affected subjects after treatment ended. The mean last weight percentile for all subjects (53.39), including both age groups, was slightly above the median.

Growth velocity

Mean growth velocity for the follow-up period (5.73 +/-4.10 cm/yr) was twice that for the treatment period (2.47 +/-2.22 cm/yr). The mean growth velocities in girls were slightly slower than those of boys in both study periods. Mean growth velocities for subjects <11 years old were higher than those for subjects ≥11 years old during both study periods. Mean growth velocities are expected to be lower in subjects whose growth had reached a plateau during the late teenage years.

To assess the impact of treatment on growth, the growth velocities during study treatment and follow-up were compared to age- and sex-standardized norms for the US population; growth velocity percentiles relative to these norms were determined. The mean growth velocity percentile for the treatment period (9.43 +/-18.64) was below the median (50th percentile), but that for the 24-week follow-up (58.35 +/-41.12) was above the median, thus suggesting that some catch-up growth may have occurred after the end of treatment.

Inhibited growth (<3rd percentile) was observed in 70% of subjects during the treatment phase of the study. During the follow-up period, of those subjects who had clearly inhibited growth during treatment, 34.67% had faster than normal growth (>97th percentile), 36% attained improved growth velocity (3rd to 97th percentile), and 20% continued to have inhibited growth (remained <3rd percentile after stopping the treatment).

Interim data from Long term follow up study of pegylated interferon

Interim data from the ongoing long term (5y) follow-up of children treated with the pegylated biotherapy show that 22 % (16/74) of children had a > 15 percentile decrease in height percentile, of whom 3 (4 %) children had a > 30 percentile decrease despite being off treatment for more than 1 year. In particular, decrease in mean height percentile at year 1 of long term follow-up was most prominent in prepubertal age children.

Discussion on the Clinical Safety

The overall safety profile of the PEG2b plus ribavirin observed in this paediatric study is consistent with that observed in previous adult clinical studies and also in the paediatric population treated with interferon alfa-2b plus ribavirin.

With regards to psychiatric disorders, whereas a concern about a higher rate of suicidal ideation/attempt in children had been identified in previous paediatric studies with standard interferon alfa-2bplus RBV as compared to adults (2.4% vs 1% in adults), no patient experienced such an event in this study. Furthermore, 51% of children/adolescent treated with interferon alfa-2b/RBV in previous paediatric studies experienced psychiatric adverse events vs 28% in this study. Notably, a lower rate of depression is reported in this study (2% of depression plus 2% of depressed mood, half of which being judged treatment-related) when compared to previous paediatric studies with standard INF plus RBV (13%) or when compared to adults (26% depression reported in the IDEAL study). Of note, 3% of mood altered, 8% of nervousness and 3% of aggression were nevertheless reported in this study. Although this study demonstrated low incidence of psychiatric events, based on PEG2b treatment experience in adults and previous experience with interferon alfa-2b studies in a paediatric population, the risk of severe depression and associated life-threatening events (such as suicidal ideation and suicidal attempt) cannot be ruled out. All pediatric subjects must be closely monitored for psychiatric events throughout therapy and during follow-up.

In line with the signal previously identified in children that received interferon alfa-2 plus RBV, a significant impact of treatment on height and weight is again observed in this study.
Whereas a compensatory catch up gain in weight seems to occur after treatment cessation, this is not the case as regards height. Mean decrease in height percentile from baseline to EOT was -7.73 (-10.85 for children aged 3-1, -2.5 for children aged 12-17) and mean change in height percentile from EOT to EOF was only +1.11 (+2.03 for children aged 3-11 and -0.42 for children aged 12-17), reflecting that reversal of the growth inhibition that occurred during treatment is largely incomplete at the end of the 24 week follow-up period. In addition, the fact that children/adolescents aged 12-17 continue to experience decrease in mean height percentile after treatment discontinuation further questions the reversibility of growth inhibition due to combination therapy in paediatric patients.

Twenty one out of one hundred and seven (20%) had >15 percentiles decreases in height from baseline to EOT of which 7 (6.5% of total population) had >30 percentiles decreases. These data are comparable to observation from paediatric studies with standard interferon where 20/97 (21%) of children had >15 percentiles decreases in height from baseline to EOT of which 10 (10% of total population) had >30 percentiles decreases. Therefore, at equal treatment duration both standard and pegylated IFN impact growth in the same way. At 6 months follow-up, 21.5% (23/107) of patients had >15 percentiles decreases in height between baseline and EFU with 20% (21/107) of patients had >15-<30 percentiles decreases and 2% (2/107) had >30 percentiles decreases. Of note, according to the height for age percentile curves, a 15 percentiles decrease represents a difference of around 4 cm in height and a 30 percentiles decrease represents a difference of around 6-10 cm in height. It is noteworthy that the proportion of patients with > 15 percentiles decreases in height was substantially higher in patients treated with >48 weeks of treatment as compared to patients who received <48 weeks of pegylated interferon plus ribavirin.

With regards to mean growth velocity a clear and significant growth inhibition of children due to the bitherapy was identified in this study, with as much as 70% of children having growth velocity falling to

<3rd percentile during treatment (in previous paediatric study with IntronA plus RBV, 59% (57/97) of children had experienced <3rd percentile decrease in growth velocity). Even though a faster growth velocity was observed after treatment discontinuation in some children, it is noteworthy that 20% continued to have inhibited growth (remained <3rd percentile) at the end of 24-week follow-up, which clearly show that growth spurts on cessation of treatment did not occur for a considerable proportion of patients. For other children it was not specified whether they got back to their initial growth velocity.

Overall and in line with the SAG expert's conclusions the CHMP concluded that it cannot be ruled out that the negative impact on growth of the bi-therapy is irreversible. Long-term safety data from children/adolescents included in study P02538 are awaited to further characterise the long-term impact of bi-therapy on growth and sexual maturation. Parental height collection and sexual maturation assessment will be made to help to assess the effect of bi-therapy on growth more precisely. TSH levels and medications to treat thyroid disorders will be collected. Nutritional status will also be evaluated (annually).

Paediatric Development

The CHMP took note that:

- a waiver has been granted for children from 0 to less than 3 years of age (Decision P/63/2008 adopted on 15 August 2008).

- and that the PDCO adopted on 17 October 2008 an Opinion on Compliance with the agreed PIP (Decision P/63/2008 adopted on 15 August 2008) under Article 23 of Regulation EC (No) 1901/2006, as amended, for the above mentioned product and that the PDCO concluded in accordance with Article 28(3) and Article 45(3) of the said Regulation to agree that the development of this product has complied with all measures in the agreed PIP.

For the purpose of the application of the Article 45(3) of Regulation EC (No) 1901/2006, significant studies in the agreed paediatric investigation plan have been completed after the entry into force of that Regulation, In addition, the Summary of Product Characteristics reflects the results of studies conducted in compliance with this agreed paediatric investigation plan.

Risk Management Plan

The RMP requires further updating with regards to the version number. The MAH has submitted on the 24 September 2009 an updated version within the context of the PSUR, the assessment of which is ongoing.

Readability Test

Rebetol 40 mg/ml Oral Solution
The test submitted globally satisfies to Guidelines requirements. However the success criteria have not been achieved and no change has been performed to improve the failing results, which is the aim of a readability test.

The test cannot be considered as acceptable at this stage, the MAH is asked:

-to put the format in aligned on the left.

-to ensure that the ink is sufficiently dark to allow a good contrast when printed on "real" paper

-to put the leaflet into a double-sided format

-to perform a third round of interviews

Rebetol 200 mg hard capsules
The test is considered as acceptable, but the MAH is asked:
-to explain the number of females subjects included in the group,
-to give further information on the answer time,
-to ensure using at least a 8 points font size,
-to align the text on the left hand margin,
-to insert as large as possible spaces between the sections.

The MAH will conduct a third round for the Rebetol 40 mg/ml Oral solution PI and will submit final results.

II. OVERALL CONCLUSION AND BENEFIT RISK ASSESSMENT

The MAH applied for an extension of the indication for pegylated interferon alfa-2b (Peginterferon/ViraferonPeg) plus ribavirin (Rebetol) in children from 3 years of age. As for adults, the pegylated interferon is expected to improve convenience for patients (once weekly administration vs 3 times a week).

A single pivotal study (P02538) is submitted to support the paediatric extension. Study P02538 is a Phase 3/1B, open-label, multicenter study (including 10 sites in EU), where 107 pediatric subjects (two age strata 3-11 n=67; 12-17 years of age, n=40) were all treated with PEG2b plus ribavirin for up to 48 weeks and followed for an additional 24 weeks post-treatment. The objectives of the Part 1 of the study were to assess the safety, the efficacy and the pharmacokinetics of peginterferon alfa-2b Plus Ribavirin in naïve pediatric patients with Chronic Hepatitis C. The second part of the study (long-term follow-up) has the objectives to confirm durability of the virologic response and to characterize the long-term safety of the combination, including growth and sexual maturation, in pediatric subjects. This 5 years long-term part of the study is still ongoing.

Of note, an extension of the indication for the combination therapy of Rebetol with standard interferon alfa-2b was granted in 2005 on the basis of data from a pivotal study having a similar design. By the time the extension of indication of IFN plus ribavirin was granted in paediatric patients from 3 years of age the safety profile of both agents (psychiatric adverse events, negative growth impact during treatment with partial catch up at short term follow up) was a concern taking into account also the slowly progressive disease in most children. The long-term growth data have added particular concerns to the initial reservations against the early introduction of the bitherapy in childhood. Indeed, based on the 5 years growth data with the standard IFN and ribavirin, the CHMP concluded that the reversibility of the marked growth impact observed during treatment is uncertain. This was also the conclusion of the recent SAG expert meeting.

Although pegylated interferon is considered to have a clear therapeutic advantage over standard interferon in terms of efficacy (like for adults) the safety signal of non reversible growth inhibition identified with standard interferon raise the same safety concern on the use of the pegylated bitherapy in childhood.

The CHMP agreed that the benefit/risk assessment in the paediatric population is particularly complex since several factors have to be taken into account making each child an individual case. Factors related to the disease such as likelihood of therapeutic response in terms of genotype, co-morbidities such as HIV-co-infection, and the histological evidence of disease progression, need to be taken into account as well as factors that may be pejorative in terms of growth impact. As such it is recommended that the treatment is initiated after the pubertal growth spurt i.e. once the adult height has been achieved. Furthermore, the threat of a growth alteration might be differently handled in a child according to the predicted adult height.

Beyond existing objective criteria that might justify the early introduction of the bitherapy in childhood, the psychosocial burden of a continuous replication in children constitutes a subjective factor that influences the decision to treat children.

Therefore the CHMP agreed that the most reasonable attitude is to adequately warn prescribers and patients about the safety concerns so that a well balanced decision can be taken whether to treat or not on a case-by case basis. This is all the more reasonable that the benefit/risk assessment is multi-factorial (as also discussed by the SAG experts).

Overall, the SPC and PIL contain the key issues to be considered in the decision making process for treating paediatric patients, i.e. the decision to treat should be made on a case by case basis and the safety profile of the bitherapy should be carefully taken into account when deciding not to defer the treatment until adulthood.

In particular, it is important to consider that the bitherapy induced a growth inhibition of which reversibility is currently uncertain. Furthermore the disease characteristics of the child are also important to be taken into account in this decision making process, i.e. evidence of disease progression notably fibrosis, existence of co-morbidities that may negatively influence the disease progression (such as HIV-co-infection), as well as prognostic factors for response, (HCV genotype and viral load).

Overall, expected benefit of treatment should be carefully weighed against the safety findings observed for children and adolescents in the clinical trials. Whenever possible the child should be treated after the pubertal growth spurt. The MAH will have to make particular efforts to adequately collect growth data in the long term follow up of the pegylated IFN. The SAG experts have indeed significantly questioned the reliability of the MAH approach (lack of standardisation of technique for taking measurement, lack of collection of parental heights).

Finally, the CHMP considered the benefit/risk balance of pegylated IFN/ribavirin in children from 3 years of age positive. The product information clearly highligts the factors that have to be taken into account in the decision making process when not deferring the treatment until adulthood.

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