1 SCIENTIFIC DISCUSSION

1.1 Introduction

Chronic hepatitis C is a major health issue in adults. Hepatitis C virus (HCV) accounts for 70% of the cases of chronic hepatitis in industrialised countries.
The public health problem is the progression towards cirrhosis and hepatocellular carcinoma. In adults, HCV is incriminated in 40% of decompensated cirrhosis, 60% of hepatocellular carcinoma and 30% cases where hepatic transplantation is indicated. 6 different genotypes have been identified. The most frequently encountered are genotype 1 and genotypes 2/3 in Europe. Genotype 1 has been shown to be associated with a more severe disease.
Neither the epidemiology of chronic hepatitis C in children, nor the clinical features and course are super imposable to the adult pathology.

As evidenced in adults, the mode of contamination plays a key role in the history of the disease. In industrialised countries, transfusion-acquired CHC has almost completely disappeared, and perinatally-acquired disease accounts for almost all the reported incidence *[Bortolotti & al. J Ped Gastroenterol Nut 2001;33:562-66]*., this means a few amount of a unique inoculum, hence a relatively mild disease, infrequently associated with severe liver damage..
This mode of contamination, the fact that the fibrosis progression is slower when contamination occur in the younger age *[Poynard & al., Lancet 1997;349:825-32]*, and the low rate of alcoholism may account for the less severe features of chronic hepatitis C in children when compared to adults. Nevertheless, the "wait and see" strategy that prevailed up to now tends to be re-considered in the scientific community (AALSD Practice Guideline. Hepatology vol 39, n°34, 2004)

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

Three dossiers have been submitted by Schering-Plough to support the paediatric extension of indication of hepatitis C treatment (interferon α-2b (INF) + ribavirin):

- an Application for an extension of indication for Rebetol 200 mg, capsules (ribavirin)
- an Application for an extension of indication for Introna/Viraferon (interferon α-2b)
- an Application for a Marketing Authorisation for a syrup formulation of ribavirin, especially developed to be administered to children weighing < 47kg.

3.2 Quality aspects

Introduction

Rebetol is formulated as a multidose oral solution containing 40 mg/ml of ribavirin as active substance.

The other ingredients include sucrose, glycerol, sorbitol liquid crystallising, propylene glycol, sodium citrate, citric acid anhydrous, natural and artificial bubble gum flavour, sodium benzoate and purified water.

It is presented in an amber glass bottle with a child-resistant polypropylene/low-density polyethylene closure. An oral syringe, graduated in increments of 0.5 ml in a scale ranging from 1.5 to 10 ml, is provided.

Drug Substance
No change has been made to the active substance already authorised for Rebetol 200 mg hard capsules (EU/1/99/107/01-03).

Drug Product

- **Pharmaceutical Development**

This new oral formulation has been mainly developed for paediatric patients.
All the excipients selected are commonly used for this kind of formulation and they have been selected based on compatibility studies with the drug substance. Regarding the TSE risk, the oral solution does not include any components of ruminant origin.

The amber glass bottle and the low-density polyethylene closure liner coming in contact with the drug product are of PhEur quality and they are in compliance with European regulation on foodstuffs.
The oral syringe comprising a natural low-density polyethylene barrel fitted with a white polystyrene plunger is CE marked and it has been approved for its intended use. The accuracy of the dose delivered by this medical device has been demonstrated according to PhEur.

- Manufacture of the Product

The finished product is produced using a standard process comprising the following steps: compounding, mixing, filtration and filling.
Satisfactory validation data have been provided for three full-scale batches.

- Product Specification

Batch analysis data provided meet the specification at the time of release and confirm the robustness and reproducibility of the manufacturing process.

- Stability of the Product

Stability of the Product before reconstitution
Under conditions (25ºC/60%R.H.), data are available data under accelerated conditions are available (40ºC/75% R.H.). A photostability study has shown that the finished product is not light-sensitive.

In-use stability of the reconstituted solution
In use stability of the solution was tested. The solution showed to be stable during the proposed in-use shelf life and under the storage conditions defined in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

No change has been made to the active substance already authorised for Rebetol 200 mg hard capsules (EU/1/99/107/01-03). The pharmaceutical form selected is adequate taking into account the properties and stability of the active substance. The excipients are commonly used in this kind of formulation and the packaging material is well documented. The manufacturing processes was developed and optimized to obtain reproducible finished product batches. Stability tests under ICH conditions indicate that the products are stable for the proposed shelf life.

1.3 Non-clinical aspects

(see overall discussion)

3.4 Clinical aspects

Pharmacokinetics

Introduction
As above explained, pharmacokinetic data collected in children derive from the 4 submitted studies

The corresponding clinical development submitted was the same for the 3 Applications pertaining to Rebetol and Intron A (i.e. new application for Rebetol syrup, type II variations for Rebetol 200 mg capsule and IntronA) and consisted of 4 open studies with only one phase III study:

- phase I open uncontrolled study P00392 aimed at assessing the bioavailability of the syrup formulation of ribavirin.
- phase I open study P00018 part 1 (cohort 1) was a dose-ranging PK/PD study aiming at selecting the optimal dosage of ribavirin capsule in the paediatric population, based on safety, kinetic and antiviral PD criteria, respectively primary, secondary and tertiary endpoints.
- phase I open study P00018 part 2 (cohort 2) was a clinical pharmacology PK/PD study set up to assess the safety (primary objective) and antiviral efficacy (secondary objective) of the selected 15 mg/kg ribavirin capsule dosage in combination with interferon α-2b.
- phase III open uncontrolled study P00321 assessed the efficacy of the combination of the 15 mg/kg/day dosage of ribavirin (administered either as capsule or syrup formulation, depending on the weight) in combination with interferon α-2b in the treatment of hepatitis C in children, based on virological and biochemical criterion.

Comparative "bioavailability" of 200mg capsules and oral solution

Study 00392 was set up to assess the bioavailability of the syrup formulation of ribavirin.

Study design**:**
Phase I, open-label, uncontrolled, single dose bioavailability study with no ribavirin capsule control group conducted in healthy adult volunteers The objective of this study was to evaluate the pharmacokinetics of ribavirin following a single dose of ribavirin syrup (40 mg/ml) in healthy adult subjects prior using this oral solution in the P00321 study.

Results :
The absorption of ribavirin was shorter for syrup formulation (Tmax ≈ 1 h) than for capsule formulation (Tmax ≈ 1.5 to 2 h). The mean ribavirin concentration profile resulting from the administration of syrup was within 10 % of concentration-time data collected in four studies (C96 – 214, C96 – 398, C95 – 165 and C95 – 155) previously conducted with capsule administration. The C_{max} and AUC values were comparable to values obtained in previous studies with capsule in healthy adults

In the clinical study 00321 the mean trough ribavirin concentrations at weeks 12, 24, 40 and 48 were similar following administration with the oral solution (40mg/ml) and the 200mg capsules.

Study P00018 cohorts 1 and 2

Open-label, uncontrolled, randomized, parallel-group multiple-dose (cohort 1) or fixed-dose (cohort 2) study for a 48-week period with a subsequent follow-up of 24-week. PK characteristics derive from the same patients in both studies and are presented below as an integrated PK summary.

Study Participants
Main Inclusion criteria: patients aged 5-16 with histologically-proven chronic hepatitis C and HCV-RNA positive by PCR.Naïve with regard to ribavirin treatment.Naïve or relapse post response to prior INF therapy.Stratification by age group (5-11 yrs and 12-16yrs).

Treatments
All patients received Intron A 3MIU/m^2 SC three times per week.

Cohort 1
61 patients were enroled in 17 sites and were randomly assigned in parallel (stratified by age: 5-11 years or ≥ 12-16 years) to 1 of the following treatment groups:

Rebetol 8 mg/kg/day po (5 – 11 years n = 13, ≥ 12 – 16 years n = 18)

Rebetol 12 mg/kg/day po (5 - 11 years n = 12, ≥ 12 – 16 years n = 8)
Rebetol 15 mg/kg/day po (5 - 11 years n = 11, ≥ 12 – 16 years n = 9)
The daily ribavirin dose was administered in two divided doses as 50 mg capsules.
Dose levels are fixed for 12 weeks. Patients assigned to the 8 and 12 mg/kg/day group could receive a dose escalation if they have not achieved a 2 log decrease in their HCV-RNA levels.
Patients with an HCV-RNA positive at 24 weeks were withdrawn.

Cohort 2
The 55 patients enrolled received the 15 mg/kg daily dose selected based on data obtained in cohort 1, including 20 having received the 15 mg/kg dose during part 1 (5-11 years n=16; ≥12-16 years n=19).

Objectives:
The primary objective shared by both parts of study 0018 was the assessment of the safety and tolerability of the combination of Intron A plus Rebetol in paediatric subjects with CHC assessed by adverse events and clinical laboratory evaluations through week 12.

The specific secondary objective of part 1 study were to measure the multiple-dose PK of IntronA plus Rebetol in paediatric subjects with CHC assessed by a week 4 PK assessments..

The tertiary objective was to assess the efficacy of IntronA plus Rebetol assessed by serum ALT levels and HCV-RNA levels at week 4 and 12 in paediatric subjects with CHC.

The specific objective of part 2 study was as secondary objective to assess the efficacy of IntronA plus Rebetol at the optimal dose on antiviral PD (HCV-RNA levels, ALT levels) in paediatric subjects with CHC.

Results for cohort 1
PK results
Table 1 shows the PK results for ribavirin and table 2 those for interferon alfa-2b

Table 1 **Protocol 00018:** PK parameters of ribavirin

Ribavirin dose (daily in 2 divided doses)	**C_{max} (ng/mL)**	**AUC_{0-12} (ng.hr/mL)**	**T_{max} (hr)**	**CL/F (L/hr/kg)**
8 mg/kg/day				
mean	2249	18527	3.00	0.23
% CV	43	28	134	26
n	19	19	19	19
12 mg/kg/day				
mean	2747	25364	1.36	0.24
% CV	16	16	63	15
n	18	18	18	18
15 mg/kg/day				
mean	3275	29774	1.94	0.27
% CV	25	26	83	27
n	17	17	17	17

Table 2 **Protocol 00018:** PK parameters of interferon alfa-2b

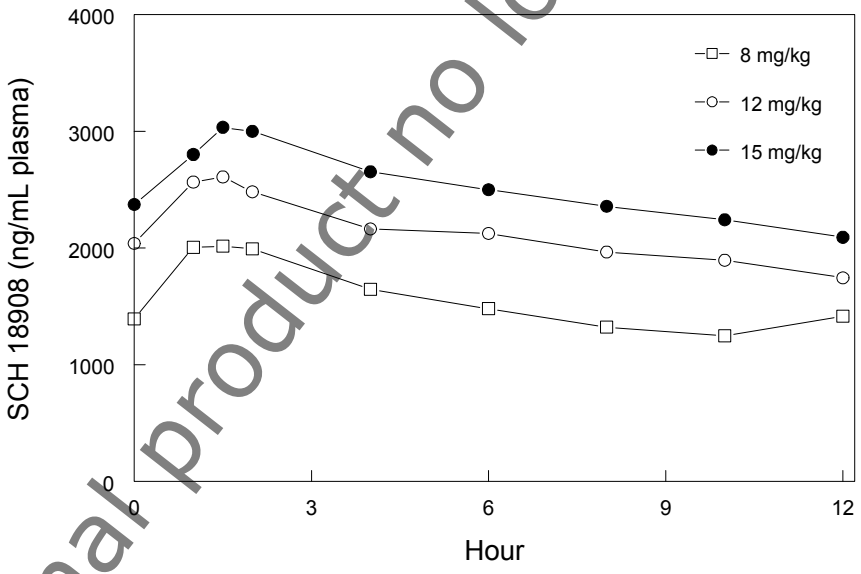
Interferon alfa-2b dose	**C_{max} (IU/mL)**	**AUC_{0-24} (IU.hr/mL)**	**T_{max} (hr)**
3 million international units/m^2 three times a week.	50.5	622	5.93
mean	48	48	36
% CV			

Determination of "optimum dose"
A greater that 2-log 10 reduction in serum HCV-RNA levels at week 12 was noted with all three doses, with the largest log reduction (3 log) occurring with the 15mg/kg/day dose. 15mg/kg/day was selected as the optimal dose for further evaluation.

Comparison of PK data between cohort 1 and cohort 2
The mean trough ribavirin concentrations between weeks 12 and 48 were similar for those taking 15 mg/kg/day in cohort 1 (n=17) and those in cohort 2 (n=25).

Pharmacokinetic results / ribavirin

Mean Ribavirin Profiles after 4 Weeks of Treatment :



Paediatric pharmacokinetic parameters were compared with those obtained from previous studies conducted in adults receiving both ribavirin and interferon alfa 2b or pegylated interferon. At week 4 paediatric pharmacokinetic parameters at 8, 12 and 15 mg/kg/day corresponded to adult pharmacokinetic parameters at doses 800, 1000 and 1200 mg/day respectively as shown above.

The **mean trough ribavirin concentration** between week 12 and week 48 after 15 mg/kg/day were very similar in cohort 1 and 2.

Study P00321

Study P00321 investigating the efficacy and safety of the combination of interferon alfa-2b 3MIU/m2 three times weekly plus ribavirin 15 mg/kg/day (in two divided doses) for 48 weeks in paediatric subjects with either syrup or capsule formulation, depending on the weight (< or ≥ 47kg) (3 – 11 years, n = 38; ≥ 12 – 16 years, n = 17 for syrup/3–11 years, n = 3; ≥ 12 – 16 years, n = 12 for capsules) with chronic hepatitis C.

Trough ribavirin and interferon alfa-2b concentrations were measured

Results: The mean trough ribavirin concentration following syrup and capsule were similar and close to the values measured in cohort 2 of study P00018.

Conclusions on Pharmacokinetics:

Study 00392 was set up to assess the bioavailability of the syrup formulation of ribavirin.

Individual and mean values overlapped between the capsule and oral solution formulations indicating that similar exposure was achieved with both formulations.

The validation reports for ribavirin in human plasma and for interferon alfa-2b in human serum were satisfactorily provided.

Clinical efficacy

Study Phase III P00321
The objective of the study was to assess the efficacy, safety and tolerability of the combination of Intron A plus Rebetol with syrup and capsule formulations for 48 weeks in paediatric subjects with chronic hepatitis C.

Methods:Open-label, fixed dose, single arm phase 3 study for a 48-week period with a subsequent follow-up of 24-week.The inclusion criteria were: Age 3-16 years male or female, HCV-RNA positive by PCR, liver biopsy compatible with a diagnosis of chronic hepatitis, obtained within 1 year prior to enrolment, no previous interferon, ribavirin or combination interferon + ribavirin treatment, HIV and HBV negative. The exclusion criteria were previous interferon, ribavirin or combination interferon + ribavirin treatment, parenteral antiviral or immunomodulatory therapy within the previous 2 years.

Treatments
Intron A 3MIU/m2 SC three times a week in combination with Rebetol 15 mg/kg/day po in 2 divided doses. Rebetol was administered either as capsule or as syrup formulation, based on the patient's weight at study entry : capsule for subjects 9-16 years weighing ≥47 kg, syrup for others (3-8 yrs and 9-16 weighing <47 kg).

Endpoints :There are two endpoints: sustained loss of detectable serum HCV-RNA (<100 copies/ml) at the end of the 24-week and follow-up period, normalisation of ALT levels.

Demography and baseline characteristics.
Participant flow 43 patients completed the follow-up period, 7/15 in the capsule group and 36/55 in the syrup group (discontinuations mainly due to treatment failure).
Baseline data : Overall, 78.5% patients (55/70) received the syrup formulation, As in study 00018, 3/4 of patients (74%) were genotype 1 (n=52), 17 patients were genotype 2 or 3. The source of exposure rate seems to have changed in the last few years with now a predominantly perinatally-acquired disease (35% in cohort 1 P00018, 45% in cohort 2 P00018 and 60% in P00321).

Primary efficacy variable results

Virological response : Overall, the sustained virological response obtained with the recommended 15 mg/kg daily dose was 49% (34/70). The rate of sustained virological response was higher for subjects infected with Genotype 2/3 (82%) than for subjects infected with Genotype 1 (38%).

Sustained virologic response by baseline demographic data and disease characteristics

Protocol P00321 : Sustained virologic response by demographic data and baseline disease characteristics	
Number (%) of subjects	
INTRON A 3 MIU/m² TIW and REBETOL	
	All subjects (n = 70)
Genotype and baseline HCV-RNA (copies/ml)	
Gen.1 and ≤ 2 million	16/30 (53)
Gen.1 and > 2 million	4/22 (18)
Gen.2/3 and ≤ 2 million	6/8 (75)
Gen.2/3> and 2 million	8/9 (89)

As expected, the genotype 1 and a viral load > 2 million copies / ml seem to be predictive of a less sustained response rate.

Normalization of ALT level results – secondary efficacy variable:

ALT levels normalised at the end of follow-up period in 23/24 (96%) of sustained responders. Among non responders, 24 had abnormal ALT levels at baseline; only 7/24 (29%) had normal ALT levels at the end of follow-Up.

Dose response study P00018

This Phase I open study P00018 was divided into 2 parts : part 1 (cohort 1) was a dose-ranging PK/PD study aiming at selecting the optimal dosage of ribavirin capsule in the paediatric population, based on safety, kinetic and antiviral PD criteria
Part 2 (cohort 2) assessed the safety, PK characteristics and PD effects of the selected 15 mg/kg daily dose, in 55 patients including 20 having received the 15 mg/kg dose during part 1.
The design of Study 00018 (cohorts 1 and 2) is detailed in the Pharmacokinetics section.

Efficacy results

Study 00018 cohort 1

Demography and baseline characteristics : The great majority of patients included had genotype 1 (65 to 95%, depending on the treatment arm, 77% in the 15 mg/kg group), and a high baseline viral load (68 to 75%, 71% in the 15 mg/kg group had a viral load > 2 millions copies/ml).

- **Virological response**

Protocol 00018 cohort 1 : Virologic response (serum HCV-RNA < 100 copies/ml) **in all genotypes**			
Number (%) of subjects[a]			
	I/R (8)	I/R (12)	I/R (15)
Weeks	Without Site 10 (n=20)	Without Site 10 (n=19)	Without Site 10 (n=17)
End of Follow-Up	7(35)	7(37)	8(47)

I/R (8)=INTRON A + REBETOL 8 mg/kg/day; I/R (12)=INTRON A + REBETOL 12 mg/kg/day; I/R (15)=INTRON A + REBETOL 15 mg/kg/day.
a: Subjects with positive HCV-RNA or missing data at 48 Weeks of Treatment counted as non responders.

This lower than expected response for I/R (12) could reflect the higher proportion of the more difficult to treat genotype 1 subjects . However there is a definite dose-dependant response.

Protocol 00018 cohort 1 : Virologic response (serum HCV-RNA <100 copies/ml) ***in genotype 1***			
Number (%) of subjects[a]			
	I/R (8)	I/R (12)	I/R (15)
Weeks	Without Site 10 (n=13)	Without Site 10 (n=18)	Without Site 10 (n=13)
End of Follow-Up	3(23)	6(33)	5(38)

I/R (8)=INTRON A + REBETOL 8 mg/kg/day; I/R (12)=INTRON A + REBETOL 12 mg/kg/day; I/R (15)=INTRON A + REBETOL 15 mg/kg/day.

a: Subjects with positive HCV-RNA or missing data at 48 Weeks of Treatment counted as non responders.

Protocol 00018 cohort 1 : Virologic response (serum HCV-RNA <100 copies/ml) ***in genotype 2***			
Number (%) of subjects[a]			
	I/R (8)[b]	I/R (12)	I/R (15)
Weeks	Without Site 10 (n=5)	Without Site 10 (n=1)	Without Site 10 (n=4)
End of Follow-Up	4(80)	1(100)	3(75)

I/R (8)=INTRON A + REBETOL 8 mg/kg/day; I/R (12)=INTRON A + REBETOL 12 mg/kg/day; I/R (15)=INTRON

A + REBETOL 15 mg/kg/day.

a: Subjects with positive HCV-RNA or missing data at 48 Weeks of Treatment counted as non responders.

b: One subject in the I/R (8) group was HCV genotype 4; this subject was a non responder at End of Follow-Up.

- ***Biochemical response***

Among the sustained responders, 13 subjects had abnormal ALT levels at baseline; ALT normalised in 11/13 (85%) at Follow-Up week 24. None of the sustained responders with normal baseline ALT levels had abnormal ALTs during Follow-Up

Among non responders, 22 subjects had abnormal ALT levels at baseline; ALT normalised in 8/22 (36%) during Follow-Up. 2/16 (13%) of the non responders with normal baseline ALTs had abnormal ALTs during Follow-Up.The time-course of ALT levels parallels the virological response. As has been observed in adult subjects, the decrease in viral level was more rapid in cohort 1 subjects infected with HCV genotypes 2 and 3.

Efficacy Results Study 00018 Cohort 2

Demography and baseline characteristics: The great majority of patients included had genotype 1 (87%) compared to 13% with genotype 2 or 3, and a high baseline viral load (68% had a viral load > 2 millions copies/ml). The source of HCV exposure (transfusion or perinatally-acquired hepatitis C) seems to be well-balanced within the included subjects.

- ***Virological response***

Protocol 00018 cohort 2 : Virologic response (serum HCV-RNA < 100 copies/ml) ***in all genotypes, genotype 1 and 2/3***			
Number (%) of subjects			
I/R (15)			
Week	All genotypes (n = 31)	Genotype 1 (n = 27)	Genotype 2/3 (n = 4)
FU 24	12 (39)	8 (30)	4 (100)

Protocol P00018 cohort 2: Sustained virologic response for all subjects and subjects with ***genotype 1 by viral level***		
Number (%) of subjects		
I/R (15)[a,b]		
HCV-RNA at baseline (copies/ml of serum)	All (n = 31)	Genotype 1 (n = 27)
≤ 2 million > 2 million	5/10 (50) 7/21 (33)	3/8 (36) 5/19 (26)

a : all 5 subjects with genotype 2/3 had a sustained virologic response (2 of the 5 had ≤ 2 million copies/ml at baseline and 3 had > 2 million copies/ml at baseline.b : sustained response = serum HCV-RNA < 100 copies/ml at FU week 24.
Overall the virological as well as the biochemical data obtained in cohort 2 confirms the cohort 1 results.

Discussion on Clinical Efficacy

During the assessment process several issues were considered:

- **Efficacy results :**

In the genotype 1 subgroup of this open uncontrolled study, the reported rate of sustained virological response (38%) does not appear significantly superior to the response rates reported in the literature with INF monotherapy in the paediatric population *[Di Ciommo & al. Interferon alpha in the treatment of chronic hepatitis C in children : a meta-analysis. J Viral Hepat 2003;10:210-214] and [Jacobson & al. An analysis of published trials of interferon monotherapy in children with chronic hepatitis C. J pediatr Gastroenterol Nutr 2002;34:52-58]*.In the genotypes 2/3 population, the rate of sustained virological response (82%) is high, as expected. In view of this high response rate, the genotypes 2/3 population could represent a legitimate target population.
However, the study included <25% genotype 2/3, and the corresponding sample size (n=17, 4 received capsules and 13 the syrup) is very limited needed to be further substantiated. The 100% reported rate observed in 17 genotype 2/3 patients in an open uncontrolled study compensates the relatively low % observed in the 52 genotype 1 patients. Therefore, very few patients increase to a great extent the overall population response rate.

- **Target population**

the protocols for the studies required that the patient have an elevated ALT or evidence of inflammation and/or fibrosis on liver biopsy. In the P00321 study, pretreatment liver biopsy was available for 65 of 70 patients and all of these patients had evidence of inflammation, the majority of which was of mild to moderate severity. Nearly all patients were observed to have hepatic fibrosis (60/65) of whom **56 had grade 1** and 4 had grade 3. Although chronic hepatitis C is a slowly progressive disease, it is reasonable to expect that in patients of the young age in this study, nearly all of whom had evidence of fibrosis, that a substantial proportion will have further progression in the face of ongoing inflammation.

- **Histology**

the final decision to treat a pediatric patient must be made by the treating physician weighing all aspects of the benefit and risk for each child. It can be anticipated that the physician will take into account the age of the child, severity of hepatic inflammation and histologic evidence of disease progression as well other factors when making a decision to treat a pediatric patient.
As requested, the liver histology data from the Phase III study (P00321) is presented. Moreover,
The MAH recommends adding the following statement to Section 4.1 Therapeutic Indications of the SPC: "Evidence of disease progression, such as hepatic inflammation and fibrosis, as well as prognostic factors for response, HCV genotype and viral load, should be considered when deciding to treat a pediatric patient. The benefits of treatment should be weighed against the safety finding observed for pediatric subjects in the clinical trials.
The CHMP noted that only 4 patients had bridging fibrosis. **Therefore the overall population enrolled in the pivotal clinical study obviously consists in patients with mild to moderate hepatitis C**. As a matter of fact in this population, up to now the general consensus recommended a "wait and see" attitude. It was generally admitted that the treatment should be considered on a case by case basis. Of note HIV co-infection was part of the exclusion criteria.

- **Optimal dose of interferon á-2b**

The CHMP requested more information on the determination of the optimal dose of interferon á-2b. The 3 MIU/m2 dose used in combination with Rebetol provided a twice as high plasma concentration as in adults. This was particularly critical with regard to the poor safety profile of interferon á-2b. The MAH replied that the dose selected, 3 MIU/m^2 TIW, was based on a pilot study in 12 pediatric

patients with HCV that showed the 3 MIU/m^2 TIW dose was safe, well tolerated, and had antiviral activity. The tolerability of a dose of 6 MIU/m^2 TIW has also been previously demonstrated in 72 pediatric patients with chronic hepatitis B for up to a total of 24 weeks (after a 1-week lead-in period of 3 MIU/m^2 TIW). Also Mean AUCtf and Cmax for interferon in pediatric patients were approximately double the corresponding adult values. This finding is consistent with the difference in dose administered to children compared to that administered to adults. The pediatric dose (3 MIU/m^2) was approximately double that of the dose per body surface area administered to adults in the study from which this data was taken. However, when dose-normalized , calculated AUC and Cmax values for pediatric patients are similar to those of adults.

The CHMP noted that the dose justification is only based on limited data in children and extrapolation from adult patients.

- **Combination of ribavirin and peginterferoná-2b**

The CHMP also noted that in adults, the combination of ribavirin and peginterferoná-2b has become the state of the art in the treatment of CHC, and is the treatment strategy recommended for the treatment of genotype 1 patients in the NIH consensus conference on the management of hepatitis C (2002).
This combination was demonstrated to provide a much better efficacy than the combination of ribavirin and interferon α-2b (54% versus 47%), especially in genotype 1 patients, who were very predominantly included in this clinical program. With optimised doses of Rebetol in combination with peginterferonα-2b, adjusted on body weight, the sustained virological response rate was 61% versus 47% in combination with interferon α-2b.
Therefore the MAH was asked to specify if a clinical development is ongoing/planned with the combination of peginterferoná-2b and ribavirin in the paediatric population
The MAH replied that the clinical program in pediatric patients was initiated in 1998, prior to the availability of data on the safety and efficacy of PegIntron plus ribavirin in adults. A clinical trial in pediatric patients with CHC of PegIntron plus ribavirin is currently being initiated. Until the results of this study are available, the only available therapy which has demonstrated efficacy in pediatric patients with CHC is the combination of 3 MIU/m2 IntronA plus 15 mg/kg/day ribavirin.

- **Missing data**

The CHMP also noted that there is too much missing data in children aged 12 and above to enable comparison between data obtained with the capsule and the syrup formulations. The MAH replied that missing follow-up virology data (HCV-RNA at 24 week follow-up) for the ITT analysis presents a particular problem in patients that are HCV-RNA negative at the end of treatment since most of these patients become sustained responders. For patients in these studies who were negative at end of treatment and who had the 24 week follow-up assessment the relapse rate was low, 15%.
To address the issue of patients with a negative HCV-RNA at the end of treatment and a missing value at the end of follow-up, the MAH performed a further assessment to estimate the likelihood of a sustained response given a negative HCV-RNA at the end of treatment. Then, the Sponsor estimated that the adjusted sustained response rate for capsules (51%) was comparable to the sustained response rate for solution (53%). The CHMP noted that such estimations should be considered with caution with regard to their inherent limitations (hypothesis of similar response between patient with missing and non-missing data).

- **Week 24**

The CHMP requested further information on the week 24 response. The early viral kinetic data, although limited, suggest that the response at week 12 of treatment could be used to predict treatment outcome. However, the MAH proposes that week 24 response be used for recommending treatment interruption in non-responders. As suggested by the CPMP, the MAH has assessed for all pediatric patients receiving IntronA 3MIU/m2 plus Rebetol 15 mg/kg the positive predictive value (PPV) and the negative predictive value (NPV) of a patient achieving a sustained virologic response based

on the response at week 12 or 24 of treatment. HCV-RNA negativity and multiple log10 decreases at these time points were assessed.

Based on the Intron A/Rebetol data for adults which showed that 24 and 48 weeks of therapy for HCV 2 and 3 patients were equally effective, the MAH recommends that the SPC specify that children with HCV genotypes 2 and 3 should be treated for 24 weeks.

This predictive value is even more difficult to establish in children since the available clinical data are currently very limited. Therefore, it appeared reasonable to draw the same recommendation in term of treatment duration and stopping rules as for adults.

Clinical safety

Patient exposure:

A total of 118 received interferon alfa-2b 3 MIU TIW/m^2 plus ribavirin 15 mg/kg/day. Approximately one-half (58%) of the subjects completed the 48 treatment period.

Adverse events

Treatment emergent adverse events with at least one SAE in Protocol Nos. P00018 Cohort 1, P00018 Cohort 2 and P00321		
	All Subjects (n=118)	
	All Grades	Severe
Total Reporting Any AE[a]	**100% (118))**	**19% (23)**
Body as a Whole	**98% (116)**	**3% (4)**
Influenza-like symptoms	31% (6)	<1% (1)
Central/Periph Nerv Syst	**31% (37)**	**<1% (1)**
Endocrine	**6% (7)**	**<1% (1)**
Hypothyroidism	4% (5)	<1% (1)
Gastrointestinal	**84% (99)**	**2% (2)**
Musculoskeletal	**53% (62)**	**3% (3)**
Psychiatric[a]	**51% (60)**	**3% (4)**
Behavior disorder	5% (6)	<1% (1)
Depression	13% (15)	<1% (1)

a: There was 1 life-threatening adverse event, a suicide attempt in subject P00018-17/0227, who received capsules. This subject was discontinued from the study, and psychiatric evaluation and antidepressants were initiated, with resolution of the suicidal ideation.

All patients reported at least one adverse event. The most commonly reported AE were consistent with a flu-like syndrome, or were gastrointestinal (84%), psychiatric (51%), musculoskeletal (53%), neurological (31%).Almost half of the overall included subjects (51%) experienced a "psychiatric" AE during the study with 13% of them being depression cases. This incidence is similar between the two formulation groups while the incidence rate of non-specific psychiatric AEs is higher in subjects receiving oral solution (67%) compared to those receiving capsules (37%).

Serious adverse events and deaths
No deaths were reported during the paediatric clinical development.

Serious adverse events studies P00018 Cohort 2 and P00321						
Subject Number (Age/Sex)	Start Date	End Date	Adverse Event	Relationship [a]	Outcome	Ribavirin Dose Form
Serious Adverse Events During Treatment						
P00018-13/0214 (14/F)	70	70	Suicidal ideation	**Probable**	Psychiatric follow-up[b]	Capsules
P00018-17/0227 (13/F)	65	65	Suicide attempt	**Possible**	Hospitalization, discontinuation	Capsules
P00321-18/1801 (9/M)	97	106	Infection after circumcision	Unlikely	Hospitalization	Solution
	179	ongoing	Depression (no prior history)	**Probable**	Dose Interrupted, discontinued	
P00321-21/2109 (16/F)	154	158	Diabetes Mellitus	Unlikely	Hospitalized, dose interrupted, additional therapy	Solution
P00321-24/2405 (5/F)	1	2	Vomiting	Unlikely	Hospitalized	Solution
P00321-35/3501 (4/F)	20	21	Diarrhea	Probable	Hospitalized, dose reduced	Solution
Serious Adverse Events During Follow-Up						
P00321-01/0102 (10/F)	FU day 163	FU day 168	Perforated appendix/ appendectomy/ peritonitis	Unlikely	Hospitalized, additional therapy	Solution
P00321-22/2203 (8/M)	FU day 123	FU day 125	Appendicitis/ appendectomy,	Unlikely	Hospitalized	Solution
	FU day 348	FU day 349	Asthma	Unlikely	Hospitalized	

a: Determined by the investigator.
b: Additional therapy and dose reduction for depression.

Two additional patients belonging to study P00018, cohort 1 experienced suicidal ideation in the treatment or FU period.
The corresponding incidence is 2.4% (4/overall 166 patients) which has to be compared to the 1% observed in adults.
Three of the 4 subjects who had suicidal ideation or a suicidal attempt were adolescents; the other one was a child aged 9 without any prior history of psychiatric disorders.Although the incidence of depression was lower than in adults (13% vs 31%), it is of particular relevance in this fragile population, as attested by the high 2.4% rate of suicidal ideation/attempt.
The risk of depression and suicide is of particular relevance in the adolescent population. Data on suicide have shown conclusively that adolescents are one of the most "at risk" populations studied, as reported in the 2000 report from the Committee on Adolescence/American Academy of Pediatrics titled "Suicide and Suicide Attempts in Adolescents". The presence of chronic illness is also associated with an increase in the risk of suicide in both the adolescent and adult subject.
This should be taken into account in the assessment of the Benefit/risk ratio.

One child aged 8 experienced a severe depression with suicide attempt, which illustrates that the psychiatric risk is not confined to the adolescent age group.

Other Adverse events of specific relevance in children

- **Weight loss / Growth retardation**

25% patient experienced weight loss. Mean -9.1 changes in height percentile and -12.6 in weight percentile were observed during treatment. At the end of follow-up, there remained only a -2 change in percentile for weight. A question remained regarding the height evolution.

- **Other**

Moreover, it was underlined that growth inhibition, hypothyroidism (4%) and alopecia (23%) were particularly critical events in children.

Laboratory findings

As expected, laboratory findings evidence anemia (27%, only grade 1 and 2) and neutropenia (71%). It is important to note that 39% patients in the capsule group experienced anemia, when compared to 13% in the syrup group.

As the hematological tolerance in children seems to be better than in adults (- 1.5 g/dl vs - 2.6 g/dl), this effect may be related to older age of the subjects.

- **Discontinuations for Adverse Events**

Seven subjects discontinued treatment due to AE, 4 of them were severe or life-threatening. Two SAE occurs in the I/R (15) group and the two other with the solution formulation. Two neutropenia cases, one with each formulation, occurs in two females aged 14 and 15, respectively 174 and 65 days after treatment onset. The case of suicide attempt occurs in a 13-years old female with psychiatric antecedents who received the capsule formulation two months after treatment start. The depression and behavior disorder occurs in a 9-years old male without any depression risk factors and received the solution.

With regard to these results, the SAE incidence is similar with both formulations with no better hematological or psychiatric tolerance with the solution formulation.

When including all ribavirin treatment groups, there were 3 suicidal ideation and 1 attempted suicide among a total of 166 treated children. Of note,3/4 of these cases were adolescents.

- **Dose modifications with Interferon alfa-2b and ribavirin 15 mg/kg**

Two third of required dose modification occurred for interferon alfa-2b and not ribavirin.

One third of subjects required dose modification (5% in the I/R (8) group, 35% in the I/R (12) group and 47% in the I/R (15) group due to AEs) which seems to be dose-related.

There were 13% of ribavirin dose modification, mainly with the capsule formulation.

Anemia and neutropenia are the most common reasons for dose modification.

There was "only" 3% incidence of dose adjustment for psychiatric adverse events.

Discussion on Clinical Safety

The risk was not considered as completely elucidated and raised concerns specific to the intended paediatric populationThe observed tolerance profile of ribavirin in children grossly matches the tolerance profile of the combination in adults, with even a better tolerance to anemia (less frequent and milder), which is not surprising in young children, and less frequent depression (13% versus 31% in naïve adults), **but with growth inhibition characterized by a decrease in height (mean percentile decrease of growth velocity of 9 %) and weight (mean percentile decrease of 13%) and a higher rate of suicidal attempt/ideation (2.4% versus 1%).**

Particularly, the higher rate of suicidal ideation/attempt confirms that the risk of depression and suicide is of particular relevance in the adolescent population. Data on suicide have shown conclusively that adolescents are one of the most "at risk" populations studied, as reported in the 2000

report from the Committee on Adolescence/American Academy of Pediatrics titled "Suicide and Suicide Attempts in Adolescents".

The presence of chronic illness is also associated with an increase in the risk of suicide in both the adolescent and adult subjects.
The severe depression in a young boy (<10 yrs) further attests that the psychiatric risk is not confined to the adolescent age group.

Moreover, it is to be underlined that depression (13%), anorexia (51%), hypothyroidism (4%) and alopecia (23%) are particularly critical events in children.

Overall, the CHMP stated that the safety profile of the combination is of particular concern in this paediatric population (suicidal ideation/attempt and depression, anorexia, growth inhibition, hypothyroidism and alopecia). This has to be assessed in the light of the low need to treat and lack of demonstration children with severe evolution of the disease. .
The MAH agrees that the benefits of treatment should be carefully weighed against the safety findings observed for pediatric subjects in the interferon alfa-2b/ribavirin trials; It was agreed that the final decision to treat a pediatric patient would have to be made on a case by case basis by the treating physician taking into account several critical factors to characterize the disease status and carefully weighing and the potential risk for the child.
In this field, it was anticipated that the physician will take into account the age of the child, severity of hepatic inflammation, histologic evidence of disease progression and other factors when making a decision to treat a pediatric subject; however, the exact requirements to make this decision was considered difficult to be mandated in the product label. Therefore, the MAH proposes adding the following statement to Section 4.1 Therapeutic Indications of the SPC:
"Evidence of disease progression, such as hepatic inflammation and fibrosis, as well as prognostic factors for response, HCV genotype and viral load, should be considered when deciding to treat a pediatric patient. The benefits of treatment should be weighed against the safety finding observed for pediatric subjects in the clinical trials. **"**The CHMP agreed upon the particular difficulties in straightforwardly defining the target population and underlines the need of a careful case by case basis assessment of the potential benefit and risk. The proposal of the applicant to introduce a statement warranting attention of prescribers on the factors to be considered in this careful assessment was considered reasonable.

- **Weight loss**

The CHMP noted that 25% patients experienced weight loss. Mean -9.1 changes in height percentile and -12.6 in weight percentile were observed during treatment. At the end of follow-up, there remained only a -2 change in percentile for weight. The MAH was requested to provide complete available information concerning the effect on growth. The MAH replied that the mean change in height percentiles in all subjects for the Treatment period was -9.11. The mean change in percentiles in all subjects for the Follow-Up period was +1.96. In the capsule and solution groups, mean decreases during Treatment were partially compensated for by mean increases during Follow-Up (+2.00 and +1.92, respectively). Generally, the mean data indicate that linear growth inhibition observed during treatment is not permanent, and partially compensatory increase in linear growth rate is observed during post-treatment Follow-Up period.
The mean change in weight percentile in all subjects was -12.6 during Treatment and +10.52 during Follow-Up. A similar pattern was observed at End of Treatment and at End of Follow-Up in the capsule and solution groups (-12.5 and +8.58; -12.7 and +12.76, respectively). This suggests that there is a nearly compensatory "catch-up" weight gain for affected subjects after treatment has ended.

However, the CHMP noted that the data provided were open to criticism and did not allow to draw definite conclusion with regard to the potential impact of treatment on the growth. Indeed, the company only provided pooled data, precluding a proper assessment of the incidence and seriousness of the growth delay in children. Even if the mean data suggest that there might be a compensatory "catch up" weight and height gain after treatment has ended, one can not exclude that some children may experience a significant and/or long-standing growth delay. A falloff from the pre-treatment

growth curve for some children can not be excluded due to the lack of individual data regarding growth development.
Consequently, it was considered that the SmPC should point out the impairment of growth velocity observed in the paediatric population during treatment. Moreover, the MAH was strongly encouraged to collect substantiated data on this issue from the ongoing clinical trial in paediatric patients treated with the combination of Peginterferon-alpha 2b and ribavirin. Finally, the precise mechanism behind such effect would deserve to be explored by the MAH.

- **Psychiatric disorders**

The CHMP noted that 37% patients in the capsule group and 67% in the syrup experienced psychiatric disorders, but an identical 13% of depression was observed in both groups. Conversely, 39% in the capsule group experienced anaemia, compared with 13% in the syrup group. The MAH commented in the Clinical Expert Report on the difference in the reporting of psychiatric adverse events between the capsule and the oral solution groups. There was no clear explanation other than the observation that the difference appears to be due to a higher incidence of the non-specific psychiatric events such as somnolence, behaviour disorder and insomnia. It could be speculated that the difference could be related to the differences in reporting of adverse events, i.e., parents reporting observations for younger children and self-reporting for older children.
The CHMP stated that the MAH's response was very limited and did not help in clarifying the reason for the differences observed in the safety profiles of both Ribavirin formulations. In the perspective of an ongoing clinical development in children, this issue would need to be further explored by the MAH.

- **Complementary safety data provided during the procedure :**

In order to further the safety profile of the drug, the applicant was requested to provide long term safety data and data on the thyroid function :

1. **long term safety data especially regarding the effect on (neuro) endocrine function including the impact on growth and sexual development. Special attention were also to be given to psychiatric and behavioural reactions.**

In response, the MAH provided data on patients enrolled in the study P01906, which is a 5-year follow-up study of the children treated in the pivotal IntronA/Rebetol studies.

2. **Additional data with regard to the thyroid disorders and the need for monitoring of thyroid functions.**

Moreover, the applicant was requested to substantiate the impact of the use of the combination on the thyroid function. In response the applicant provided the results derived from a cohort of children followed by Pr Wirth a paediatrician in Germany.

The MAH recommendation for evaluation of thyroid abnormalities every 3 months seems appropriate. However, the assessment of thyroid function **prior to initiation** currently recommended for adults should also apply for children.
Further data on this issue should be available from the ongoing study in paediatric patients treated with the combination of Peginterferon-alpha 2b and ribavirin. The MAH is strongly encouraged to collect any informative data on thyroid disorder from the five-year follow-up study P01906.

3. **Post-marketing data**

The safety of interferon+Rebetol was only documented in a limited number of children. Interferon alfa-2b has been licensed in the US for the treatment of chronic hepatitis B in children at a higher dosage (6 MIU/m^2 TIW) than that applied for in the indication chronic hepatitis C (3 MIU/m^2 TIW). The CHMP requested all available post-marketing data on the safety of this dose in children to give a more complete picture of the safety profile of interferon. The MAH provided a report which summarized post-marketing surveillance data in patients ≤ 17 years of age with chronic hepatitis

treated with IntronA (with or without ribavirin). A total of 115 spontaneously reported cases were identified. The overall pattern of adverse events was consistent with either underlying disease or the known adverse effects of interferon alpha. No new safety concerns were identified upon review of these cases.

A total of 115 cases, of which 34 serious were presented. Among the serious cases reported, 14 were considered to be related to the treatment. Among these 14 cases, 3 did not appeared to be labelled (Kawasaki syndrome vs hypersensibility reaction, lymphoma, septic arthritis). Confounding factors are present in the three cases. Globally, no new safety concerned emerged from the data presented.
The company states that there was no apparent correlation between any reported adverse event and interferon dose. However, such a correlation seems to exist for granulopenia and is suggested for seizure and alopecia.
No estimation of the exposed population is provided. Consequently, the frequency of the adverse events reported cannot be assessed.
Six cases with a fatal outcome were reported. None was attributable to the treatment according to the company. All cases presented with risk factors and significant alternative aetiology. However, a contributory role of the drug can be totally excluded in two cases. The first one concerned a 16 y.o male with chronic atypical hepatitis B who discontinued treatment with INTRONA after 1 week because of decreasing WBC and platelets. No improvement was noticed after drug withdrawal and the patient was diagnosed with panmyelophtisis 19 days after cessation of therapy. He did not response to corrective therapy and died of a suspected pulmonary haemorrhage 4 months after cessation of interferon treatment. The second case involved an HIV-positive 12 y.o male with hepatitis B, tuberculosis and nephritic syndrome, who presented pancreatitis 12 days after starting IntronA. Interferon therapy was discontinued but the patient subsequently developed an important worsening of HIV and died about 7 weeks after stopping interferon.
Furthermore, 8 cases of psychiatric disorders, of which 3 serious, were reported. Among them, 2 cases of depression, of which 1 serious, were reported. One of the case is reported in a 9 y.o girl patient who has already experienced depression during a previous course of therapy with VIRAFERON. The two cases of attempted suicide, of which only 1 is serious, presented with confounding factors.

OVERALL DISCUSSION

With regard to non clinical data :

The MAH accepted to perform the requested juvenile animal study.

Overall, the non clinical investigation is proposed to consist of one Dose range-finding study and one Juvenile toxicity study to assess effects on growth, skeletal formation, and reproductive development and function.
The results of these studies will be available by the end of 2005.

With regard to clinical data

The CHMP agreed that although the PK data collected so far could be considered as reassuring the MAH is committed to further substantiate the comparability of exposures between both ribavirin formulations through the collection of samples from children enrolled in a planned phase Ib/III study with ribavirin and pegylated interferon,.

The clinical development performed by the MAH has mainly enrolled children **with mild to moderate hepatitis C**. However, up to known, in this population the current consensus recommended a "wait and see" attitude. Indeed, contrarily to adults hepatitis C is most often a mild disease with a slow and delayed fibrosis progression. Chronic infection in children is asymptomatic in most cases, with minimal histological lesions in the large majority of cases. No hepatocellular carcinoma (HCC) has been reported up to now in children with chronic HCV hepatitis. Such an attitude appears especially reasonable in the light of the safety profile of the ribavirin+interferon combination particularly worrying for the paediatric population (risk of suicidal attempt especially critical in adolescents, potential deleterious impact on growth). Nevertheless, it was admitted that the "wait and

see" strategy that prevailed up to now in children tends to be re-considered in the scientific community (AALSD Practice Guideline. Hepatology vol 39, n°34, 2004). Therefore, it was agreed that the use of ribavirin+interferon could be considered in children provided that the decision to treat was subsequent to a careful case by case basis assessment taking into account in particular, the disease status as evidenced by the virological, biochemical and histological features and carefully weighing the potential safety adverse effects associated with the ribavirin+interferon combination.
These considerations were to be translated into the indication.
Therefore the CHMP proposed the following text in section 4.1 Therapeutic indications.

Children and adolescents:
Rebetol is intended for use, in a combination regimen with interferon alfa-2b, for the treatment of children and adolescents 3 years of age and older, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for serum HCV-RNA.
The decision to treat should be made on a case by case basis, taking into account any evidence of disease progression such as hepatic inflammation and fibrosis, as well as prognostic factors for response, HCV genotype and viral load. The expected benefit of treatment should be weighed against the safety findings observed for paediatric subjects in the clinical trials (see sections 4.4, 4.8 and 5.1).
The MAH agreed.

The paediatric development programme with the pegylated interferon combined with ribavirin is ongoing.

It is anticipated, that the complete study data, including the complete pharmacokinetic analyses, will be available and provided by first quarter 2008.

Conversely to adults, the recent deletion of the strict contra-indication in case of existence of , or history of severe psychiatric condition (down-graded as a warning) was not considered appropriate at this stage for children (considering the particular concern about a higher rate of suicidal attempt/ideation (2.4% versus 1% in adults). This was to be re-considered later on in the light of the clinical experience to be accumulated in adults in this difficult-to-treat population. The CHMP proposed the following contraindication section 4.3
Children and adolescents: Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation, or suicide attempt. The MAH agreed.

The CHMP also requested long-term safety data**.**

The MAH proposed a five year follow-up of the patients treated in the ongoing pivotal IntronA/Rebetol studies in children (P00018 and P00321) and presented an interim assessment of the follow-up for children's growth and the occurrence of Serious Adverse Events to assess long-term disturbances, including those mentioned to be of interest by CHMP**.**
It is anticipated the complete study data for the long-term follow-up protocol will be available and provided to the CHMP in 2007.

The CHMP proposed the following text in Section 4.4 Special warnings and special precautions for user, considering that attention of prescribers should be warranted (specific warning) on a potential irreversible effect on growth in some patients.

Growth and Development*: During a 1-year course of therapy there was a decrease in the rate of linear growth (mean percentile decrease of 9 %) and a decrease in the rate of weight gain (mean percentile decrease of 13 %).. A general reversal of these trends was noted during the 6 months follow-up post treatment. However, based on interim data from a long-term follow-up study, 12 (14 %) of 84 children had a >15 percentile decrease in rate of linear growth, of whom 5 (6 %) children had a >30 percentile decrease despite being off treatment for more than 1 year. There are no data on long term effects on growth and development and on sexual maturation.*
The MAH agreed.

The MAH is committed to provide safety data from post-marketing experience and to complete the case reports by specific information allowing to appreciate the virological, biochemical, histological and clinical status of the children.
These information will be reported within the forthcoming PSURs.

The CHMP also requested additional safety data from Pr Wirth studies.
The CHMP requested that the information on the higher incidence of thyroid abnormalities (increase TSH) reported in paediatric population compared to the adult patients should be added in SmPC (Section 4.4 and 4.8).

In line with the CHMP request, the MAH has made a proposal in term of thyroid monitoring in Section 4.4 Special warnings and special precautions for user:
Supplemental monitoring specific for children and adolescents

...

Thyroid Monitoring: Approximately 12% of children treated with interferon alfa-2b and ribavirin developed increase in TSH during interferon alfa-2b treatment. Another 4% had a transient decrease below the lower limit of normal. Prior to initiation of IntronA therapy , TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. IntronA therapy may be initiated if TSH levels can be maintained in the normal range by medication. Thyroid dysfunction during treatment with interferon alfa-2b and ribavirin has been observed. If thyroid abnormalities are detected, the patient's thyroid status should be evaluated and treated as clinically appropriate. Paediatric patients should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).

The MAH's recommendation for evaluation of thyroid abnormalities every 3 months was appropriate for the CHMP.Overall, further data on thyroid disorder should be available from the ongoing study in paediatric patients treated with the combination of Peginterferon-alpha 2b and ribavirin. The MAH is strongly encouraged to collect any informative data on thyroid disorder from the five-year follow-up study P01906.

3.5 Overall conclusions, benefit/risk assessment and recommendation

Quality

No change has been made to the active substance already authorised for Rebetol 200 mg hard capsules (EU/1/99/107/01-03). The product is formulated, manufactured and controlled in a way that is characteristic for an oral solution. Batch analysis data indicate a consistent product from batch to batch. Some minor outstanding quality issues, which could be clarified on an ongoing basis, remained at the time of the opinion.

Clinical and pharmacology and toxicology

Benefit/risk assessment

The CHMP comes to a positive conclusion with regard to the combined use of ribavirin+interferon alpha 2b in children from 3 years with chronic hepatitis C.
However, the final wording of the proposed CHMP indication, was aimed at discouraging a wide use of this combination in children and to incite to a careful case by case balance of the benefit and risk before deciding to treat children.
This was especially critical since the safety profile of the combination was regarded as concerning in the target population (impact on growth, psychiatric adverse events including suicidal attempt and ideation).

The CHMP considers that a preclinical study was of critical importance to clearly and quickly better appreciate the potential overall impact of the ribavirin safety profile in children and, in particular, to assess the potential of ribavirin to affect growth and development. Also in ongoing and planned studies (especially the study with ribavirin and pegylated intereferon), the MAH should further substantiate the impact of ribavirin + interferon on growth and sexual development, psychiatric and behavioural reactions, endocrine functions.

Overall, the benefit/risk of the use of ribavirin+interferon in children from 3 years of age could be considered favourable, with a wording of indication discouraging a wide use of this combination of concerning safety profile and with post-approval commitments mainly aiming at further substantiating the potential impact of the safety profile of this treatment in children and closely following the use of this treatment in this new target population

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered that the benefit/risk ratio of Rebetol 40 mg/ml oral solution in the treatment of "Rebetol is intended for use, in a combination regimen with interferon alfa-2b, for the treatment of children and adolescents 3 years of age and older, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for serum HCV-RNA. The decision to treat should be made on a case by case basis, taking into account evidence of disease progression such as hepatic inflammation and fibrosis, as well as prognostic factors for response, HCV genotype and viral load. The expected benefit of treatment should be weighed against the safety findings observed for paediatric subjects in the clinical trials (See sections **4.4**, **4.8** and **5.1**).
Rebetol monotherapy must not be used.
There is no safety or efficacy information in children or adolescents on the use of Rebetol with pegylated or other forms of interferon (i.e., not alfa-2b)." was favourable and therefore recommended the granting of the marketing authorisation for this new pharmaceutical form.