CLINICAL REVIEW

Application Type: BLA
Submission Number : 103949
Submission Code: NA

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Reviewer Name: Julie-Ann Crewalk, MD
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Established Name: Peginterferon alfa-2b
(Proposed) Trade Name: PegIntron®
Therapeutic Class: Interferon - alfa
Applicant: Schering-Plough Research Institute

Priority Designation: P

Formulation: Single-use vial containing 50, 80, 120, or 150 μg per 0.5 mL vial (with 1.25 mL vial diluent) and
REDIPEN® 50, 80, 120, or 150 μg per 0.5 mL in single use syringe

Dosing Regimen: PegIntron 60μg/m^2/week subcutaneous injection plus REBETOL capsule or liquid 15mg/kg/day orally with food in two divided doses.

Indication: PegIntron is an antiviral indicated for chronic hepatitis C (CHC) in combination with REBETOL in patients (≥ 3 years) with compensated liver disease not previously treated with interferon alpha
Intended Population: Pediatric Ages 3 -17 years.

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The BLA for PegIntron® (pegylated interferon alfa 2b) (PEG2b) in combination with Rebetol® (ribavirin) for the treatment of chronic hepatitis C virus (HCV) infection in children 3 to 17 years of age should be approved. Schering-Plough Research Institute (the Applicant) submitted adequate data characterizing the efficacy and safety of PegIntron® in pediatric patients ages 3 – 17 years. This conclusion is reached following review of the application containing data from 107 pediatric patients aged 3 to 17 years with chronic hepatitis C infection treated with weekly subcutaneous injection of PegIntron® and twice per day oral dosing of Rebetol®. Subjects with genotype 2 and genotype 3 (if they had a baseline viral load less than 600,000IU/ml) received treatment for 24 weeks. All other subjects received 48 weeks of treatment. In children receiving body surface area (BSA)-adjusted dosing of PEG2b (60μg/m^2/wk), the estimate of exposure during treatment was calculated to be 58% higher than observed in adults receiving 1.5 μg/kg. The higher exposure of PEG2b did not result in an increase of adverse events when compared to the adult population.

Overall, the use of PEG2b plus ribavirin was shown to be efficacious in the pediatric population aged 3 – 17 years. The overall sustained virologic response (SVR) rate was 69/107 (64.5%) for all HCV genotypes. The SVR rates were 72.5% (29/40) in older subjects (12 to 17 years) and 61.2% (41/67) in younger subjects (3 to 11 years). The overall relapse rate was only 6.7%. The safety profile of PEG2b plus ribavirin was acceptable with fewer side effects when compared to the adult safety profile. There were no deaths or serious life threatening adverse events in this study. Growth inhibition and hypothyroidism were two notable adverse reactions in this current study which are being evaluated in an ongoing 5 year follow-up study. While these risks are significant, they represent less risk than the long term effects of untreated hepatitis C such as cirrhosis, hepatocellular carcinoma, and liver failure. This BLA does not include data on use of PEG2b in patients < 3 years of age.

1.2 Risk Benefit Assessment

There are many side effects noted with PEG2b in combination with ribavirin such as: anemia, neutropenia, pyrexia and influenza-like illnesses. However, these side effects were much less common in the pediatric population. Within the pediatric population, events such as hypothyroidism and growth abnormalities were more concerning, but overall they represent less risk than the long term effects of untreated hepatitis C such as cirrhosis and liver failure.

1.3 Recommendations for Postmarketing Risk Management Activities

The effects of growth and thyroid abnormalities seen in the current study must be evaluated over a longer duration to assess final outcome. The applicant's ongoing five year observational study

will evaluate these potential risks associated with use of the combination of PEG2b and ribavirin. The two primary objectives of this long-term follow-up study are to: Confirm the durability of the virologic response in pediatric subjects with chronic hepatitis C who were sustained responders at 24 weeks post-treatment of this current protocol (P02538), and to characterize the long-term safety in pediatric subjects who were treated with peginterferon alfa-2b plus ribavirin. Because the growth abnormalities are a new safety signal for PegIntron, the long-term safety data was requested in a new Post-marketing Requirement in the approval letter under FDAAA:

1. Complete the 5 year follow-up observational study of pediatric subjects enrolled in Part 2 of the pediatric study P02538, to assess long-term or delayed toxicity including the effect of PegIntron™ on height and weight and the durability of treatment response. Submit data for at least 50 pediatric subjects completing 5 year follow-up.

The timetable for completion of the 5 year follow-up study is:

Final Report Submission: March, 2014

1.4 Recommendations for other Post Marketing Study Commitments

There are no further post marketing study commitments required at this time.

2 Introduction and Regulatory Background

2.1 Introduction

Hepatitis C virus (HCV) infection affects approximately 170 million people worldwide resulting in chronic liver disease in both adults and children. HCV is also the leading cause of death from liver disease in the United States with approximately 3.2 million affected individuals nationwide. There is an estimated prevalence of HCV infection in the pediatric population of 0.1-0.2% translating to approximately 150,000 infected children. According to the Centers for Disease Control and Prevention (CDC) and the CDC's National Notifiable Disease Surveillance System (NNDSS), there was a peak incidence of HCV infection in the late 1980's, with a plateau since 2003 and a subsequent increase in 2006. This increase was more common among adult intravenous drug users. In 2006 rates of infection increased slightly in those aged 15 – 24 years (0.37 per 100,000). Cases reported among persons aged < 15 years are relatively uncommon. While vaccination has reduced rates of hepatitis B virus infection, there is no current vaccination for HCV.

Acute HCV infection tends to be subclinical in all age groups. In 2006, based on CDC surveillance, there were a total of 802 adult and pediatric reported HCV cases in the U.S. The pediatric data revealed that 50% of children < 5 years of age were hospitalized for HCV infection, and 66% of pediatric patients reported jaundice. Overall, the infection rates were lower for the pediatric population. Assessment of patients infected during childhood through

transfusion suggests approximately 40-55% of infected children will progress to chronic hepatitis C, compared with rates of up to 80-90% in adults.

A previous clinical study demonstrated comparability of pediatric pharmacokinetics of non-pegylated interferon alfa-2b and ribavirin to that reported in the adult population. Two pediatric open-label studies of hepatitis C virus infection assessed the safety and efficacy of INTRON A plus REBETOL. Overall, sustained virologic response (SVR) was achieved in 46% of subjects. In these subjects, 36% SVR was reported in subjects with Genotype 1 and 84% in subjects with Genotype 2 or 3. The pediatric response rates were comparable to published adult hepatitis C virus infection clinical trials for subjects receiving a comparable regimen.

PegIntron plus REBETOL use in children has not previously been evaluated in a clinical trial. In order to improve the chance for successful treatment in children, the current trial was conducted to determine whether the pegylated form of interferon alfa-2b in combination with ribavirin could increase the SVR rate, while still providing a safe and convenient dosing regimen

2.2 Product Information

Pegylated interferon alfa-2b (PegIntron) is a cytokine and an inducer of the antiviral immune response which in combination with ribavirin has been approved for treatment of adults with chronic hepatitis C virus infection. The current application provides data to support the extension of treatment in pediatric patients ages 3 - 17 years.

2.3 Availability of Proposed Active Ingredient in the United States

Currently approved therapy for adult patients includes peginterferon alfa-2b, given weekly plus weight-based ribavirin. Approved therapy for pediatric patients includes INTRON A® plus REBETOL®. PegIntron® plus REBETOL use in children has not been previously evaluated in a large clinical trial. Both PegIntron and REBETOL are commercially available in the U.S. and many other countries and are not in short supply.

2.4 Important Safety Issues with Consideration to Related Drugs

Flu-like symptoms and psychiatric symptoms (depression, anxiety) are known adverse events with interferon treatment. Pyrexia is a common adverse event in adults; therefore temperatures were part of the routine vital signs both before and after treatment in this pediatric study. Abnormal laboratory values possibly associated with treatment include: elevated liver function tests, elevated creatinine and hemolytic anemia (due to ribavirin). Neutropenia and thrombocytopenia were also seen in previous adult studies of interferons. Hypothyroidism is associated with interferon treatment although the mechanism is unclear. Adverse events related to interferons that may warrant special consideration in pediatrics include height and weight inhibition. While catch-up growth was observed off therapy, the degree interferon affects overall weight and, more specifically, height is not known.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

There are currently several treatments approved by the Food and Drug Administration (FDA) for the treatment of CHC in adults (7). However, only non-pegylated interferon alfa-2b and ribavirin is approved for the treatment of CHC in children. Of note, in adults and children, combination therapy is now the standard of care with interferon monotherapy indicated only for certain circumstances. The current protocol is only for combination therapy in children. The current study was acknowledged by the FDA on September 16, 2004 following multiple teleconferences to fulfill this post-marketing commitment.

Below is a listing of the previous therapeutic approvals of interferons for the indication of HCV in adults and children. Please refer to previous reviews for a complete description of all regulatory actions.

Intron-A and Rebetol (interferon alfa-2b + ribavirin) - approved in 2003 for pediatric patients 3-16 years of age

Roferon A + Ribavirin (interferon alfa-2a + ribavirin) - approved in 1996 for adults
Intron A + Rebetol (interferon alfa-2b + ribavirin) - approved in 1998 for adults
PegIntron + Rebetol (peginterferon alfa-2b + ribavirin) - approved in August 2001 for adults
PegIntron (peginterferon alfa 2b) Powder for SQ injection - approved in 2001 for adults
Pegasys + Copegus (peginterferon alfa-2a + ribavirin) - approved in 2002 for adults

2.6 Other Relevant Background Information

Not Applicable

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Overall, the submitted data appears to be of good quality and integrity. The data sets were easily accessed. On review of the submitted laboratory data, serum electrolytes and hematocrit appeared to not be included in the datasets. These values were, however, submitted in Section 16.2.8.2 of the submitted clinical study report. It is unclear as to why these values were not included in the datasets, however upon reviewing these missing laboratory values for each patient, there were only scattered abnormal values which did not persist beyond the treatment period. There were no serum bicarbonate values submitted.

3.2 Compliance with Good Clinical Practices

It appears that the clinical trial was conducted in compliance with Good Clinical Practices and in accordance with acceptable ethical standards.

3.3 Financial Disclosures

The 1.3.4 Financial Certification and Disclosure form and its attachments were reviewed. All investigators denied financial interests with the applicant.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (CMC)

Both PegIntron and REBETOL are approved FDA products. No new CMC information was supplied with this submitted supplement.

4.2 Clinical Microbiology

HCV has many genotypes that show a varied range in their response to PEG2b and ribavirin treatment. True viral resistance to interferons has not been reported for any of the different genotypes. See complete review by Dr. Narayana Battula.

4.3 Preclinical Pharmacology/Toxicology

No further Pharmacology/Toxicology information was included in this submission.

4.4 Clinical Pharmacology

See Section 4.4.3 and the complete Clinical Pharmacology review by Dr. Jenny Zheng.

4.4.1 Mechanism of Action

PEG-interferon alpha-2b is a cytokine and an inducer of the antiviral immune response. The pegylated form increases the half life and therefore the efficacy of interferon. The method of action consists of PEG-interferon alpha-2b utilizing the JAK-STAT signaling pathway. PEG-interferon alpha-2b will bind to interferon-alpha receptor 1 and 2 (IFNAR1/2). Upon binding, the Tyk2 protein associated with IFNAR1 is phosphorylated which in turn phosphorylates JAK1 associated with IFNAR2. The phosphorylated signal transducer and activator of transcription then dissociate from the receptor and join with p48 and IRF9 to form the interferon stimulate transcription factor-3 (ISGF3). This transcription factor then moves into the nucleus where it will transcribe several genes, one of which influences the immune response.

PEG-interferon alpha-2b acts as a multifunctional cytokine by transcribing several genes, including interleukin 4 (IL4). This cytokine is responsible for inducing T helper cells and ultimately results in the stimulation of B-cells to proliferate and increase their antibody production. Ultimately, this process results in reduction of HCV viremia.

4.4.2 Pharmacodynamics

No pharmacodynamic evaluations were submitted for this application.

4.4.3 Pharmacokinetics

The pharmacokinetics (PK) of PEG2b is described by a one-compartment model with first-order absorption and elimination. Following weekly subcutaneous (SC) doses of PEG2b at 60 μg/m^2, the mean population apparent clearance was 0.626 L/hr. Age was the most important covariate affecting apparent clearance and volume of distribution. According to the applicant, the inter-subject variation for clearance of PEG2b was 47%. The body surface area (BSA)-normalized apparent clearance of PEG2b is similar across the pediatric age groups (mean values ranging from 0.45 to 0.61 L/hr/m^2).

The PK of ribavirin is described by a two-compartment model with first-order absorption and elimination. Body weight was the most important covariate for clearance, distributional clearance, and volume of distribution. According to the applicant, the inter-subject variation for clearance of ribavirin was 25%. The body-weight–normalized apparent clearance of ribavirin is similar across the pediatric age groups (mean values ranging from 0.25 to 0.3 L/hr/kg) and adult subjects.

Of 107 pediatric subjects enrolled, 21 (20%) participated in the Pharmacokinetic Group and underwent intensive PK sampling on treatment weeks 1, 4, and 8. This group included 3 subjects aged 3 to 5 years, 12 subjects aged 6 to 11 years, and 6 subjects aged 12 to 17 years. The other 86 subjects were in the Profile Pharmacokinetic Group and underwent sparse PK sampling. All subjects underwent the same medication regimens and clinical monitoring as outlined in the protocol. Approved dosing was based on previous clinical results and not from the results of this PK study.

In children receiving BSA-adjusted dosing of PEG2b (60 μg/m^2/wk), the estimate of exposure during treatment was calculated to be 58% higher than observed in adults receiving 1.5 μg/kg. The PK of ribavirin (at 15 mg/kg/day) were similar to those reported in a prior study of ribavirin in combination with interferon alfa-2b in pediatric subjects and in adults subjects. The higher exposure of PEG2b did not result in an increase of adverse events when compared to the adult population.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

Only one study was submitted in the supplement. Table 5.1 summarizes the study design for the pediatric trial submitted by the sponsor, Schering-Plough Research Institute, a division of Schering Corporation, in BLA 103949/5171.

Table: 5.1: Synopsis of the Submitted Protocol

Title:	Assessment of the Safety and Efficacy, Tolerability, and Pharmacokinetics of Peginterferon Alfa-2b (SCH 54031; PEG2b) Plus Ribavirin (SCH 18908) in Pediatric Patients with Chronic Hepatic C (Protocol P02538)
Study Centers:	Multi-Centered with 22 US and Non-US Sites
Study Period:	March 11, 2005 – November 13 2007
Design:	Global, Multicentered, Open-Label Phase 3 / 1B study
Objective(s):	1) Assess the safety, efficacy, and tolerability of pegintron alfa-2b plus ribavirin in pediatric subjects with chronic hepatitis C (CHC) 2) Measure the multiple dose pharmacokinetics of PEG2b and ribavirin in pediatric subjects with CHC.
Population:	107 children aged 3 – 17 years (67 aged 3-11 years; 40 aged 12-17 years)
Diagnosis and Criteria for Inclusion	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-hepatitis C virus (HCV) or HCV-RNA for at least 6 months prior to screening, with a liver biopsy (historical or pre-treatment) showing evidence of fibrosis and/or inflammatory activity.
Regimen	PEG2b 60 μg/m2 by subcutaneous injection weekly, plus ribavirin 15 mg/kg/day orally in two divided doses. The maximum dose of ribavirin was not to exceed 1200 mg/day. Ribavirin was to be administered with food.
Duration	Subjects with HCV Genotypes 1, 4, 5, 6, or high-viral-load (≥600,000 IU/mL) Genotype 3 were to receive up to 48 weeks of treatment plus 24 weeks of follow-up. Subjects with HCV Genotype 2 or low-viral-load (<600,000 IU/mL) Genotype 3 were to receive 24 weeks of treatment plus 24 weeks of follow-up.
Criteria for Evaluation:	**Efficacy:** Efficacy was evaluated using measurements of plasma HCV-RNA. **Safety:** Safety and tolerability assessments included monitoring of adverse events (AEs) with particular interest in serious adverse events (SAEs); physical examinations; clinical laboratory tests; measurement of vital signs; and other assessment when clinically indicated. **Pharmacokinetics:** The population pharmacokinetics of PEG2b and ribavirin were evaluated with intensive and sparse pharmacokinetic sampling.
Statistical Methods:	The primary endpoints were the safety and efficacy of PEG2b and ribavirin. The primary efficacy variable was the proportion of subjects in each group that exhibited sustained virologic response (SVR), defined as undetectable plasma HCV-RNA at 24 weeks post-treatment. The proportion of sustained virologic responders was estimated using the normal approximation to the binomial, and 95% confidence intervals (CI) 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) and by HCV genotype. The multiple-dose pharmacokinetics of PEG2b and ribavirin, SVR, and normalization of ALT levels were summarized by age group. The proportions of subjects with SAEs, dose modification/ discontinuation due to AEs, World Health Organization (WHO) Grade 3 and 4 neutropenia, and Hgb <10 g/dL were summarized by age group. Mean height and weight percentiles and growth velocity percentiles were summarized over time

5.2 Review Strategy

The clinical information provided by the sponsor for this open labeled one arm study was reviewed. The submitted materials included the Study Overview, Clinical Study Report, Data Sets and Case Report Forms. In addition, this reviewer performed some independent analysis of the data using JMP statistical software. The proposed label was also reviewed and revisions were recommended based on the provided information.

5.3 Discussion of Individual Studies

Only one clinical trial for the use of Peg2b and ribavirin in children was submitted. Overall, this study was a global, multicenter, non-randomized, open-label Phase 3/IB study. For additional details of study design, see Section 5.1.

The objectives of the study were to 1) assess the safety, efficacy, and tolerability of pegintron alfa-2b plus ribavirin in pediatric subjects, ages 3 through 17 years, with chronic hepatitis C (CHC), and 2) measure the multiple dose pharmacokinetics of PEG2b and ribavirin in pediatric subjects with CHC. The study enrolled 107 subjects, 67 aged 3-11 years and 40 aged 12 -17 years. Of the total 107 enrolled, there were 21 who underwent intensive PK sampling, while the remaining 86 underwent routine or sparse PK sampling. Please refer to Section 6 and Section 7 for the Efficacy and Safety Review.

The protocol mandated 24 weeks of treatment for subjects infected with genotype 2 or genotype 3 with HCV-RNA < 600,000 IU/mL and 48 weeks of treatment for subjects infected with other genotypes (including genotype 3 with HCV-RNA > 600,000 IU/mL. These recommendations were based on accumulated evidence from adult clinical trials documenting better treatment outcomes for genotypes 2 and 3. The 24 and 48 week regimens based on genotype represent the approved treatment regimens for adults.

6 Review of Efficacy

Efficacy Summary:

The use of PegIntron® plus ribavirin was shown to be efficacious in the pediatric population aged 3 – 17 years as measured by SVR . The overall SVR rate was 69/107 (65%) for all HCV genotypes. There was no difference in SVR rates between the 3-11 year olds (61%) and the 12 – 17 year olds (73%). Pediatric subjects with HCV Genotype 1 and low baseline viral load (<600,000 IU/mL) had a higher SVR rate than those with high baseline viral load (72% vs. 29%, respectively). SVR in pediatric subjects infected with HCV Genotype 1 was lower (53%) compared with those infected with HCV Genotypes 2, 3 and 4 (93%, 93% and 80%, respectively). The overall relapse rate was 7%. Relapse occurred more often in female subjects with HCV Genotype 1. Eight subjects infected with Genotype 3 and high viral load at baseline were treated for 24 weeks instead of the protocol-defined 48 weeks (a protocol violation); all achieved SVR. There was a difference in SVR rates between treatment group with 26/27 (96%) obtaining SVR in the 24 week treatment group (genotypes 2 and some 3) and 44/80 (55%) obtaining SVR in the 48 week treatment group (genotypes 1, 4, and some 3). Possible confounders to the above data include: protocol violations in 21% of the population and the potential for spontaneous reduction of HCV viral load without treatment. There were 63 subjects who had a HCV viral load < 400 at follow-up week 4 and 70 patients at follow-up week 24.

Please refer to the Statistical Review by Dr. Lei Nie for a more detailed discussion of the efficacy results.

6.1 Indication

Pegylated interferon alfa-2b in combination with ribavirin is indicated for the treatment of chronic hepatitis C (CHC) in children 3 to 17 years of age with compensated liver disease and who have not received previous interferon treatment.

6.1.1 Methods

The primary endpoint was the proportion of subjects with a sustained virologic response (SVR), defined as undetectable plasma HCV-RNA (hepatitis C virus ribonucleic acid) at the end of 24 weeks following the end of treatment (EOT). The FDA Statisticians analyzed the SVR data submitted for each subject. Secondary endpoints included the multiple-dose pharmacokinetics of PEG2b and ribavirin. The PK data was analyzed by the FDA Clinical Pharmacologists.

6.1.2 Demographics

Sixty-three percent (67/107) of subjects were between 3 and 11 years old and 37% (40/107) were between 12 and 17 years old. Slightly more than half of those enrolled (52%) were female. The majority (89%, 95/107) of the subjects were white. The source of HCV exposure was vertical transmission in 70% (75/107) of the subjects; the proportion of subjects with transfusion-associated or parenteral source of exposure was 11% (12/107). Overall, 67% (72/107) were infected with HCV Genotype 1 and 54% had low viral load at baseline (plasma HCV-RNA <600,000 IU/mL). The proportion of subjects with high viral load (≥600,000 IU/mL) in this study (46%) was lower compared with similar adult studies, where 69% of subjects had a high viral load. Table 6.1.2a demonstrates the demographic characteristics of the enrolled subjects by treatment group.

Table 6.1.2a: Demographics of Enrolled Subjects by Age and Assigned Treatment Group

	Subjects Assigned 24 Week Treatment Group (Genotypes 2 and low VL 3) N = 27			**Subjects Assigned 48 Week Treatment Group (Genotypes 1,4, and high VL 3) N = 80**			**All Subjects N = 107**		
Age Group: (years)	**3-11** (n=13)	**12-17** (n = 14)	**All** (n= 27)	**3-11** (n=54)	**12-17** (n = 26)	**All** (n = 80)	**3-11** (N = 67)	**12-17** (N = 40)	**All** (N = 107)
Age (yr)[a]									
Mean	7.1	13.7	**10.5**	7.0	14.2	**9.4**	7.0	14.0	**9.7**
(SD)	(1.8)	(1.3)	**(3.7)**	(2.6)	(1.6)	**(4.1)**	(2.4)	(1.5)	**(4.0)**
Median	7.0	14.0	**12.0**	7.0	14.5	**9.0**	7.0	14.0	**9.0**
Range	4-9	12-16	**4-16**	3-11	12-17	**3-17**	3-11	12-17	**3-17**
Sex (%)									
Female	6 (46)	6 (43)	**12 (44)**	34 (63)	10 (38)	**44 (55)**	40 (60)	16 (40)	**56 (52)**
Male	7 (54)	8 (57)	**15 (56)**	20 (37)	16 (62)	**36 (45)**	27 (40)	24 (60)	**51 (48)**

	Subjects Assigned 24 Week Treatment Group (Genotypes 2 and low VL 3) N = 27			**Subjects Assigned 48 Week Treatment Group (Genotypes 1,4, and high VL 3) N = 80**			**All Subjects N = 107**		
Race									
White	12 (92)	11 (79)	**23 (85)**	48 (89)	24 (92)	**72 (90)**	60 (90)	35 (88)	**95 (89)**
Non-White	1 (8)	3 (21)	**4 (15)**	6 (11)	2 (8)	**8 (10)**	7 (10)	5 (13)	**12 (11)**
Asian	1 (8)	2 (14)	3 (11)	3 (6)	1 (4)	4 (5)	4 (6)	3 (8)	7 (7)
Black	0	0	0	0	0	1 (1)	1 (1)	0	1 (1)
Multiracial	0	1 (7)	1 (4)	1 (4)	1 (4)	3 (4)	2 (3)	2 (5)	4 (4)
Ethnicity (%)									
Hispanic	2 (15)	1 (7)	3 (11)	13 (24)	5 (19)	18 (23)	15 (22)	6 (15)	21 (20)
Not Hispanic	11 (85)	13 (93)	24 (89)	41 (76)	21 (81)	62 (78)	52 (78)	34 (85)	86 (80)
Body Weight (kg)[b]									
Mean	25.3	56.8	**41.6**	28.7	57.7	**38.1**	28.1	57.4	**39.0**
(SD)	(5.2)	(10.1)	**(17.9)**	(11.8)	(12.0)	**(18.0)**	(10.9)	(11.2)	**(18.0)**
Median	25.0	56.8	**34.0**	29.5	56.1	**34.9**	27.0	56.4	**34.7**
Range	15 – 34	34–73.4	**15-73.4**	13.5-58	37.4-87	**13.5-87**	13.5-58	34-87	**13.5-87**
Body Height (cm)[b]									
Mean	125.8	166.0	**146.6**	124.7	162.6	**137.0**	124.9	163.8	**139.5**
(SD)	(9.0)	(10.2)	**(22.5)**	(16.8)	(8.4)	**(23.0)**	(15.5)	(9.1)	**(23.2)**
Median	126.5	162.3	**144.4**	127.3	163.8	**139.4**	127.0	164.0	**139.5**
Range	102.5 – 137.4	144 – 178.5	**102.5 178.5**	95.3-163.5	144.5-179.8	**95.3 – 179.8**	95.3-163.5	144 – 179.8	**95.3 – 179.8**

Modified Table 6 from Clinical Study: Values are rounded up to nearest 10th. a: age at study entry; b: recorded at Screening Visit 2

MO Comment: The mean ages within each treatment group were similar to the median. In review of the submitted information by the sponsor, there were more children in the 6 - < 12 age range (85%) compared to the 3 - < 6 age range (15%). This may be due to easier recruitment of older children. The age disparity decreased only slightly in the 48 week treatment subgroup with 37% between 3 - < 6 years and 63% aged between 6 - < 12 years. The majority of patients were white (89%) and non-Hispanic (80%) which may limit the safety and efficacy profile generalizability to this population.

Baseline biopsies were available for 99% (106/107) of the subjects of which 82% had minimal fibrosis (F1). No subjects had documented cirrhosis. Most subjects had mild (44%) or moderate (30%) liver inflammation and 18% had severe inflammatory activity. The majority of subjects had no steatosis (71%) or mild >0 - ≤5% steatosis (22%). Four subjects had >5% - ≤32%

steatosis, and half of these subjects were infected with HCV Genotype 3, known to be associated with a higher degree of steatosis than other HCV genotypes.

Subjects weighing less than 47 kg received ribavirin oral solution; therefore, the younger children (3-11 years old) received oral solution (94%, 63/67), and most adolescents (12-17 years old) received capsules (78%, 31/40). Table 6.1.2b below shows the patient disease characteristics by age group.

Table 6.1.2b: Baseline Disease Characteristics

Characteristics	**3-11 year olds N = 67**	**12 -17 year olds N = 40**	**All Subjects N = 107**
Source of Exposure (%)			
Vertical	**52 (78)**	**23 (58)**	**75 (70)**
Sporadic	5 (7)	7 (18)	12 (11)
Transfusion	2 (3)	5 (13)	7 (7)
Parenteral	2 (3)	3 (8)	5 (5)
Years Since Exposure			
Mean (SD)	6.2 (2.5)	12.3 (4.1)	8.5 (4.2)
Median	7.0	13.0	8.0
Range	0.4 – 11.0	1.5 – 16.0	0.4 – 16.0
Missing	5	7	12
Genotype by RNA Viral load			
1 < 600,000 IU/ml	26 (39)	13 (33)	**39 (36)**
1 > 600,000 IU/ml	20 (30)	11 (28)	31 (29)
Missing	1 (1)	1 (3)	2 (2)
2 < 600,000 IU/ml	6 (9)	5 (13)	**11 (10)**
2 > 600,000 IU/ml	0	4 (10)	4 (4)
3 < 600,000 IU/ml	3 (4)	2 (5)	5 (5)
3 > 600,000 IU/ml	6 (9)	3 (8)	**9 (8)**
Missing	1 (1)	0	1 (1)
4 < 600,000 IU/ml	3 (4)	0	**3 (3)**
4 > 600,000 IU/ml	1 (1)	0	1 (1)
Missing	0	1 (3)	1 (1)
Metavir Fibrosis Score (%)			
F0 = None	9 (13)	04 (10)	13 (12)
F1 = Portal fibrosis w/o septa	**54 (81)**	**34 (85)**	**88 (82)**
F2 = Portal fibrosis w septa	1 (1)	1 (3)	2 (2)
F3 = Numerous Septa	1 (1)	0 (0)	1 (1)
F4 = Cirrhosis	0 (0)	0 (0)	0 (0)
Missing	2 (3)	1 (3)	3 (3)
Metavir Activity Score (%)			
None	3 (4)	3 (8)	6 (6)
Mild	**27 (40)**	**20 (50)**	**47 (44)**
Moderate	22 (33)	10 (25)	32 (30)
Severe	13 (19)	06 (15)	19 (18)
Missing	2 (3)	1 (3)	3 (3)
Liver Steatosis (%)			
0	**46 (69)**	**30 (75)**	**76 (71)**

> 0% - ≤ 5%	16 (24)	8 (20)	24 (22)
> 5% - ≤ 32%	3 (4)	1 (3)	4 (4)
Missing	2 (3)	1 (3)	3 (3)

Table 7 of the Clinical Study Report

MO Comment: The majority of children were infected through vertical transmission, with a higher percentage exposed in the lower age group which we would expect in a pediatric population. The majority of patients had Genotype 1 HCV (65%). Regardless of genotype, 58 patients (54%) had a low viral load, 45 patients (42%) had a high viral load and 4 (4%) patients had missing baseline data. Please refer to the Statistical Review with regards to sustained virological response (SVR) endpoint in association with degree of viral load.

6.1.3 Patient Disposition

One hundred seven subjects were enrolled at 22 sites. Of the 107 subjects, 27 were assigned to 24-week treatment and 80 subjects were assigned to the 48 week treatment group depending on their infecting genotype. All of the 27 24 week subjects completed the treatment and follow-up phases. In the 48 week treatment group only 51 of the 80 subjects (63.8%) completed the treatment phase and 79 (98.8%) completed the follow-up phase. The primary reason for discontinuation of study treatment was treatment failure. A subgroup of 21 subjects in the Pharmacokinetic Group underwent intensive PK sampling; this group included 3 subjects aged 3 to 5 years, 12 subjects aged 6 to 11 years, and 6 subjects aged 12 to 17 years. The other 86 subjects were in the Profile Pharmacokinetic Group that underwent sparse PK sampling. Table 6.1.3 shows the disposition by age and treatment group.

Table 6.1.3a: Subject Disposition by Treatment Group and Age

	Subjects Assigned 24 Week Treatment Group N = 27		**Subjects Assigned 48 Week Treatment Group N = 80**		**All Subjects**		
Age Group: (Years)	3-11	12-17	3-11	12-17	3-11	12-17	All
Treatment Phase							
Enrolled	13	14	54	26	67	40	107
Discontinued	0	0	19	10	19	10	29
Adverse Event	--	--	0	1	0	1	1
Treatment Failure	--	--	17	9	17	9	26
Subject did not Wish to Continue	--	--	2	0	2	0	2
Completed Treatment	13	14	35	16	48	30	78
Follow Up Phase							
Entered Follow Up	13	14	53	26	66	40	106
Completed Follow Up	13	14	53	26	66	40	106
Did Not Enter Follow Up	--	--	1	0	1	0	1

Table 4 from the Clinical Study Report

6.1.4 Analysis of Primary Endpoint(s)

The primary analysis included all subjects who were assigned a subject number. The primary endpoints were the safety and efficacy of PEG2b and ribavirin. The primary efficacy endpoint was the proportion of subjects with SVR, defined as undetectable plasma HCV-RNA at the end of 24 weeks following end of the treatment (EOT). SVR is the accepted efficacy endpoint for treatment trials of new HCV therapies. Previous adult studies demonstrated that almost all subjects who had undetectable HCV-RNA at follow-up week (FW) 12 attained SVR (remained HCV-RNA undetectable at FW 24). Therefore, the applicant performed a "carry forward" analysis, in which subjects who had undetectable HCV-RNA at follow-up week (FW) 12 and missing data at FW 24 were considered sustained responders.

6.1.5 Analysis of Secondary Endpoints(s)

The secondary analysis was to include all subjects who received at least one dose of study medication. All subjects who were assigned a subject number received at least one dose of study medication; therefore, the secondary efficacy analysis (All Treated population) was identical to the Intent-to-Treat population (ITT). Secondary endpoints included the multiple-dose pharmacokinetics of PEG2b and ribavirin.

6.1.6 Other Endpoints

There were no other endpoints addressed in this study.

6.1.7 Subpopulations

The pediatric population was further subdivided into children 3- 11 years of age (n = 67) and children 12-17 years of age (n = 40). Subjects were also subdivided based on their genotype and baseline viral load. (Please refer to Table: 6.1.2b)

MO Comment: Given the small sample size of this study, no major conclusions can be made from any differences found between the subpopulations.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

There was only one dose studied for PEG2b and ribavirin in the current protocol.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

When EOT response was achieved in patients, there was very little relapse in the pediatric population. Relapsers were defined as subjects who had undetectable HCV-RNA at the last treatment visit, but rebounded to detectable HCV-RNA at the last follow-up visit. According to the sponsor, the relapse rate in this study was 6.7%. A total of 75 subjects had undetectable HCV-RNA at the EOT; of these, 5 female subjects with Genotype 1 relapsed within 4 weeks of treatment discontinuation. Please refer to the Statistical Review for further information.

6.1.10 Additional Efficacy Issues/Analyses

No additional efficacy issues were addressed in the submission.

7 Review of Safety

Safety Summary

Overall, the safety profile of PEG2b plus ribavirin was acceptable with fewer side effects observed in pediatric subjects when compared to the adult safety profile. There were no deaths or serious life threatening adverse events in this study. Three patients (3%) experienced serious adverse events including: tachycardia with a concern for Wolff Parkinson White, an episode of syncope following carbon monoxide poisoning, and a bicycle accident. The first two occurred prior to the initiation of treatment therapy and were, therefore, not felt to be related to treatment. The last subject, who was on therapy, fell from his bike; the cause of which is unclear. Severe Adverse Events (AEs) were reported in 8% of subjects, the most common one being pyrexia.

The most common AEs (>25%) in pediatric subjects were similar to those associated with PEG2b plus ribavirin combination therapy in adults and previously reported in non-pegylated interferon alfa-2b/ribavirin pediatric trials. These AEs included pyrexia, headache, vomiting, neutropenia, fatigue, anorexia, abdominal pain, and injection site erythema. Most AEs were mild or moderate in severity. Twenty-eight percent of subjects reported psychiatric or behavioral reactions such as nervousness (8%), restlessness (3%) or aggression (3%). Psychiatric AEs were more common in the 3- 11 year old group. Depression occurred in only 2% of subjects, in contrast to the adult population in which depression was reported in approximately 31% of subjects or compared to pediatric subjects treated with nonpegylated interferon alfa-2b (13%). All of the psychiatric AEs were mild or moderate in severity and none necessitated PEG2b dose reduction or discontinuation.

Laboratory abnormalities such as anemia, neutropenia, and thrombocytopenia were less frequent than in the adult studies. Most of the changes in laboratory parameters associated with PEG2b plus ribavirin therapy were mild or moderate as classified by modified WHO criteria. Grade 3 or 4 decreases in neutrophil counts occurred in 16% of all subjects. One subject had Grade 3 thrombocytopenia, which resulted in the only discontinuation of study treatment attributed to an adverse event. Hematological abnormalities were more common in subjects 12 to 17 years old than in subjects 3 to 11 years old.

Clinical hypothyroidism was reported as an AE in 3 female subjects with an additional 2 female subjects having asymptomatic increases in TSH. All 5 subjects were treated with levothyroxine for hypothyroidism or elevated TSH, and three remained on levothyroxine at the end of the 24-week follow-up. Twenty-three percent of subjects had at least one abnormal TSH value during the study treatment or follow-up phases. Female subjects had a higher incidence (32%) of TSH

elevation compared with male subjects (14%). The younger age group had a higher tendency to develop elevated TSH earlier in treatment (by TW 24) than the older age group.

Overall, 25% of subjects had at least one AE that resulted in dose reduction. Anemia (7%), neutropenia (12%), and weight loss (10%) were the most common AEs that resulted in dose reductions. Dose reductions due to hematological AEs were more frequent in subjects 12 to 17 years old (30%) than in subjects 3 to 11 years old (9%). Two subjects discontinued treatment because of AEs. One was due to thrombocytopenia and the other due to personal choice; however there were multiple AEs which may have contributed to this decision.

The most notable pediatric-specific safety issue was related to growth; more specifically weight loss and growth inhibition. Weight loss was common during the treatment phase of the study; however, a catch-up weight gain did occur after the end of treatment. The mean last weight percentile for all subjects at the end of the follow-up was above the US national median (53%). The mean last height percentile for all subjects at the end of follow-up remained slightly below the median for the US population (44%). The long-term effect of PEG2b plus ribavirin treatment on growth and thyroid functioning will be further examined in the 5-year long-term follow-up phase of this study.

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

Only the submitted study: *Assessment of the Safety, Efficacy, Tolerability and Pharmacokinetics of Peginterferon Alfa-2b Plus Ribavirin in Pediatric Patients with Chronic Hepatitis C* was used to evaluate the safety of this combination drug regimen.

7.1.2 Adequacy of Data

Safety data from the 107 enrolled patients were reviewed. Safety data were reported for all subjects who received at least one dose of the study drug. The following variables were assessed: dose discontinuations and or modifications due to adverse events (AEs), serious adverse events (SAEs), common adverse events, World Health Organization (WHO) Grade 3/4 neutropenia, and hemoglobin values < 10g/dL. Safety assessments included monitoring AEs and SAEs; physical examinations including laboratory tests, adverse events, and measurement of vital signs including height and weight. The Medical Dictionary for Regulatory Activities (MedDRA), version 10.1 was used for AE coding.

There was some missing laboratory data in the submitted Case Report Forms (CRFs), the majority of laboratory information, except serum electrolytes and hematocrit, were found in the submitted datasets. The serum electrolytes and hematocrit were found in the appendices, but were not part of the datasets. Serum bicarbonate values were not submitted.

There were some protocol violations in this study. One subject (014044) was excluded from per-protocol efficacy because she did not meet inclusion criteria five which required a HCV-RNA result. The subject did complete 48 weeks of treatment and had undetectable HCV-RNA throughout the treatment and post-treatment follow-up periods. Subject 008103 was outside the protocol-specified window of 2 days between enrollment and the start of dosing. The initiation of study treatment was delayed because the subject had to undergo additional testing to rule out a potential cardiac problem. Subject 024019 did not have their HCV RNA laboratory testing done at Schering-Plough Research Institute (the main lab for HCV-RNA quantitative polymerase chain reaction (HCV-RNA/qPCR) testing, and HCV genotyping,) but rather at another laboratory. Of note this subject had undetectable HCV RNA from TW 4 – FW 12, but had detectable levels at FW 24 and was considered a relapser. This subject was enrolled into the 5 year follow-up study and the HCV RNA was again undetectable at the Year 1 visit. A back-up sample from FW 24 was re-tested and there was no HCV RNA detected indicating a sustained response. None of the mentioned subjects were excluded from the safety analysis.

7.1.3 Pooling Data across Studies to Estimate and Compare Incidence

There was no pooling of data as this review is based on only one submitted study.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The study was designed to allow discontinuation of treatment if there was a poor response at Treatment Week (TW) 12 or 24. Rules for discontinuation were based on the adult treatment guidelines for Chronic Hepatitis C (CHC): Subjects with Genotypes 1, 4, or 3 (with high viral load $\geq$ 600,000 IU/mL) whose HCV-RNA viral load had dropped < 2 $\log_{10}$ and remained detectable compared to their baseline value, were to discontinue therapy at TW 18 or TW 30. Of those assigned to the 48 Week Treatment group, 35 (64%) completed treatment and 16 (33%) discontinued due to poor response. One subject discontinued due to a laboratory adverse event. See Table 6.1.3 for the enrollment disposition of the patients. Table 7.2.1 below shows the duration of treatment by assigned treatment week.

Table 7.2.1: Duration of Treatment by Assigned Protocol Treatment

Duration of Treatment	**24 Week Treatment N = 27**	**48 Week Treatment N = 80**	**All n= 107**
Mean	168.7 days	273.2 days	246.8 days
SD	3.7 days	92.6 days	92 days
Range	159 – 180 days	106 – 344 days	106 – 344 days

Modified Table 19 from Clinical Study

MO Comment: All subjects assigned to the 24 week group completed follow-up and there were no discontinuations. See Section 7.3.3 for further evaluation of the subjects who discontinued.

7.2.2 Explorations for Dose Response

Two previous interferon alfa-2b plus ribavirin studies conducted by the applicant identified 15 mg/kg/day as the optimal ribavirin dose for use in children; the dose selected for the current study. Two ribavirin dose formulations were used: capsules (200 mg) and oral solution (40 mg/mL). The dose of PEG2b used for this clinical study was 60 μg/m2 administered weekly. According to the sponsor, this dose is approximately equivalent to the dose licensed for adults (1.5 μg/kg weekly), based on calculated conversion to BSA.

7.2.3 Special Animal and/or In Vitro Testing

There was no special animal or in vitro testing included in this study.

7.2.4 Routine Clinical Testing

Safety was evaluated by routine clinical testing including physical examination, vital signs, measurements of growth, and routine labs. Screening Visit 1 included: medical and hepatic disease history, vital signs, height and weight, liver biopsy and labs (hematology, nonfasting chemistry panel, pregnancy test, and HCV viral load and genotype). Screening Visit 2 involved a physical exam, vital signs with the same growth parameters including a BSA. If there were no historical data for chest x-ray, EKG, and ocular exam within 6 months of this screening date, then this was also completed at the second screening visit. The second screening visit also included repeat labs including hematology, a 12 hour fasting chemistry panel, pregnancy test, TSH, and ANA. Given the teratogenicity of ribavirin, confirmation of adequate birth control was obtained at both screening visits. A history of concomitant medications and adverse events was also elicited at each screening visit.

Laboratory values that were not submitted in the data sets include hematocrit, and serum electrolytes (sodium, potassium, chlorine, bicarbonate). They were all, except serum bicarbonate, located within the appendices of the clinical study and reviewed for any consistent abnormalities.

7.2.5 Metabolic, Clearance, and Interaction Workup

Renal elimination accounts for approximately 30% of peginterferon clearance and therefore a dose decrease in patients with moderate or severe renal failure is recommended. The mean PegIntron elimination half-life is roughly 40 hours.

Previous adult studies showed that PegIntron resulted in a 28% mean increase in CYP2C8/9 (warfarin, phenytoin) activity and a 66% mean increase in CYP2D6 (flecainide) activity.

Caution should be used when using these medications. Other interactions (in adults) include a 16% increase in mean AUC in methadone after 4 weeks of PegIntron dosing.

Ribavirin, has been shown to decrease the phosphorylation of pyrimidine nucleoside analogs such as stavudine, lamivudine, and zidovudine in in-vitro studies. Potential toxicities of these medications should therefore be monitored.

Please refer to the Clinical Pharmacology Review for further information.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The sponsor attempted to detect adverse events throughout the study by asking questions at each follow up visit during and after treatment. Flu-like symptoms and psychiatric symptoms (depression, anxiousness), for example, are known adverse events with interferon treatment. Pyrexia is a common adverse event in adults; therefore, temperatures were part of the routine vital signs both before and after treatment in this pediatric study. Hepatotoxicity and nephrotoxicity were monitored by laboratory values of liver function tests, and BUN/creatinine levels. Anemia, a common adverse event due to ribavirin, was assessed by hemoglobin values during routine laboratory draws. Neutropenia and thrombocytopenia were also assessed by the routine CBC and differential cell counts. PEG2b and ribavirin are not known to have an effect on QT prolongation.

Vital sign and laboratory measurements that warrant special consideration include: height and weight parameters and TSH levels to evaluate for hypothyroidism. Height and weight were recorded at screening visits and at each follow up visit during and after treatment because growth delay or arrest has been reported with interferons. While catch-up growth was observed off therapy in earlier studies, it is not known to what degree interferon affects overall weight and more specifically height. Hypothyroidism is associated with interferon treatment. TSH values were therefore obtained at regular intervals to assess for this adverse event. A five year study was also implemented to evaluate the long term effects of growth and hypothyroidism.

7.3 Major Safety Results

All safety assessments were based on data from all 107 enrolled subjects. All 27 subjects who were assigned to 24 weeks of treatment 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; 26/29 discontinued due to poor response to the treatment. Only one subject discontinued due to an AE. The overall safety profile of the PEG2b plus ribavirin observed in this pediatric study is consistent with that observed in previous adult clinical studies and also in the pediatric population treated with non-pegylated interferon alfa-2b plus ribavirin.

7.3.1 Deaths

There were no deaths during this study.

7.3.2 Nonfatal Serious Adverse Events

There were no life-threatening adverse events reported. Three percent of the subjects in the 12 to 17 years of age group reported Serious Adverse Events (SAEs). These events were considered by the Investigators to be unlikely related to study drugs. The summary of the SAEs are as follows:

Subject 008103 was a 12 year old white, non-Hispanic female who had an EKG done for intermittent palpitations on Study Screen 2 (6/26/06). The EKG showed possible Wolff Parkinson White Syndrome (WPW). Follow up electrophysiology testing did not confirm this diagnosis and she was permitted into the study. Her first dose of the study medications occurred on 09/07/06 after the SAE was reported and resolved. There were no further episodes or concern for WPW. The SAE was not thought to be related to the study medication because it occurred before study medications were implemented.

Subject 024019 was a 13 year old male treated for 1) carbon monoxide poisoning on (b) (6) following an episode of 2) syncope. The SAE occurred prior to the initiation of study medications. The symptoms resolved with oxygen treatment. Again, this was not thought to be related to study medication because the SAE occurred prior to the administration of ribavirin and PEG2b.

Subject 001028 was a 12 year old white, non-Hispanic male who fell off of his bicycle on (b) (6) and was hospitalized overnight for observation with a temporary interruption of ribavirin dosing. No reported history provided a reason for the fall. The fall was considered to be unlikely due to the study medications.

MO Comment: The first two subjects who suffered from palpitations and syncope, respectively, clearly did not experience these events as a result of drug use given the onset was before study medications were implemented. O**n further evaluation of other adverse events from this patient, patient 001028, was noted to have complaints of dizziness (9/23 – 11/27) and nausea (9/23 - 2/10) which occurred during the same time frame as the reported SAE. These events were given mild to moderate severities respectively, with possible association to the medication. It is possible that the fall from the bicycle may have come from dizziness or even from the nausea, which indirectly may be attributable to the study medication, but this explanation is speculative.**

7.3.3 Dropouts and/or Discontinuations

Twenty-nine patients discontinued the study medication. Twenty six (90%) of those subjects discontinued due to treatment failure. Two (6.9%) subjects discontinued for personal reasons not

related to therapy, and one discontinued due to an adverse event. The two patients who discontinued therapy for personal reasons include:

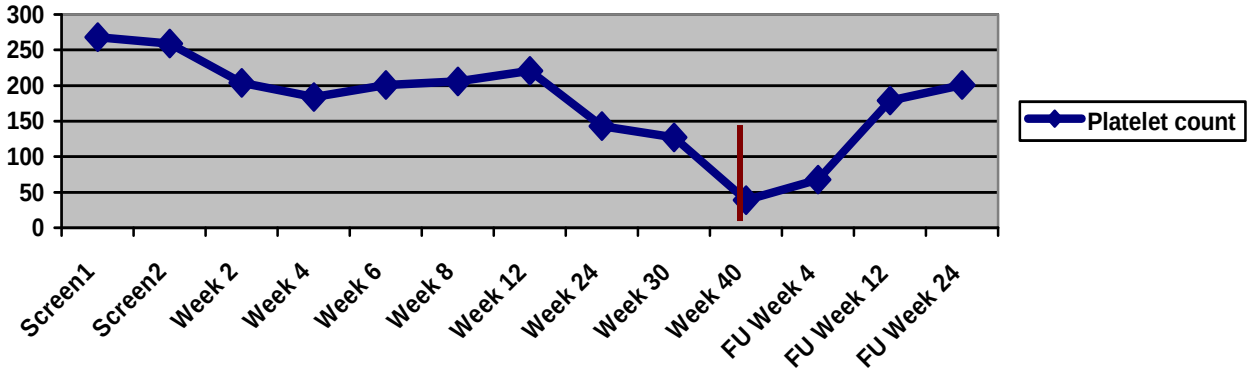
Subject 001023 was a 10 year old male who discontinued therapy approximately 6 months after it was initiated. Review of his adverse events, revealed two episodes of fever each lasting one day and 34 continuous days of dry skin which resolved 1-3 months prior to his study discontinuation.

Subject 008006 was a 7 year old female who received almost one year of therapy before discontinuing therapy. This patient, however, had many ongoing adverse events such as fatigue, generalized body aches, joint pain, fevers, emesis and chills before and after discontinuation of the study medications.

MO Comment: It is difficult to ascertain why patient 008006 discontinued the study. The lengthy list of reported adverse events may have contributed to her decision to withdraw. It may therefore be more accurate to include this subject as someone who discontinued due to an adverse event. This would bring the total of subjects who discontinued due to an adverse event to 1.9%. This change should be reflected in the label.

Subject 027401 discontinued the study due to an adverse event of thrombocytopenia. This patient was a 15 year old male with reported Grade 3 thrombocytopenia (Range 25 - < 50) lasting from 7/11 – 7/14. The study medications were discontinued on 7/14 with subsequent improvement during follow up. Other concomitant medications included ibuprofen for flu-like symptoms. Figure 7.3.3 shows a time line of the thrombocytopenia. Each value represents the lowest platelet value for that collection visit and the red vertical bar represents the time the study medications were discontinued.

Figure 7.3.3: Platelet Count (x 10^3/L) at Each Study Visit



MO Comment: Treatment with PEG2b plus ribavirin is known to have effects on white blood cells (WBC), red blood cells (RBC), and platelets. PEG2b monotherapy is known to cause thrombocytopenia in adults and ribavirin is known to potentiate this affect. This decrease in platelets was likely a result of the study medication. A causative relationship is substantiated by the lack of concomitant medications which might have caused this decrease and the normalization of the platelet count after discontinuation of the medications.

7.3.4 Dose Modification or Interruptions due to Adverse Events

There were 27 (25%) subjects who modified their doses of PEG2b or ribavirin due to an AE. The most common adverse events that led to dose modifications included: anemia (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) compared to the 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. Anemia (hemoglobin <10 g/dL) and weight loss were the most common AEs that led to ribavirin dose modifications. The dose-modification rate in this study was very similar to that observed in pediatric non-pegylated 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. This study also demonstrated that fewer pediatric subjects needed dose modifications compared with adults in clinical trials in which 42% (217/511) of adult subjects receiving PEG2b and ribavirin had dose reductions, and 14% (74/511) were discontinued due to AE.

MO Comment: The applicant attributed the weight loss in children to the ribavirin, although interferon is a known cause of anorexia and weight loss. It is unlikely that the weight loss was a result of ribavirin alone, especially given the overall growth abnormalities seen in the pediatric population attributed to PEG2b.

7.3.5 Significant Adverse Events

Severe AEs were reported in 9 subjects (8%): seven subjects were in the 3 to 11 year old age group, and two subjects were in the 12 to 17 years old age group. The most common severe AE was pyrexia reported in four subjects (4%). Other less frequent severe AEs included injection site pain, ALT increased, pain in extremity, headache, and neutropenia. No subjects had life-threatening AEs. Table 7.3.5 shows the reported severe AEs by the subjects' age.

Table 7.3.5: Severe Adverse Events by Age Group

SAE	Subjects 3- 11 Years N = 67 (%)	Subjects 12 -17 Years N = 40 (%)	All Subjects Enrolled N = 107……%
Total Subjects Reporting Severe AE	**7 (10)**	**2 (05)**	**9 (08)**
Pyrexia	3 (04)	1 (03)	4
Injection Site Pain	1 (01)	0 -	1
ALT Increase	1 (01)	0 -	1

Pain in Extremity	1	(01)	0	-	1
Headache	1	(01)	0	-	1
Neutropenia	0		1	(03)	1

Table 22 from Clinical Study Report

MO Comment: The ALT increase was transient and had normalized by TW 24. The above mentioned severe AEs were managed through concomitant medications or they resolved spontaneously.

7.3.6 Submission Specific Primary Safety Concerns

Specific primary safety concerns include psychiatric, metabolic effects (more specifically thyroid abnormalities), and decreases in height and growth.

Psychiatric

Psychiatric disorders are clinically important AEs associated with interferons. The sponsor attempted to detect psychiatric adverse events throughout the study by asking questions at each visit during and after treatment. Of the subjects enrolled 28% (30/107) had at least one AE that was categorized under the system/organ class of *Psychiatric Disorders*. Psychiatric disorders were less frequent in subjects 12 to 17 years old (18%, 7/40) compared with subjects 3 to 11 years old (34%, 23/67). In the 3- to 11-year-old group, the most frequently reported psychiatric AEs were nervousness (13%, 9/67), aggression (4%, 3/67), restlessness (4%, 3/67), and affect lability, mood alteration, agitation, anxiety, depression, and insomnia (3%, 2/67 each). Overall, the depression rate (2%, 2/107) was notably lower than reported in adults (31%, 160/511) or in pediatric subjects treated with non-pegylated interferon alfa-2b (13%). All AEs within the psychiatric disorder category were deemed mild or moderate in severity, and no subjects were discontinued or had dose modifications because of psychiatric AEs. A total of five subjects received treatment for adverse events within this category of disorders. One subject received diphenhydramine for insomnia. One subject received lorazepam for the treatment of anxiety, and three subjects received ibuprofen for a variety of symptoms including, but not limited to: affect lability, and insomnia, and irritability No patients received antidepressants.

MO Comment: Overall, the eliciting of psychiatric events appears subjective based on the parent's interpretation, especially in the younger aged children. The pediatric study shows a more favorable profile of adverse events. The increase in psychiatric events in the younger age population of 3 -11 year olds compared to 12 – 17 year olds may be due to the decrease ability of the younger patients to communicate as well verbally which may lead to "acting out" more often than the 12 – 17 year old patients.

Metabolic

Adverse events involving endocrine function, in particular hypothyroidism and hyperglycemia, are associated with interferon therapy. While elevated glucose levels were documented, no cases of diabetes were identified. During this trial, three clinical hypothyroidism events were reported in female subjects. Five female subjects received levothyroxine treatment for hypothyroidism or asymptomatic elevated TSH. Three subjects stayed on levothyroxine at the end of the 24-week

follow-up. No subjects discontinued or had dose modification because of hypothyroidism or abnormal TSH. Subjects are being followed for thyroid problems for an additional 5 years in the long-term follow-up study. More information on TSH and glucose levels will be discussed below in Section: 7.4.2 Laboratory Findings

Growth

Impaired growth caused by interferon treatment is a problem of special importance in the pediatric population. While a catch up growth was seen in both height and weight after treatment termination, it is unclear when or if the catch up growth will be sufficient in the pediatric population. The long-term impact on the subjects' growth will be evaluated further in the 5 year long-term follow-up phase of this study. See Section 7.4.3 for more information regarding this risk factor.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

A total of 2855 adverse events were reported by the 107 subjects, an average of 27 adverse events per patient (range: 1-132). Only three of these adverse events were considered serious AEs with an additional 9 adverse events considered severe. The most common adverse events were pyrexia (80%), headache (66%), emesis (34%), neutropenia (33%), fatigue (30%) and anorexia (29%). The adverse event profile is similar to the adult adverse event profile; however overall, children had fewer adverse events. Table 7.4.1 compares the adverse events between the current pediatric study and previous adult studies.

Table 7.4.1: Adverse Events Occurring in > 5 % of Patients

Adverse Event	**ADULTS ≥ 18 Years PegIntron Rebetol N = 511 n (%)**	**PEDIATRIC (3- 11 Years) PegIntron Rebetol N = 67 n (%)**	**PEDIATRIC (12- 17 Years) PegIntron Rebetol N = 40 n (%)**
Application Site			
Injection Site Inflammation	383 (75)	21[a] (31)	15[a] (38)
Body as a Whole			
Influenza Like Illness	---	4 (6)	6 (15)
Fatigue / Asthenia	337 (66)	33 (49)	15 (38)
Rigors	245 (48)	18 (27)	5 (13)
Fever	**235 (46)**	**60 (90)**	**26 (65)**
Weight Decrease	148 (29)	14 (21)	6 (15)
Malaise	20 (4)	06 (9)	4 (10)
Central Nervous System			
Dizziness	107 (21)	09 (13)	06 (15)
Headache	317 (62)	46 (69)	25 (63)
Endocrine			
Hypothyroidism	26 (05)	7[b] (10)	2[b] (5)
Gastrointestinal			

Nausea	220 (43)	14 (21)	8 (20)
Anorexia	164 (32)	43[c] (64)	12[c] (30)
Diarrhea	112(22)	10 (15)	6 (15)
Vomiting	72 (14)	33 (49)	3 (08)
Abdominal Pain	66 (13)	31[d] (46)	16[d] (40)
Hematological Disorders			
Neutropenia	133 (26)	16 (24)	19 (48)
Anemia	61 (12)	4 (6)	8 (20)
Leukopenia	31 (06)	7 (10)	4 (20)
Thrombocytopenia	26 (05)	1 (1)	2 (5)
Musculoskeletal			
Myalgia	286 (56)	15 (22)	5 (13)
Arthralgia	174 (34)	14 (21)	4 (10)
Pain in Extremity	--	8 (12)	3 (8)
Psychiatric			
Insomnia	204 (40)	2 (3)	1 (3)
Depression	158 (31)	2 (3)	0
Anxiety / Emotional lability / Irritability	240 (47)	11 (16)	5 (13)
Agitation	41 (8)	2 (3)	2 (5)
Nervousness	31 (6)	9 (13)	0
Respiratory System			
Dyspnea	133 (26)	--	--
Coughing	118 (23)	20 (30)	4 (10)
Pharyngitis	61 (12)	9[e] (13)	3[e] (8)
Pharyngolaryngeal pain	--	10 (15)	5 (13)
Sinusitis	31 (6)	1 (1)	2 (5)
Skin and Appendages			
Alopecia	184 (36)	13 (19)	6 (15)
Pruritus / Injection site	148 (29)	5 (7)	0
Rash	123 (24)	5 (7)	3 (8)
Dry Skin	123 (24)	12 (18)	3 (8)
Eczema	---	8 (12)	1 (3)
Vision Disorders			
Eye Pain	--	5 (7)	1 (3)
Blurred Vision	26 (05)		
Conjunctivitis	20 (04)		

Modified Table 20 from Clinical Study and PegIntron label for Adult Adverse reactions in > 5 %
a: combined injection site erythema and pain; b: includes increase TSH; c: includes: anorexia and decreased appetite;
d: includes abdominal pain upper and stomach discomfort; e: includes streptococcal pharyngitis
----: Missing value

MO Comment: Pyrexia was more common in the pediatric population compared with the adult population. Events such as headaches, hypothyroidism and GI associated AEs had a similar incidence between both age groups.

7.4.2 Laboratory Findings

Most of the observed laboratory findings were mild to moderate (Grade 1 -2) according to the modified WHO criteria (see Table 7.4.2a). Grade 3 decreases in neutrophil count occurred in

13% (14/107) of all subjects: 9% (6/67) of subjects 3 to 11 years old and 20% (8/40) of subjects 12 to 17 years old. Grade 4 decreases in neutrophil count occurred in 3% (3/107) of subjects and only in the 12- to 17-year-old group. One patient had Grade 3 thrombocytopenia in the 12- to 17-year-old group, which resulted in the only discontinuation of study treatment due to an AE, and 3 subjects (3%) had Grade 3 elevation in their alanine aminotransferase (ALT). Table 7.4.2a from the Clinical Study shows the breakdown of laboratory abnormalities by age group and according to modified WHO criteria.

MO Comment: On review of the serum electrolytes and hematocrit, no major abnormalities were identified. Decreases in hematocrit were often associated with decreases in hemoglobin. Very few subjects had decreases in hematocrit alone and if decreases occurred, they were transient. Very few abnormalities in sodium or potassium levels occurred and were sporadic and self resolving when they did occur. Creatinine levels were normal in the majority of patients. Potential serum bicarbonate abnormalities related to PEG2b and ribavirin use cannot be assessed. In previous studies, abnormal bicarbonate levels were not identified. A literature search resulted in findings of an adult with a low bicarbonate requiring supplementation. However, this male was also on concomitant anti-viral medications for HIV which are known to cause this abnormality.

Table 7.4.2a Laboratory Values by Age Group

Laboratory Value [a,b]	**Subjects 3-11 Years (n = 67)**		**Subjects 12 -17 Years (n = 40)**		**All Subjects (n = 107)**	
	n	(%)	n	(%)	n	(%)
Hemoglobin (g/dL)						
≥ 11.0 (Grade 0)	48	(72)	25	(63)	73	(68)
9.5 - < 11.0 (Grade 1)	19	(28)	13	(33)	32	(30)
8.0 - < 9.5 (Grade 2)	0		2	(5)	2	(2)
6.5 – 7.9 (Grade 3)	0		0		0	
< 6.5 (Grade 4)	0		0		0	
WBC (x 10^9/L)						
> 2.9 (Grade 0)	46	(69)	16	(40)	62	(58)
2.0 – 2.9 (Grade 1)	20	(30)	22	(55)	42	(39)
1.5 - < 2.0 (Grade 2)	1	(1)	2	(5)	3	(3)
1 – 1.4 (Grade 3)	0		0		0	
< 1.0 (Grade 4)	0		0		0	
Laboratory Value [a,b]	**Subjects 3-11 Years (n = 67)**		**Subjects 12 -17 Years (n = 40)**		**All Subjects (n = 107)**	
	n	(%)	n	(%)	n	(%)
Platelets (x 10^9/L)						
> 100 (Grade 0)	67	(100)	38	(95)	105	(98)
70 – 100 (Grade 1)	0		1	(3)	1	(1)
50 - < 70 (Grade 2)	0		0		0	
25 - < 50 (Grade 3)	0		**1**	**(3)**	**1**	**(1)**
< 25 (Grade 4)	0		0		0	
Neutrophils (x 10^9/L)						
> 1.5 (Grade 0)	20	(30)	5	(13)	25	(23)

1.0 – 1.5 (Grade 1)	22	(33)	15	(38)	37	(35)
0.75 - < 1.0 (Grade 2)	19	(28)	9	(23)	28	(26)
0.5 - < 0.75 (Grade 3)	**6**	**(9)**	**8**	**(20)**	**14**	**(13)**
< 0.5 (Grade 4)	0		**3**	**(8)**	**3**	**(3)**
AST (U/L)						
< 2 x Baseline (Grade 0)	59	(88)	37	(93)	96	(90)
2 x Baseline (Grade 1)	1	(01)	2	(5)	3	(3)
2.1 – 5 x Baseline (Grade 2)	7	(10)	1	(3)	8	(7)
5.1 – 10 x Baseline (Grade 3)	0		0		0	
> 10 x ULN (Grade 4)	0		0		0	
ALT (U/L)						
< 2 x Baseline (Grade 0)	60	(90)	38	(95)	98	(92)
2 x Baseline (Grade 1)	0		1	(3)	1	(1)
2.1 – 5 x Baseline (Grade 2)	5	(7)	0		5	(5)
5.1 – 10 x Baseline (Grade 3)	**2**	**(3)**	**1**	**(3)**	**3**	**(3)**
> 10 x ULN (Grade 4)	0		0		0	

Table 12 from Clinical Study
a: Modified WHO Criteria: Grade 1 = Mild; Grade 2= Moderate; Grade 3 = Severe; Grade 4 = Life Threatening
b: Summary of worst category observed within that period per subject per laboratory test..

Hematology

Treatment with PEG2b plus ribavirin can affect the white blood cells (WBC), red blood cells (RBC), and platelets. PEG2b monotherapy can decrease neutrophil and platelet counts. Ribavirin can cause hemolytic anemia and may elicit a reactive thrombopoiesis. Overall, no subjects had Grade 3 or 4 anemia. Fourteen subjects (13%) had Grade 3 neutropenia and 3 subjects (3%) had Grade 4 neutropenia.

The events of anemia in this study were managed through dose reductions. There was a larger mean change from baseline hemoglobin observed in the 12 -1 7 year old patients (- 2.57 g/dL) compared to the 3 -11 year old patients (-1.94 g/dL). No subjects received erythropoietin, required a blood transfusion, or discontinued treatment because of anemia. Because of hemolytic anemia associated with ribavirin, elevations in uric acid and bilirubin were assessed and were noted starting at TW 2. Two subjects (3%) in the group 3-11 years old and 6 subjects (15%) in the group 12-17 years old had grade 1 hyperbilirubinemia. No subjects discontinued treatment or had their dose reduced because of hyperbilirubinemia.

Absolute neutrophil counts (ANC) declined with the initiation of treatment, followed by a plateau as early as TW 2 that was maintained to the end of treatment. Subjects aged 12 to 17 years had slightly lower baseline levels of neutrophils, and consequently nadir values were slightly lower in the older group. Leukocyte counts, including neutrophils, returned toward baseline levels after therapy discontinuation. According to protocol requirements, PEG2b was reduced if the neutrophil count decreased to $<0.75 \times 10^9$/L. Fourteen subjects (9% of those aged 3 to 11 years and 20% of those aged 12 to 17 years) met these criteria for dose modification. Only 11 of them, however, received reduced doses. Of the 3 subjects remaining, 2 continued treatment on full doses of PEG2b, because repeat testing showed improved neutrophil counts

above 1.0 x10^9/L. One subject had a low neutrophil count at an early discontinuation visit. In addition, 3% (3/107), in the 12 – 17 year age group, had Grade 4 neutropenia and met the criteria for dose discontinuation. All 3 subjects (Subjects 002104, 021024, and 027041) were retested and had a subsequent result above the discontinuation level. None of these subjects were therefore discontinued due to neutropenia, and they were managed only with PEG2b dose reduction. The Table 7.4.2b below demonstrates the percentage of subjects with a low neutrophil count.

Table 7.4.2b Number (%) of Subjects Who Had a Neutrophil Count Less Than 0.75 x 10^9/L

Absolute Neutrophil Count	Number (%) of Subjects[a]					
	Subjects Aged 3 - 11 n=67		Subjects Aged 12-17 n=40		All Subjects n=107	
0.5 - <0.75 x 10^9/L[b]	6	(9)	8	(20)	14	(13)
<0.5 x 10^9/L[c]	0	-	3	(8)	3	(3)

Table 31 from Clinical Summary. Summary of the worst category observed within the period per subject per laboratory test.
a: Only subjects with at least one treatment value for a given laboratory test are included.
b: Criterion for dose reduction.
c: Criterion for permanent discontinuation of treatment.

The patient who discontinued therapy due to thrombocytopenia is discussed above in Section 7.3.3 Drop Outs and Discontinuations.

Liver Transaminases

Grade 3 elevations in ALT occurred in 3% (3/107) of all subjects. After discontinuation of treatment, 2 of the 3 subjects had continued elevated ALT levels that returned to normal by Follow-up Week (FW) 24. The last subject had an elevated ALT that normalized within one month while the subject was still on treatment and remained normal during the follow-up period. No subjects were discontinued or had dose modifications because of ALT elevations.

Thyroid Stimulating Hormone (TSH)

Development of TSH abnormalities is associated with interferon treatment and occurred in 23% (25/107) of the subjects in this study: 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 mild TSH elevations (<10 mU/L). In this study, hypothyroidism was reported as a clinical adverse event in three female subjects (3%, 3/107) and a total of 5 female patients were treated for hypothyroidism or elevated TSH. This incidence is similar to that reported in previous pediatric studies with non-pegylated interferon alfa-2b (4%, 5/118) or adult studies with PEG2b (5%, 26/511).

MO Comment: It was initially unclear why five subjects were being treated for hypothyroidism when only three subjects were reported with hypothyroidism AEs. The sponsor clarified this question: Adverse events of hypothyroidism were based on the subjects' clinical symptoms in three (009092, 018055, and 023046) of the five female

subjects who received levothyroxine treatment. The two other patients (008006 and 008017) received levothyroxine treatment based on increased blood levels of TSH but did not have any clinical symptoms. These two subjects were therefore not recorded as an adverse event of hypothyroidism. A summary of these last two patients who received levothyroxine treatment are described below. The total number of 5 patients treated for hypothyroidism should be included in the label.

Subject 008006 was a 7 year old white female with a history of Genotype 1b HCV infection who had an elevated TSH level of 14.6 mU/L on day 172 of treatment and an elevated thyroglobulin level on day 214. The subject was treated with levothyroxine secondary to the elevated laboratory values on day 214 and discontinued treatment during follow up on day 425. This subject was noted to have a continuous increase in weight and height throughout the study (44.0 kg to 51.6 kg, 129.0 cm to 137.0 cm) and follow up TSH levels were in the normal range at 1.6 mU/L.

Subject 008017 was a 4 year old white female with a history of Genotype 1a HCV infection who had an elevated TSH level of 12.7 mU/L on day 208 of and an elevated thyroglobulin level on day 226. This subject was treated with levothyroxine on day 226 and was diagnosed with "subclinical hypothyroidism" as a rationale to initiate therapy. This subject was noted to have a continuous increase in weight and height throughout the study (19.0 kg to 22.4 kg, 109.0 cm to 118.0 cm) and follow up TSH levels were in the normal range at 3.0 mU/L.

The sponsor notes that none of these subjects were discontinued or had dose modifications because of the abnormal TSH values.

Glucose

Some fluctuation of mean fasting blood glucose levels occurred during the study with a slight decline during the treatment period and a return to baseline during the follow-up period in both age groups. These changes were considered mild and transient and included fasting glucose values both below and above normal reference range. An abnormal glucose level was reported as an adverse event only in one subject (008033), who had increased blood glucose for 4 days starting on Study Day 122. No cases of diabetes were identified during this study.

MO Comment: Of note, Subject 008033 had glucose levels measured by an adult sibling using a home test kit, so the accuracy of the kit and technical skills of the sibling testing the sugar level may have been a factor in the abnormal glucose reading. According to the applicant, all subsequent glucose values for this subject, reported by the central laboratory, were within normal ranges.

7.4.3 Vital Signs

Clinically significant changes in vital signs from the Screening 2 visit were recorded as AEs. The most common findings in vital signs were pyrexia and a decrease in weight, both of which have been associated with PEG2b plus ribavirin therapy. Decreases in weight will be discussed in Section 7.6.3. See Table 7.4.3a for reported adverse vital signs.

Table 7.4.3a: Adverse Vital Signs by Age Group

	Subjects 3 – 11 Years (N = 67) n (%)	Subjects 12 –17 Years (N = 40) n (%)	All Subjects (N = 107) n (%)
Adverse Event			
Pyrexia[a]	61 (91)	26 (65)	87 (81)
Weight Decrease	14 (21)	6 (15)	20 (19)
Tachycardia[b]	2 (03)	0	02 (02)
Hypotension	0	1 (03)	01 (01)

Modified Table 36 from Clinical Study
a: includes body temperature increase; b: includes sinus tachycardia

MO Comment: Pyrexia and weight loss were clearly the two main vital signs affected in this study. Pyrexia was reported 625 times as an adverse event. The majority of reports (85%) were considered mild in severity, while 4 reports (0.6%) were considered severe. There were 85 total missing records. There does not appear to be a definition for pyrexia in the protocol and most likely, reports of "fever" were from parents or caregivers caring for the child. The mean recorded temperature from the case report forms was 36.4 Celsius. Tachycardia was not a frequent adverse event and may have been due to an increase in temperature or anxiety during the exam, and not necessarily due to the drug itself. Reported events of palpitations occurred in 4 subjects: 3 (4%) within the 3 -11 year age group and 1 (3%) within the 12 – 17 year age group.

Blood Pressure

Hypotension occurred in only one subject. Hypertension was not listed in any of the submitted tables as an adverse event. On review of the blood pressures, however, there were sporadic increases in blood pressures for some of the patients. Table 7.4.3b below shows the number and percentages of high blood pressures by age group. The highest systolic blood pressure (SBP) for that patient was recorded and blood pressure percentages were based on gender, age, and approximate height percentiles using the National Heart and Lung Institute Guidelines for 2000.

Table 7.4.3b: Incidence of High Blood Pressure by Age Group

	Subjects 3-11 Years N = 67 n (%)	Subjects 12-17 years N = 40 n (%)
Male		
SBP 90 -95 %	2 (3)	6 (15)
SBP 95 -99 %	6 (9)	6 (15)
SBP > 99%	2 (3)	4 (10)
Female		
SBP 90 -95 %	7 (10)	3 (7.5)
SBP 95 -99 %	11 (16)	5 (12.5)
SBP > 99%	4 (6)	4 (10)

FDA Table

MO Comment: **The high blood pressures were not continuous during the study for the majority of patients. The fluctuation of blood pressures may have been due to other variables such as the patient's pain or irritability.**

Growth

Previous pediatric studies with interferon, more specifically non-pegylated interferon plus ribavirin have shown that weight loss and inhibition of growth are associated with treatment, followed by a *catch-up* in weight and growth during the follow-up phase. Similar patterns of weight and height changes were also seen in this study. Height and weight were measured at baseline, at the end of treatment and at follow-up periods to assess the effect of the study medications on growth. Percentile assignments were made using the 2000 standard growth charts developed by the CDC. Table 7.4.3.c shows the mean change in weight and height percentiles from baseline to the end of treatment by age group.

Table 7.4.3.c: Mean Changes in Weight and Height Percentiles

Growth Parameter %	3 – 11 Years n = 67	12 – 17 Years n = 40	All Subjects N = 107
Weight: Baseline to EOT			
Mean (SD)	- 17.1 (13.4)	- 12.8 (10.13)	- 15.5 (12.4)
Range	- 58.0 to + 11.6	- 36.1 to + 6.33	- 58.0 to + 11.6
Weight: EOT to EOF			
Mean (SD)	12.68 (11.2)	11.63 (12.5)	12.3 (11.6)
Range	-9.82 to + 45.13	- 18.7 to + 47.1	- 18.7 to + 47.1
Last Mean Weight (SD)	50.5 (30.3)	58.3 (27.8)	53.4 (29.5)
Height: Baseline to EOT			
Mean (SD)	- 10.9 (10.6)	- 2.5 (7.5)	-7.7 (10.4)
Range	- 36.5 to + 18.9	- 27.1 to + 13.4	-36.6 to + 18.9
Height: EOT to EOF			
Mean (SD)	2.0 (9.2)	- 0.42 (5.4)	1.1 (8.1)
Range	- 22.6 to + 34.2	-12.8 to + 15.2	- 22.6 to 34.2
Last Mean Height	42.3 (25.8)	47.5 (30.4)	44.3 (27.6)

Combined Tables 37 and 38 of Clinical Study
Subjects who reached > 240 months in age, were not reported because weight and height percentiles could not be calculated using CDC charts

The mean last weight percentile (53.4), for all subjects including both age groups, was slightly above the median of the U.S. population. With regards to height, the data demonstrates that younger children's (3-11 years old) growth was more affected when compared to the older (12-17 years old) aged children. The mean last height percentile in the follow-up period (44.3) was slightly below the median of the U.S. population.

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) which is to be expected given the history of catch up growth after treatment. The mean growth velocities in boys were slightly faster than those of girls in both study periods. Mean growth velocities for subjects <11 years old were also slightly higher than those for subjects > 11 years old during both study periods. Growth velocity

percentiles relative to US standardized norms were determined. The mean growth velocity percentile for the treatment period (9.4 ± 18.6) was below the median (50th percentile), but that for the 24-week follow-up (58.4 ± 41.1) was above the median, thus suggesting that some catch-up growth may have occurred after the end of treatment.

According to the sponsor, severely inhibited growth velocity (<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, 34.7% had faster than normal growth velocity (>97th percentile), 36% attained improved growth velocity (3rd to 97th percentile), while 20% continued to have inhibited growth velocity (remained <3rd percentile). The long-term impact of the PEG2b plus ribavirin treatment on growth will be evaluated in the 5-year long-term follow-up study.

MO Comment: The 20% of subjects with continued inhibited growth velocity at the end of follow-up, while less than the remaining patients who do show some degree of catch up growth, represents a significant group of children for whom it is not known if a return to normal or near normal growth will occur. This risk represents a major concern requiring monitoring in the long term 5 year follow up study and will be reported in the current label. One must, however, balance the risk of potentially developing cirrhosis or hepatocelllular carcinoma if HCV is left untreated against the preservation of growth.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were performed 6 months prior to beginning the study and only if clinically indicated during the study. QT prolongation was not assessed.

7.4.5 Special Safety Studies

Other safety tests which were conducted in this study as clinically indicated: Chest x-rays, 12-lead electrocardiograms (ECGs), and ocular examinations. A 5 year follow-up study is ongoing to assess the effects of PEG2b and ribavirin on height and weight, as well as the long term effect of the medications on TSH values.

7.4.6 Immunogenicity

Serious hypersensitivity reactions to PEG2b such as urticaria and anaphylaxis, or skin reactions such as Stevens Johnson syndrome and toxic epidermal necrolysis were not seen in this study. Overall, hypersensitivity is rarely been seen with alpha interferon therapy. Only one patient had an adverse event under immune system disorders. This patient developed nasal allergies and subsequent seasonal allergies on study day 261 and the symptoms continued intermittently from this date until study day 490. Symptoms were mild in severity and were not attributed to the medication. Given the time line, this assessment seems reasonable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not applicable; this was a non-randomized, single arm, open label study. Only a single dose and regimen was evaluated.

7.5.2 Time Dependency for Adverse Events

Not applicable; this was a non-randomized, one arm open labeled study

7.5.3 Drug-Demographic Interactions

In general, thyroid disease is more common in females than in males, and this was reflected in this study in which the female subjects were more likely to have clinical hypothyroidism on PEG2b treatment compared with male subjects. At least one elevated TSH value was reported in 32% (18/56) of female subjects, including approximately the same proportion in each age group (33% [13/40] of subjects 3-11 years old and 31% [5/16] 12-17 years old). Male subjects had a lower incidence of elevated TSH (10%, 5/52), and all instances occurred in subjects 3 to 11 years of age. In the male subjects, the TSH elevations were transient and subclinical (<10 mU/L), and all had spontaneous normalization of TSH by the last follow-up visit. In comparison, five female subjects received levothyroxine treatment for elevated TSH.

7.5.4 Drug-Disease Interactions

All subjects in this study had some degree of liver disease. None of the pediatric subjects had significant renal disease.

7.5.5 Drug-Drug Interactions

Interferon alfa-2b may increase blood levels of zidovudine (AZT, Retrovir). While this reaction may improve zidovudine's effectiveness, it also may increase the risk of blood and liver toxicity. Therefore, the dose of zidovudine may need to be reduced as needed. Concomitant use of didanosine and ribavirin is not recommended due to reports of fatal hepatic failure, peripheral neuropathy, pancreatitis, and lactic acidosis.

Interferon alfa-2a and interferon alfa-2b may increase the time it takes for theophylline (e.g., THEO-DUR) to be eliminated from the body. Therefore, the dose of theophylline may also need to be reduced.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

PegIntron, has not been tested as a carcinogen. Ribavarin, however, is mutagenic and genotoxic and should be considered as a potential carcinogen.

7.6.2 Human Reproduction and Pregnancy Data

PegIntron is a Pregnancy Category C drug. Based on animal studies with rhesus monkeys in non-pegylated interferon alpha-2b, PegIntron may also have abortifacient potential. There have been no adequate studies done in pregnant women. PegIntron is recommended in fertile women only in those who are using adequate forms of birth control.

Ribavarin is classified as a Pregnancy Category X. Ribavarin may cause severe birth defects and or fetal death and is contraindicated in pregnant women or women trying to become pregnant, and in men whose female partners are pregnant. While on therapy, women should have a documented negative pregnancy test, agree to use two methods of contraception, and have monthly pregnancy tests done. Tests should also continue 6 months after treatment has been discontinued. To monitor fetal outcomes of pregnant women exposed to ribavarin, a pregnancy registry has been established, and healthcare providers are encouraged to register patients. This applies to pregnant women exposed to and ribavarin during treatment and 6 months after treatment. A box warning describes the potential risk for pregnant women in the PegIntron label.

7.6.3 Pediatrics and Effect on Growth

In summary from Section 7.4.3, severely inhibited growth velocity (<3rd percentile) was observed in 70% of subjects during the treatment phase of the study. However, there was a catch up growth pattern seen in most children. While the mechanism with which PEG2b affects growth, remains unknown, growth impairment is a major risk which will require more monitoring and data collection. The long term 5 year follow up study will characterize more clearly the final growth pattern in children on PEG2b and ribavirin treatment.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There have been no studies to assess for the abuse or withdrawal potential from interferon. PEG2b is not expected to have abuse potential based on mechanism of action.

7.7 Additional Submissions

Not applicable

8 Postmarketing Experience

No postmarketing review was done or submitted with this protocol.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

The PegIntron® label will be revised to include salient information about its use in the pediatric population, including pediatric pharmacokinetic, efficacy and safety data. Please refer to sections: 5.18, 6.1, 12.3, and 14.2 for the major changes to the label as it pertains to the pediatric population.

9.3 Advisory Committee Meeting

No advisory committee convened for this supplemental BLA.