# CLINICAL / BIOMETRICS REVIEW

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| Application Type | BLA/NDA |
| Application Number(s) | 103964/5213 & 21511/S-023 |
| Priority or Standard | Priority |
| Submit Date(s) | 2/22/11 |
| Received Date(s) | 2/22/11 |
| PDUFA Goal Date | 8/22/11 |
| Division / Office | DAVP/OAP |
| Reviewer Name(s) | Neil Rellosa, MD<br>Fraser Smith, PhD |
| Review Completion Date | 7/29/11 |
| Established Name | Peginterferon alfa-2a/ribavirin |
| (Proposed) Trade Name | Pegasys®/Copegus® |
| Therapeutic Class | Interferon-alfa/antiviral |
| Applicant | Roche |
| Formulation(s) | 180 mcg/1 mL vial or<br>180 mcg/0.5 mL prefilled syringe<br>200 mg oral tablets |
| Dosing Regimen | |
| Indication(s) | Treatment of chronic Hepatitis C |
| Intended Population(s) | Pediatric patients aged 5 to 17 years |

Template Version:  March 6, 2009

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# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

The NDA/BLA for Pegasys® (peginterferon alfa-2a) (PEG-IFN alfa-2a) in combination with Copegus® (ribavirin) for the treatment of chronic hepatitis C virus infection in patients aged 5 to 17 years of age should be approved. The applicant, Roche, submitted adequate data characterizing the efficacy and safety of Pegasys and Copegus for this indication.

## 1.2 Risk Benefit Assessment

There are many side effects associated with Pegasys-Copegus combination therapy for the treatment of chronic hepatitis C infection in patients aged 5 to 17 years of age such as psychiatric symptoms, eye disorders, influenza-like illnesses, neutropenia, anemia and growth abnormalities. These side effects and their frequencies are similar to those seen in previous approved similar products and in adult patients. These effects represent less risk than the long term effects of untreated hepatitis C such as cirrhosis or liver failure for these pediatric patients.

## 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for postmarket risk evaluation and mitigation for this submission.

## 1.4 Recommendations for Postmarket Requirements and Commitments

The applicant has requested a waiver in patients < 3 years of age. The current supplement includes adequate data from a clinical trial in patients 5 to 17 years of age and this supplement will result in labeling in that age group using the 200 mg (adult strength) Copegus tablet. The indication will be limited to pediatric patients ≥5 years of age who are able to swallow a tablet.

In 2002, CBER in collaboration with DAVP convened an Advisory Committee meeting to discuss the conduct of clinical trials for the treatment of chronic HCV infection in pediatric patients. The conclusions of the pediatricians and hepatologists on the Advisory Committee were that clinical trials of new treatments for chronic HCV in pediatric patients were needed but that there were very few patients < 3 years of age who required treatment. Since that Advisory Committee meeting, no new data are

available thus it would not be possible to enroll adequate numbers of patients < 3 years of age in a clinical trial. In addition, Pegasys was previously judged to be contraindicated in neonates and infants because it contains benzyl alcohol. Therefore, we agree with the request for waiver in patients < 3 years of age.

The only remaining age group includes patients 3 to < 5 years of age. This is the most difficult age group to enroll in a clinical trial and the applicant has proposed to collect data for the 3 to < 5 years group by different methodology. (b) (4)

(b) (4)

## 2 Introduction and Regulatory Background

Although Hepatitis C Virus (HCV) is believed to follow a more benign or milder course in pediatric patients as compared to adult patients, the true prevalence or incidence of liver disease-related morbidity and mortality in these children including those cases perinatally acquired, is still unclear. There are reports of HCV infected pediatric patients with severe hepatitis, cirrhosis, and end-stage liver disease requiring transplantation. Because of the possible risk of these co-morbidities, treatment of children and adolescent may be appropriate to prevent the progression to more severe liver disease.

The current recommended treatment for patients with chronic hepatitis C infection is combination therapy with peginterferon alfa (PEG-IFN) and ribavirin. The sponsor's products, Pegasys (peginterferon alfa-2a, PEG-IFN alfa-2a) and Copegus (ribavirin) in combination are currently approved for the treatment of chronic hepatitis C (CHC) in adults with compensated liver disease who have not been previously treated with an interferon-alfa, and adults co-infected with human immunodeficiency virus (HIV) infection, however they are not approved for the use in pediatric patients.

## 2.1 Product Information

Pegasys® is a chemically modified interferon alfa formed by the covalent attachment of a 40-kilodalton single branched methoxy polyethylene glycol moiety to recombinant human interferon alfa-2a. Copegus® is an antiviral agent used in the treatment of various viral infections. Currently both products, in combination with each other, are approved for the treatment of chronic hepatitis C in adults with compensated liver disease who have not been previously treated with an interferon-alfa, and adults co-infected with HIV. The submitted data is in support of an expanded indication for both Pegasys and Copegus to include patients 5 to 17 years of age.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

There are currently only two other treatment regimens approved and marketed in the U.S. for the treatment of CHC in children. Combination therapy with pegylated interferon and ribavirin is the standard of care while interferon monotherapy is only indicated in certain circumstances. The applicant previously had a non-pegylated interferon product, Roferon A, that was approved for use in adults for the treatment of CHC in 1986 but this product was discontinued in 2007 for reasons not related to safety or efficacy. Listed below are the currently available treatments:

| Approved Treatment | Indication | Date of Approval |
|---|---|---|
| Intron-A (interferon alfa-2b) and Rebetol (ribavirin) | Treatment of CHC in pediatric patients 3-16 years of age | 2003 |
| PegIntron (pegylated interferon alfa-2b) and Rebetol (ribavirin) | Treatment of CHC in pediatric patients 3-17 years of age | 2008 |

## 2.3 Availability of Proposed Active Ingredient in the United States

Currently, both products are commercially available in the United States but only approved for use in adult patients.

## 2.4 Important Safety Issues With Consideration to Related Drugs

The major safety issues to be considered related to interferon therapy include neuropsychiatric symptoms such as depression and suicidal ideation in patients with or without prior psychiatric disease, flu-like symptoms such as fatigue and pyrexia, bone marrow suppression that can cause severe cytopenias, and endocrine issues such as aggravation of hyperthyroidism and hypothyroidism. Issues specifically related to the treatment of pediatric patients with interferon that warrant special consideration include growth delay.

The main safety issue to consider with ribavirin therapy in general is hemolytic anemia.

Section 7 (Review of Safety) will include detailed discussions of the specific safety issues related to both Pegasys and Copegus.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

The applicant conducted Study NV172424 to prospectively investigate the efficacy of Pegasys in combination with Copegus compared to Pegasys monotherapy in the treatment of CHC among children 5 to 18 years of age. This study was conducted under BB-IND (b) (4) to fulfill a post-approval commitment (PAC) included in the December 3, 2002 Pegasys approval letter.

(b) (4)

On November 5, 2004, FDA agreed to a deferral of pediatric patients 5 to 18 years of age.

In January of 2005 and 2006, the sponsor requested feedback regarding the acceptability of NV172424 to fulfill the Pegasys PAC. On February 15, 2006, the FDA stated that this study would fulfill the PAC but that labeling changes would be limited to the age range studied.

On November 18, 2010, during a pre-filing meeting, FDA noted that study NV17424 did not include patients 3-5 years of age and an assessment for this excluded age group would be required in the filing of this submission.

### 2.6 Other Relevant Background Information

There is no other relevant background information.

# 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

Overall, the submitted data appears to be of good quality and integrity.

### 3.2 Compliance with Good Clinical Practices

It appears that the clinical trials were conducted in compliance with Good Clinical Practices and in accordance with acceptable ethical standards. An audit of one study site (site No. 41219) was conducted by the sponsor's clinical quality assurance group and major findings involving non-compliance with Good Clinical Practice were observed. However, the sponsor states that these issues were appropriately corrected and preventive actions were initiated.

### 3.3 Financial Disclosures

The1.3.4. Financial Disclosure forms were reviewed. Most investigators and sub-investigators had no disclosures to report. For two investigators, information regarding financial disclosures is not reported because these investigators were unable to be reached. However, one of these investigators was only involved in the supportive study, NR 16141. With the other investigator, 9 subjects were enrolled with 8 of them being randomized to treatment arms. Four were randomized to combination therapy and the other four subjects were randomized to the placebo control arm.

Four investigators disclosed financial arrangements and interests with companies that may be considered conflicts of interest. A total of 47 subjects were enrolled in these four centers (total of enrolled=188 subjects) and 40 of these patients were randomized into treatment arms. Within each treatment arm, these 40 patients were relatively balanced. Most of these financial holdings were related to research grants or contracts. Two of these investigators had interests directed related to the applicant. Subjects enrolled by these investigators contributed significantly to the results and conclusions of Study NV17424 and should be considered in evaluating this submission. However, the trial was randomized and blinded (for Copegus) and used an objective, virologic endpoint and these factors limit the potential for biased results.

# 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

## 4.1 Chemistry Manufacturing and Controls

Both Pegasys and Copegus are approved products. No new chemistry manufacturing or control information was supplied with this submitted supplement.

## 4.2 Clinical Microbiology

Different HCV genotypes display considerable clinical variability in their response to both Pegasys and Copegus. As stated in the current labels, viral genetic determinants associated with the variable response have not been definitively identified but are not considered related to virologic resistance as observed with other antiviral drugs. Both Pegasys and Copegus are approved FDA products. No new clinical microbiology information was supplied with this submitted supplement.

## 4.3 Preclinical Pharmacology/Toxicology

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

## 4.4 Clinical Pharmacology

### 4.4.1 Mechanism of Action

PEG-IFN alfa-2a is a cytokine and an inducer of the antiviral immune response. Pegasys' biological activity is derived from its recombinant human interferon alfa-2a moiety. PEG-IFN α-2a binds to the human type 1 interferon receptor leading to receptor dimerization which then activates intracellular signal pathways initially mediated by the JAK/STAT pathway. PEG-IFN alfa-2a is expected to have pleiotropic biological effects because of the diversity of cell types that respond to it and the potential response of multiple intracellular pathways secondary to interferon receptor activation.

The mechanism of action of Copegus' clinical antiviral activity is not fully understood however it has demonstrated direct antiviral activity in tissue culture against many RNA viruses. Ribavirin increases mutation frequency in the genomes of several RNA viruses and ribavirin triphosphate inhibits HCV polymerase in biochemical reactions.

No new mechanism of action information was included in this submission

### 4.4.2 Pharmacodynamics

No new pharmacodynamics information was included for both products in this submission.

### 4.4.3 Pharmacokinetics

No pharmacokinetics were evaluated in Study NV17424. However, Study NR16141 was a Phase 2, multicenter, non-randomized, open-label study of viral kinetics, PK, and safety of PEG-IFN alfa-2a used in subjects aged 2 to 8 years of age with CHC and was submitted along with the pivotal study, NV17424, in support of this application.

Fourteen subjects, who had not previously been treated with ribavirin or interferon, received an subcutaneous injection of PEG-IFN alfa-2a (180 µg x BSA/1.73 $m^2$ calculated dose) once weekly for 48 weeks and then followed and evaluated for an additional 24 weeks treatment-free. Sparse samples (predose, 24, 96, and 168 hours after the first dose and Week 24 dose, and predose at Weeks 4, 8, and 12) were collected in all subjects. Population PK analysis was performed using a PK model that simulated PEG-IFN alfa-2a PK in children from 2 to 17 years of age.

Results from this study showed more time was required to achieve steady-state trough levels in these children with BSA-adjusted dosing as compared to the time it took for trough levels to be achieved in adults with fixed dosing. In addition, based on AUC, the mean exposure during the dosing interval is predicted to be 25%-70% higher in these children with the adjusted BSA dosing as compared to the fixed dosing in adult patients. However, despite the slightly higher exposure, these children seemed to tolerate PEG-IFN alfa-2a. The applicant used these results to help select their dosing of Pegasys for Study NV17424.

This study was also reviewed by Clinical Pharmacology who concluded that this study did not have sufficient PK data to determine the pharmacokinetics of pediatric patients across the entire proposed population (5 to 17 year old) and therefore these results were not used for the determination of PEG-IFN alfa-2a dose. However, Clinical Pharmacology felt that there was adequate clinical information in this submission to support the proposed BSA-based dosing of Pegasys in combination with Copegus for patients at least 5 years of age with CHC. For a more detailed analysis of the clinical pharmacology issues for this submission refer to the full review by Dr. Jenny Zheng.

*Medical Officer's (MO's) comment: The contribution of the results of Study NR16141 to the efficacy and safety analysis will be discussed further in Section 6: Review of Efficacy and Section 7: Review of Safety.*

# 5 Sources of Clinical Data

## 5.1 Tables of Studies/Clinical Trials

One pivotal study, Study NV17424, and one supporting clinical study, Study NR16141, were submitted for review in this supplement. Table 5.1 summarizes the study design of these two studies.

**Table 1: Overview of Clinical Studies Providing Main Efficacy Data**

| Study, Protocol No. | Study Design | No. of Centers and Locations | Study Population | Treatment Regimen, Dose, & Duration | Efficacy Analysis Population |
|---|---|---|---|---|---|
| **Pivotal Study** | | | | | |
| NV17424 | Phase 3, multicenter, randomized, blinded (through at least Week 24 of treatment), placebo-controlled for Copegus | 11 centers in the United States | Children 5 to 18 years of age with CHC and compensated liver disease | Subjects randomized in a 1:1 ratio into one of 2 groups:<br>**Group 1**: 180µg x BSA/1.73m$^2$ of SC PEG-IFN alfa-2a once weekly & 15 mg/kg body weight/day PO RBV BID<br>**Group 2**: 180µg x BSA/1.73m$^2$ of SC PEG-IFN alfa-2a once weekly & ribavirin-placebo<br><br>Blinded treatment for 24 weeks and at week 24 those patients who exhibit virological response (VR) (ie, undetectable HCV RNA) were kept on the same blinded treatment regimen for an additional 24 weeks. At week 48, treatment discontinued and patients were followed untreated for 24 weeks more. Subjects with detectable HCV RNA at week 24 were unblinded. Those in Group 2 were treated for an additional 48 weeks with PEG-IFN alfa-2a plus ribavirin combination therapy | Total No. of patients=114;<br>Male 63<br>Female 51<br><br>Age range= 5-17 years |

| **Supporting Study** | | | | | |
|---|---|---|---|---|---|
| NR 16141 | Phase 2, multicenter, open-label study of viral kinetics, PK, and safety in patients who received PEG-IFN alfa-2a SC once weekly for 48 weeks with 24 weeks of treatment-free follow-up | 5 centers in the United States | Children 2 to 8 years of age with CHC and compensated liver disease | Subjects received injection of PEG-IFN alfa-2a SC once weekly for 48 weeks and continued to be evaluated throughout a 24-week treatment-free follow-up period.<br>The dose was obtained by multiplying the BSA in $m^2$ by the µg/ $m^2$ dose for an average adult with a BSA of 1.73 $m^2$ | Total No. of patients=14<br>Male 8<br>Female 6<br><br>Age range=2-8 years |

## 5.2 Review Strategy

The clinical information provided by the applicant from the two studies was reviewed however the major evaluation and conclusions regarding efficacy and safety were based on the data submitted for Study NV 17424, This study is reviewed in detail in Section 6: Review of Efficacy and Section 7: Review of Safety. Submitted material that was reviewed included the clinical study overview and summary, clinical study reports on efficacy and safety, data sets, and individual case report forms. In addition, independent analysis of the submitted safety data sets was performed using JMP statistical software. The proposed label was also reviewed and revisions were recommended based on the provided information.

Since these are already approved products and there are no new data or information for certain disciplines such as clinical microbiology or pharmacology/toxicology, full reviews for these disciplines were not included. The review for Clinical Pharmacology is summarized in Section 4.4 however for a more detailed analysis of the clinical pharmacology issues for this submission refer to the full review by Dr. Jenny Zheng.

Statistical review performed by Dr. Fraser Smith was incorporated into this joint Clinical/Biometrics Review in Section 6: Review of Efficacy and Section 7: Review of Safety.

## 5.3 Discussion of Individual Studies/Clinical Trials

Pivotal Study Design
Study NV 17424 was a Phase 3, multicenter, randomized, blinded (through at least Week 24 of treatment) placebo-controlled study. Subjects were randomized in a 1:1 ratio to one of the following 2 treatment groups:

**Group 1**: 180 µg x BSA/1.73 $m^2$ of PEG-IFN alfa-2a administered subcutaneously once weekly and 15mg/kg/day of ribavirin administered orally twice daily with a maximum

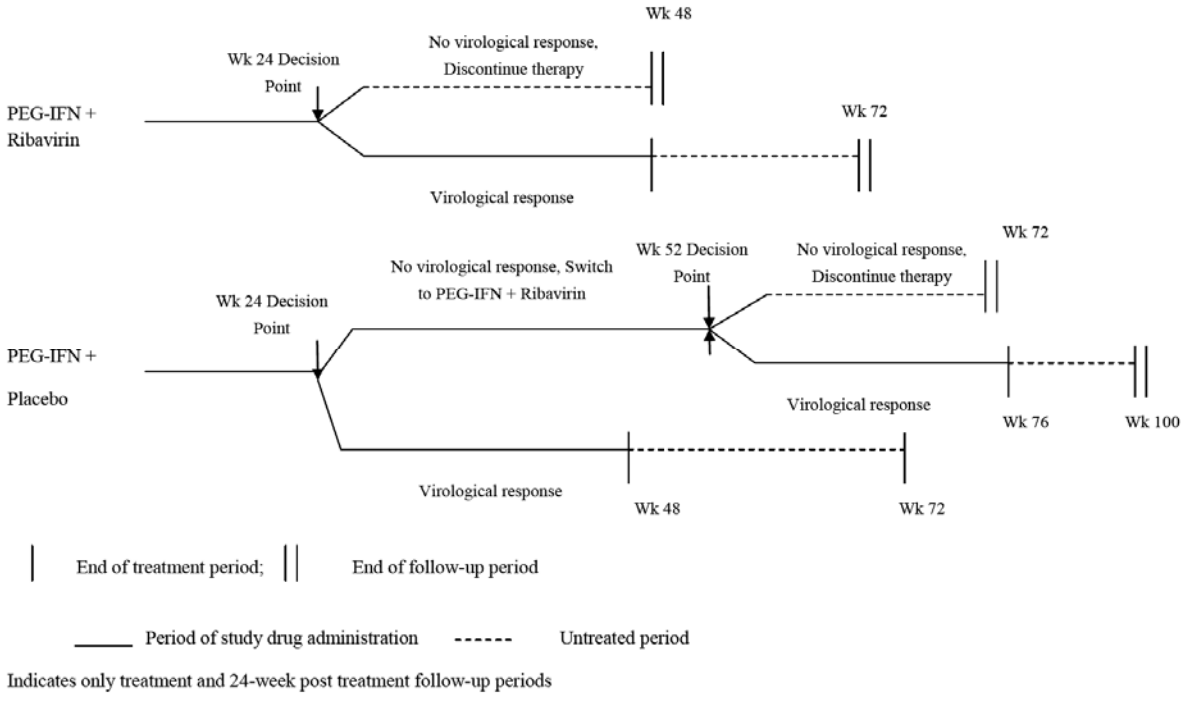
dose of 1200 mg/day for subjects with body weight ≥ 75 kg or 1000 mg/day for subjects with body weight <75 kg.

**Group 2**: 180 µg x BSA/1.73 $m^2$ of PEG-IFN alfa-2a administered subcutaneously once weekly and ribavirin-placebo administered orally twice daily

Treatment was blinded for 24 weeks and at Week 24, those subjects who exhibited a virological response (VR) (i.e. undetectable HCV RNA in plasma) were kept on the same blinded treatment regimen for an additional 24 weeks. At Week 48, treatment was discontinued and the subjects were followed untreated for 24 weeks (to Week 72).

Subjects with no virological response (i.e. detectable HCV RNA) at Week 24 were unblinded. Those subjects in Group 1 with no VR had therapy discontinued and were followed until Week 48. Those receiving PEG-IFN alfa-2a monotherapy were treated for an additional 48 weeks (to Week 52) with combination therapy with PEG-IFN alfa-2a and ribavirin. If at that point, these subjects had no virological response, therapy was discontinued and the follow-up period ended at Week 72. If at Week 52 they did exhibit a VR, they continued on combination therapy until Week 76 and followed untreated until Week 100. Figure 1 which is taken from the applicant's 2.7.3 Summary of Clinical Efficacy shows a schematic of the study design:

**Figure 1: Study Design of NV17424**




Indicates only treatment and 24-week post treatment follow-up periods

Study Dosing

The currently approved dose of Pegasys when used in combination with ribavirin for chronic hepatitis C in adults is 180 µg once weekly. The approved dose of Copegus and the duration of combination therapy with these two drugs for adults is based on viral genotype and is shown in the following table.

**Table 2: Pegasys and Copegus Adult Dosing Recommendations**

| Hepatitis C Virus Genotype | Pegasys Dose | Copegus Dose | Duration |
|---|---|---|---|
| Genotype 1, 4 | 180 µg | <75 kg=1000 mg<br>≥75 kg=1200 mg | 48 weeks |
| Genotype 2, 3 | 180 µg | 800 mg | 24 weeks |

The Pegasys dosing in this study was based on this approved dosing with BSA-adjustment.

The dose of ribavirin was 15 mg/kg of body weight daily as a split dose; this dose of Rebetol is currently approved for use in pediatric patients in the US. A 100 mg Copegus tablet was used in Study NV 17424 which is comparable to the currently marketed 200 mg Copegus tablet as demonstrated by the similarity in their dissolution profile.

Inclusion/Exclusion Criteria

The following major inclusion and exclusion criteria needed to be met for a patient to be eligible for Study NV17424:

Inclusion Criteria:

- Male or female, 5 to 18 years of age (screening must have been completed before the subject's 18$^{th}$ birthday)
- Evidence of HCV viremia by any test method present on two tests separated by at least 6 months
- Chronic liver disease consistent with CHC infection on a biopsy obtained within the past 36 calendar months as judged by a local pathologist
- Compensated liver disease (Child-Pugh Grade A clinical classification)
- Hemoglobin value screening of greater than 11g/dL for females or greater than 12 g/dL for males
- Normal thyroid-simulating hormone (TSH) level at screening
- Demonstrated ability to swallow tablets consistent with study medication use

Exclusion Criteria:

- Prior treatment with ribavirin or interferon
- Treatment with any systemic antiviral therapy less than 6 weeks prior to the first dose of study drug, treatment with acyclovir for herpetic lesions was permitted
- Treatment with investigational drug within 6 weeks prior to the first dose of study drug
- Positive test results at screening for anti-hepatitis A virus immunoglobulin M (IgM) antibody (Ab), hepatitis B surface antigen, anti-hepatitis B core IgM Ab, or anti-HIV Ab
- History or other evidence of medical condition associated with chronic liver disease other than HCV infection
- History or other evidence of bleeding from esophageal varices
- Decompensated liver disease
- History of autoimmune or immunological-mediated disease
- Absolute neutrophil count of less than 1500 cells/$mm^3$ , hemoglobin less than 11 g/dL for females or less than 12 g/dL in males, white blood cell (WBC) count greater than 1.75 x $10^9$ cells/L, or platelet count of less than 90,000 cells/$mm^3$
- Serum creatinine level of greater than 1.5 times the upper limit of normal for age
- Evidence of major depression or history of severe psychiatric disorder
- History or other evidence of chronic pulmonary or cardiac disease associated with functional limitation
- History of thyroid disease poorly controlled on prescribed medication or patients with elevated TSH accompanied by an elevation of antibodies to TPO and any clinical manifestations of thyroid disease
- Presence of poorly controlled diabetes (hemoglobin A1c greater than 8%)
- History of solid organ or bone marrow transplantation
- Evidence of severe retinopathy
- Presence of coagulopathy (International Normalized Ratio (INR) greater than 1.5)
- Active substance abuse
- Sexually active females of child-bearing potential defined as age 10 years and older and sexually active males who did not agree to practice two forms of effective contraception during study treatment and during the 6 month period following the last dose of study drug
- Females with a positive pregnancy test within 7 days of first dose of study drug or who were breast feeding
- Males whose female partners were pregnant

*MO's Comment: Overall, the general design of this clinical trial was acceptable. Inclusion/exclusion criteria reflect safety risks noted in the Pegasys and Copegus labels and previously identified in adult clinical trials of the products.*

Supportive Study Design

Study NR16141, a Phase 2 multicenter, open-label study conducted in children 2 to 8 years of age to characterize the viral kinetics, pharmacokinetics, and safety in patients who received PEG-IFN alfa-2a weekly for 48 weeks.

Fourteen subjects, who had not previously been treated with RBV or IFN, received an subcutaneous injection of PEG-IFN alfa-2a (180 µg x BSA/1.73 $m^2$ calculated dose) once weekly for 48 weeks and then followed and evaluated for an additional 24 weeks treatment-free.

*MO's Comment: The analysis and evaluation in Section 6 and Section 7 of this review will not integrate the data submitted for both studies. Comments regarding efficacy and safety in Study NR16141 will be addressed in Sections 6.1.10. and 7.7, respectively.*

# 6 Review of Efficacy

## ***Efficacy Summary***

The use of Pegasys in combination with Copegus was shown to be efficacious in the pediatric population aged 5-17 years as measured by sustained virological response (SVR, see Section 6.1.1 Methods). The overall SVR rate was 49% for all HCV genotypes for patients who received initial combination therapy versus only 20% in those patients who received therapy with Pegasys alone.

Overall, at baseline, the subjects were relatively well-matched in terms of demographics. However, it is difficult to fully evaluate whether the treatment groups were well-balanced in terms of discontinuations and drop-outs between the initially randomized therapy groups because those subjects who were in the initial monotherapy group who were non-responders were switched to compassionate combination therapy at 24 weeks.

Secondary efficacy analyses showed that with combination therapy, there was a greater sustained virological response and lower relapse rate as compared to monotherapy. In addition, exploratory efficacy parameter analyses showed that higher baseline HCV RNA is a negative predictor of SVR while combination therapy is a positive predictor compared to monotherapy. With combination therapy, a very early response at Week 5 was associated with the greatest probability of an SVR. Whereas, with monotherapy, a response at Week 12 was associated with the greatest chance of having an SVR. SVR rates for children who responded at Week 12 were approximately the same in the two treatment arms. However since there were only a small number of children on monotherapy who responded at Week 12, this finding should be interpreted with caution.

## 6.1 Indication

The proposed indication is: Pegasys in combination with Copegus is indicated for the treatment of chronic hepatitis C in children 5 to 17 years of age with compensated liver disease and who have not received previous interferon treatment.

### 6.1.1 Methods

The primary measure of efficacy was sustained virological response (SVR) according to the scheduled treatment period, defined as the percentage of patients with undetectable HCV RNA as measured by the HPS/COBAS TaqMan HCV Test (lower limit of detection is 10 IU/mL) at or after week 68 (ie, a single last HCV RNA < 10 IU/mL measured ≥ study day 477 [time window for Week 72 assessment]).

Subjects in the monotherapy arm, who did not exhibit undetectable HCV RNA at treatment week 24 had to switch to compassionate combination treatment and thus all values after the switch were not used for the assessment of SVR between the two initial treatment groups and were counted as non-responders. Subjects in the combination therapy group who did not exhibit undetectable HCV RNA at week 24 had to stop treatment at week 28 and entered the posttreatment follow-up period. Those and all other patients without measurements at or after week 68 were considered as nonresponders for the primary analysis. This definition of SVR was labeled "sustained virological response (HPS/COBAS TaqMan HCV test < 10 IU/mL) according to scheduled treatment period."

An additional analysis was performed using the definition of SVR as undetectable HCV RNA as measured by the Roche HPS/COBAS TaqMan HCV Test, (lower limit of detection = 10 IU/mL) at 24 weeks after completion of the actual treatment period (a single last HCV RNA < 10 IU/mL measured ≥ 20 weeks after treatment end [ie, ≥ 140 days after treatment end]). Again, subjects after switch from monotherapy to combination therapy as well as subjects without measurements in this time window were considered nonresponders for this SVR endpoint. This definition of SVR was labeled "sustained virological response (HPS/COBAS TaqMan HCV test < 10 IU/mL) according to actual treatment period."

Additional analyses comparing the two initial treatment groups used SVR defined as the percentage of subjects with undetectable HCV RNA as measured by the AMPLICOR HCV Test (lower limit of detection is 50 IU/mL) based on actual treatment period or scheduled treatment period. The single last HCV RNA AMPLICOR results at or after week 68 (ie, ≥ study day 477) was used for SVR (AMPLICOR HCV test < 50 IU/mL) according to scheduled treatment period, while the single last HCV RNA AMPLICOR results measured ≥ 20 weeks after treatment end [ie, ≥ 140 days after treatment end]) was used for SVR (AMPLICOR HCV test < 50 IU/mL) according to actual treatment

period. Again, subjects after switch from monotherapy to combination therapy as well as patients without AMPLICOR measurements in these time windows were considered nonresponders for these SVR endpoints.

The primary analysis of comparing SVR rates between the two initial treatment groups was performed using SVR (HPS/COBAS TaqMan HCV test < 10 IU/mL) according to scheduled treatment period.

SVR is the accepted efficacy endpoint for trials of chronic HCV, although the exact assay limits and sample timing have varied over time. In previous adult studies of P/R, SVR was defined in Study 4 of the Pegasys label as undetectable (<50 IU/mL) HCV RNA on or after study week 68 while in Studies 5 and 6 of the label it was defined as undetectable HCV RNA at the end of the 24-week treatment-free follow-up period.

6.1.2. Demographics

In Study NV17242, the Intent-to-Treat (ITT) population which was defined as all subjects randomized who received at least one dose of study medication, consisted of 114 subjects with 55 subjects in the combination therapy group (Group 1) and 59 subjects in the monotherapy-placebo group (Group 2). Table 3 below which is taken from Appendix 1 from the applicant's submission, 2.7.3 Summary of Clinical Efficacy, shows the detailed baseline demographics and baseline disease characteristics by initial randomized treatment group:

**Table 3: Summary of Baseline Demographic and Baseline Disease Characteristics by Initial Treatment Group, Intent-to-Treat Population**

| | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Ribavirin 15 mg/kg N = 55 | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Placebo N = 59 |
|---|---|---|
| Sex | | |
| FEMALE | 28 ( 51%) | 23 ( 39%) |
| MALE | 27 ( 49%) | 36 ( 61%) |
| n | 55 | 59 |
| Race | | |
| Black/African Amer. | 1 ( 2%) | 4 ( 7%) |
| White | 45 ( 82%) | 46 ( 78%) |
| Asian | 3 ( 5%) | 2 ( 3%) |
| Other* | 3 ( 5%) | 5 ( 8%) |
| Unknown | 3 ( 5%) | 2 ( 3%) |
| n | 55 | 59 |
| Ethnicity | | |
| HISPANIC OR LATINO | 5 ( 9%) | 6 ( 10%) |
| NOT HISPANIC OR LATINO | 50 ( 91%) | 53 ( 90%) |
| n | 55 | 59 |
| Age in years | | |
| Mean | 10.7 | 10.8 |
| SD | 3.34 | 3.56 |
| SEM | 0.45 | 0.46 |
| Median | 11.0 | 11.0 |
| Min-Max | 5 - 17 | 5 - 16 |
| n | 55 | 59 |
| Age in years, cat. | | |
| <=11 | 30 ( 55%) | 30 ( 51%) |
| >=12 | 25 ( 45%) | 29 ( 49%) |
| n | 55 | 59 |
| Weight in kg | | |
| Mean | 44.42 | 47.88 |
| SD | 17.544 | 22.806 |
| SEM | 2.366 | 2.969 |
| Median | 41.00 | 44.00 |
| Min-Max | 17.7 - 89.3 | 17.3 - 98.4 |
| n | 55 | 59 |
| Height in cm | | |
| Mean | 144.90 | 147.17 |
| SD | 18.333 | 22.777 |
| SEM | 2.472 | 2.965 |
| Median | 145.70 | 158.00 |
| Min-Max | 103.7 - 172.1 | 107.9 - 184.6 |
| n | 55 | 59 |

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
*Other = American Indian or Alaskan Native or Multiracial Patients
# As classified by Ishak fibrosis score based on pre-treatment liver biopsy assessed by the central pathologist
DM11 20MAY2010:20:14:11 (continued)

| | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Ribavirin 15 mg/kg N = 55 | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Placebo N = 59 |
|---|---|---|
| Body mass index in kg/m2 | | |
| Mean | 20.325 | 20.671 |
| SD | 4.3787 | 5.4095 |
| SEM | 0.5904 | 0.7043 |
| Median | 18.955 | 19.202 |
| Min-Max | 14.50 - 31.11 | 13.41 - 35.34 |
| n | 55 | 59 |
| Body surface area in sqm | | |
| Mean | 1.324 | 1.378 |
| SD | 0.3356 | 0.4306 |
| SEM | 0.0452 | 0.0561 |
| Median | 1.304 | 1.396 |
| Min-Max | 0.71 - 2.06 | 0.72 - 2.18 |
| n | 55 | 59 |
| Body surface area in sqm, cat. | | |
| >0.7 to 0.9 | 5 ( 9%) | 15 ( 25%) |
| >0.9 to 1.15 | 13 ( 24%) | 6 ( 10%) |
| >1.15 to 1.5 | 18 ( 33%) | 12 ( 20%) |
| >1.5 | 19 ( 35%) | 26 ( 44%) |
| n | 55 | 59 |
| Weight for age z-score | | |
| Mean | 0.5310 | 0.5747 |
| SD | 1.14120 | 1.22036 |
| SEM | 0.15388 | 0.15888 |
| Median | 0.5622 | 0.6491 |
| Min-Max | -2.689 - 3.295 | -2.189 - 3.170 |
| n | 55 | 59 |
| Weight for age z-score, cat. | | |
| < -1 | 5 ( 9%) | 7 ( 12%) |
| -1 to 1 | 29 ( 53%) | 31 ( 53%) |
| > 1 | 21 ( 38%) | 21 ( 36%) |
| n | 55 | 59 |
| Height for age z-score | | |
| Mean | 0.0722 | 0.2127 |
| SD | 1.06458 | 1.00726 |
| SEM | 0.14355 | 0.13113 |
| Median | 0.2653 | 0.0319 |
| Min-Max | -3.018 - 2.415 | -1.859 - 2.375 |
| n | 55 | 59 |
| BMI for age z-score | | |
| Mean | 0.6540 | 0.5597 |
| SD | 1.02690 | 1.18094 |
| SEM | 0.13847 | 0.15374 |
| Median | 0.6343 | 0.6228 |
| Min-Max | -1.741 - 2.786 | -2.223 - 2.710 |
| n | 55 | 59 |

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
*Other = American Indian or Alaskan Native or Multiracial Patients
# As classified by Ishak fibrosis score based on pre-treatment liver biopsy assessed by the central pathologist
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| | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Ribavirin 15 mg/kg N = 55 | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Placebo N = 59 |
|---|---|---|
| HCV Genotype | | |
| 1 | 45 ( 82%) | 47 ( 80%) |
| 2 | 4 ( 7%) | 3 ( 5%) |
| 3 | 6 ( 11%) | 7 ( 12%) |
| 6 | - | 2 ( 3%) |
| n | 55 | 59 |
| Probable route of HCV transmission | | |
| VERTICAL/PERINATAL | 39 ( 71%) | 47 ( 80%) |
| TRANSFUSION | 6 ( 11%) | 2 ( 3%) |
| RECIPIENT | | |
| IV DRUG USE | - | 1 ( 2%) |
| SEXUAL CONTACT | 1 ( 2%) | - |
| UNKNOWN | 9 ( 16%) | 9 ( 15%) |
| n | 55 | 59 |
| Baseline HCV RNA (IU/ML) | | |
| Mean | 5729280 | 5104445 |
| SD | 13580866 | 6159492 |
| SEM | 1901702 | 801897.6 |
| Median | 1600000 | 2800000 |
| Min-Max | 6270 - 92400000 | 394 - 26800000 |
| n | 51 | 59 |
| Baseline ALT (U/L) | | |
| Mean | 52.6 | 56.1 |
| SD | 33.47 | 38.79 |
| SEM | 4.51 | 5.05 |
| Median | 39.0 | 42.0 |
| Min-Max | 14 - 152 | 10 - 254 |
| n | 55 | 59 |
| Histological diagnosis# | | |
| Cirrhosis | - | 1 ( 2%) |
| No Cirrhosis | 54 (100%) | 55 ( 98%) |
| n | 54 | 56 |
| Ishak fibrosis score | | |
| 0 | 7 ( 13%) | 8 ( 14%) |
| 1 | 24 ( 44%) | 28 ( 50%) |
| 2 | 19 ( 35%) | 18 ( 32%) |
| 3 | 4 ( 7%) | 1 ( 2%) |
| 5 | - | 1 ( 2%) |
| n | 54 | 56 |
| Steatosis fat score | | |
| 0 | 29 ( 54%) | 34 ( 61%) |
| 1 | 21 ( 39%) | 17 ( 30%) |
| 2 | 4 ( 7%) | 5 ( 9%) |
| n | 54 | 56 |

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
*Other = American Indian or Alaskan Native or Multiracial Patients
# As classified by Ishak fibrosis score based on pre-treatment liver biopsy assessed by the central pathologist
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**Adapted from Table 17 from Section 3.1.5 of applicant's study report**

Group 1 had a higher proportion of female subjects (28 subjects, 51%) as compared to Group 2 (23 subjects, 39%). The mean age of Group 1 and Group 2 were 10.7 years and 10.8 years, respectively. Overall, the majority of subjects in this study were white. Forty-five subjects (82%) of the patients in Group 1 were white as compared to 46 patients (78%) in Group 2. Hispanic or Latino subjects made up 9% of the population in Group 1 and 10% in Group 2.

Overall, the baseline growth parameters such as weight, height, body mass index (BMI), and body surface area (BSA) for the two groups were relatively well matched. The majority of subjects in both groups were infected with HCV genotype 1. Group 1 had 45 of 55 subjects (82%) with genotype 1 virus and Group 2 had 47 of 59 subjects (80%) with genotype 1 virus. Most subjects were infected by vertical or perinatal transmission representing 71% (39 subjects) in Group 1 and 80% (47 subjects) in Group 2.

Mean baseline HCV RNA for both groups was over 5 million with 5,729,280 IU/mL in Group 1 and 5,104,445 IU/mL in Group 2. The mean baseline alanine transaminase (ALT) was 52.6 U/L for the combination therapy group and 56.1 U/L for the monotherapy group. While no subjects in Group 1 had a histological diagnosis of cirrhosis, there was one subject in Group 2 with cirrhosis.

*Medical Officer's Comments: Overall the subjects in Study NV17424 were well matched for gender, age, race, ethnicity, growth parameters, and baseline disease characteristics between the two initial treatment groups. Minor differences in baseline demographics were not considered significant.*

### 6.1.3 Subject Disposition

One hundred and fourteen subjects were randomized into one of the two initial treatment groups with 55 subjects making up the PEG-IFN alfa-2a plus ribavirin combination therapy treatment group and 59 subjects in the PEG-IFN alfa-2a monotherapy treatment group. The following table which was taken from the applicant's study reports summarizes the disposition of subjects by initial treatment group:

**Table 4: Disposition of Patients by Initial Treatment Group, All Randomized Patients**

| | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Ribavirin 15 mg/kg N = 55 No. (%) | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Placebo N = 59 No. (%) |
|---|---|---|
| Pts randomized | 55 (100) | 59 (100) |
| Pts who received study drug | 55 (100) | 59 (100) |
| Pts who completed 12 weeks of treatment | 55 (100) | 57 ( 97) |
| Pts who completed 24 weeks of treatment | 54 ( 98) | 56 ( 95) |
| Pts who completed 48 weeks of treatment(a) | 37 ( 67) | 23 ( 39) |
| Pts who completed 24 weeks of follow-up after actual trcatmcnt(ab) | 52 ( 95) | 22 ( 37) |
| Pts who completed 24 weeks of follow-up after scheduled treatment(ac) | 51 ( 93) | 23 ( 39) |
| Pts who completed 1 year of follow-up after actual treatment(ad) | 49 ( 89) | 19 ( 32) |
| Pts who completed 1 year of follow-up after scheduled treatment(ae) | 48 ( 87) | 19 ( 32) |
| Pts who completed 2 years of follow-up after actual treatment(af) | 42 ( 76) | 17 ( 29) |
| Pts who completed 2 years of follow-up after scheduled treatment(ag) | 36 ( 65) | 17 ( 29) |

(a) Excluding monotherapy patients who switched to compassionate combination therapy.
(b) At least 140 days after actual treatment end.
(c) At least 477 days after start of treatment.
(d) At least 282 days after actual treatment end.
(e) At least 617 days after start of treatment.
(f) At least 646 days after actual treatment end.
(g) At least 981 days after start of treatment.

**Adapted from Table 9 in Section 3.1.1 of the applicant's study report**

In both Group 1 and in Group 2, most subjects completed 12 weeks of treatment (100% and 97%, respectively) with only 2 subjects in the monotherapy group not completing therapy. At 24 weeks, 98% of the combination therapy group completed therapy and 95% of the monotherapy group completed therapy. In the above table, the percentage of subjects who completed the scheduled treatment duration on 48 weeks was greater in combination therapy (67%) group as compared to the monotherapy group (39%); however, subjects in the monotherapy group who switched to the compassionate combination treatment were not counted as completers at later time points in this table because they were no longer under monotherapy after the switch. An alternate accounting of subjects completing 48 weeks of therapy is depicted in Table 5 taken from the applicant's study report which shows the disposition of subjects by actual treatment group:

**Table 5: Disposition of Subjects by Actual Treatment Group, All Randomized Subjects**

| | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Ribavirin 15 mg/kg N = 55 No. (%) | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Placebo Only N = 31 No. (%) | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Plac./Ribavirin 15 mg/kg N = 28 No. (%) |
|---|---|---|---|
| Pts who received study drug | 55 (100) | 31 (100) | 28 (100) |
| Pts who completed 24 weeks of treatment | 54 ( 98) | 28 ( 90) | 28 (100) |
| Pts who completed 48 weeks of treatment | 37 ( 67) | 23 ( 74) | 28 (100) |
| Pts who completed 52 weeks of treatment | 0 ( 0) | 0 ( 0) | 28 (100) |
| Pts who completed 76 weeks of treatment | 0 ( 0) | 0 ( 0) | 12 ( 43) |

(a) At least 140 days after actual treatment end.
(b) At least 477 days after start of treatment in patients who did not switch their treatment group and at least 673 days after start of treatment in monotherapy patients who switched to compassionated combination therapy.
(c) At least 282 days after actual treatment end.
(d) At least 617 days after start of treatment in patients who did not switch their treatment group and at least 813 days after start of treatment in monotherapy patients who switched to compassionated combination therapy.
(e) At least 646 days after actual treatment end.
(f) At least 981 days after start of treatment in patients who did not switch their treatment group and at least 1177 days after start of treatment in monotherapy patients who switched to compassionated combination therapy.

**Adapted from Table 10 in Section 3.1.1 of the applicant's study report**

Seventy-four percent of those subjects in the initial monotherapy group who were not switched to combination compassionate therapy completed 48 weeks of treatment while 100% of those who failed monotherapy and were switched completed 48 weeks of combination treatment.

*MO's Comment: At the 24-week time point the proportion of subjects who completed treatment was greater in the combination therapy group as compared to the monotherapy group. In addition, at the 48-week point the proportion of subjects who completed treatment was still greater in the initial combination therapy group as compared to the monotherapy group (23 of 59 subjects, 39%).*

In terms of subjects prematurely withdrawn from study treatment during the initial 24 weeks of the study, relatively equal number of subjects were withdrawn from the study in the monotherapy group (5%) as compared to the combination therapy group (2%). As illustrated in Table 6 below, these withdrawals were all due to safety reasons. These withdrawals will be discussed in more detail in Section 7.3.3:

**Table 6: Summary of Reasons for Premature Withdrawal From Study Treatment During the First 24 Weeks by Initial Treatment Group, Intent-to-Treat Population**

| Reason for Withdrawal | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Ribavirin 15 mg/kg N = 55 No. (%) | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Placebo N = 59 No. (%) |
|---|---|---|
| Safety | 1 ( 2) | 3 ( 5) |
| Abnormality of Laboratory Test | 0 | 0 |
| Adverse Event(a) | 1 | 3 |
| Death | 0 | 0 |
| Non-Safety | 0 ( 0) | 0 ( 0) |
| Insufficient Therapeutic Response | 0 | 0 |
| Early Improvement | 0 | 0 |
| Violation of Selection Criteria at Entry | 0 | 0 |
| Other Protocol Violation | 0 | 0 |
| Refused Treatment(b) | 0 | 0 |
| Failure to Return | 0 | 0 |
| Other | 0 | 0 |
| Total | 1 ( 2) | 3 ( 5) |

(a)=Including intercurrent illness (b)=Including 'did not co-operate', 'withdrew consent'
Percentages are based on N.

**Adapted from Table 11 in Section 3.1.2 in the applicant's study report**

In terms of the entire study treatment period including the group of patients who were initially on PEG-IFN alfa-2a monotherapy then switched to compassionate combination therapy, the overall proportion of subjects who were prematurely withdrawn from treatment was 26% in monotherapy group, 33% in the initial combination therapy group, and 57% in the compassionate combination therapy group. As seen in Table 7, overall, a larger proportion of subjects were withdrawn for non-safety reasons than for safety reasons in both the initial combination therapy group and the compassionate combination therapy group. The main reason the majority of patients were prematurely withdrawn for non-safety reasons in both the initial combination therapy group (100%) and the compassionate combination therapy group (93%) was because of insufficient therapeutic response. No subjects in the monotherapy group were prematurely withdrawn from treatment because of insufficient therapeutic response because these subjects were rolled into the compassionate combination therapy arm. This should be viewed in the context of 28 of 59 subjects (47%) in the initial monotherapy arm rolling into the open-label compassionate combination therapy because of insufficient response. Three subjects (10%) in the monotherapy group were prematurely withdrawn from treatment due to non-safety reasons including refusal of treatment (1 subject) and failure to return (2 subjects). These safety reasons for premature withdrawal will be discussed in more detail in Section 7.3.3.

**Table 7: Summary of Reasons for Premature Withdrawal From Study Treatment by Actual Group**

| Reason for Withdrawal | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Ribavirin 15 mg/kg N = 55 No. (%) | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Placebo Only N = 31 No. (%) | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Plac./Ribavirin 15 mg/kg N = 28 No. (%) |
|---|---|---|---|
| Safety | 7 ( 13) | 5 ( 16) | 1 ( 4) |
| Abnormality of Laboratory Test | 0 | 0 | 0 |
| Adverse Event(a) | 7 | 5 | 1 |
| Death | 0 | 0 | 0 |
| Non-Safety | 11 ( 20) | 3 ( 10) | 15 ( 54) |
| Insufficient Therapeutic Response | 11 | 0 | 14 |
| Early Improvement | 0 | 0 | 0 |
| Violation of Selection Criteria at Entry | 0 | 0 | 0 |
| Other Protocol Violation | 0 | 0 | 0 |
| Refused Treatment(b) | 0 | 1 | 1 |
| Failure to Return | 0 | 2 | 0 |
| Other | 0 | 0 | 0 |
| Total | 18 ( 33) | 8 ( 26) | 16 ( 57) |

(a)=Including intercurrent illness (b)=Including 'did not co-operate', 'withdrew consent'
Percentages are based on N.

**Adapted from Table 12 in Section 3.1.2 of applicant's study report**

*MO's Comment: Overall, the subject dispositions of the two initial treatment groups were relatively well matched. The two groups had similar, small proportions of subjects prematurely withdrawn from treatment, mainly for safety reasons, in the first 24 weeks. However, after the initial 24 weeks, it becomes more difficult to interpret the balance of subject disposition in terms of premature withdrawals and overall completion of the study treatment when comparing combination therapy versus monotherapy because of the therapy switch for a large portion of the initial monotherapy group. While in the initial combination therapy group a large portion of subjects did not complete the study because of insufficient therapeutic response, those patients who had an insufficient therapeutic response in the monotherapy group were immediately placed in the switch group.*

### 6.1.4 Analysis of Primary Endpoint(s)

The primary objective of this trial was to assess the risk/benefit of PEG-IFN alfa-2a and ribavirin combination therapy compared with PEG-IFN alfa-2a monotherapy in pediatric subjects.

The primary endpoint was sustained virologic response (SVR) according to scheduled treatment period defined as the percentage of subjects with undetectable HCV RNA as measured by the HPS/COBAS TaqMan HCV Test (lower limit of detection: 10 IU/mL) at or after week 68 (i.e., a single last HCV RNA < 10 IU/mL measured ≥ study day 477).

All subjects in the monotherapy arm who did not reach undetectable HCV RNA by Week 24 (Amplicor HCV PCR RNA ≥ 50 IU/mL) were discontinued from monotherapy and allowed to switch to compassionate combination treatment; thus, any values after the switch were classified as failures for the primary endpoint.

All subjects without viral load measurements in the relevant time window for SVR at Week 72 (≥Week 68, Day 477) were considered to be non-responders in the primary efficacy analysis.

The intent-to-treat analysis population was defined as all subjects randomized who received at least one dose of study medication. All subjects were analyzed according to their randomly allocated treatment group irrespective of the treatment received. All primary and secondary efficacy parameters were analyzed using this population. This population was also called the all patients treated population.

Forty-nine percent (49%, n=27) of the 55 children randomized to Pegasys/Copegus achieved an SVR compared to only 20% (n=12) of the 59 children randomized to Pegasys monotherapy (p=0.002). This represented a 29% improvement in SVR for children on combination therapy compared to those on Pegasys monotherapy with a 95% C.I. ranging from 11-45%. These and other analyses are summarized in Table 8.

**Table 8: Primary Efficacy Endpoint: Sustained Virologic Response (ITT), Protocol NV17424**

| | Pegasys / Placebo | Pegasys / Copegus |
|---|---|---|
| | N=59 | N=55 |
| SVR[1] | 12 (20%) | 27 (49%) |
| Difference (95% C.I.) (Pegasys/Copegus – Pegasys/Placebo) | | 29% (11%, 45%) |
| Odds Ratio[2] (95% C.I.) | | 3.8 (1.7, 9) |
| Relative Risk[3] (95% C.I.) | | 2.4 (1.4, 4.3) |
| p-value for test of superiority[4] | | 0.002 |
| Adjusted Mantel-Haenszel Odds Ratio | | 5.1 (1.9, 14) |
| Adjusted Mantel-Haenszel Relative Risk | | 2.4 (1.4, 4.2) |
| p-value for test of superiority[5] | | 0.001 |
| Breslow-Day Test of Homogeneity of the Odds Ratio | | 0.87 |

[1] SVR defined as HCV RNA < LOD (10 IU/mL) at Week 72 (≥Week 68, Day 477) using TaqMan HCV Test.
[2] Ratio of Odds Pegasys/Copegus to Odds Pegasys/Placebo
[3] Ratio of Probability of Response for Pegasys to Copegus to Probability of Response for Pegasys/Placebo
[4] Two-sided Fisher's Exact Test
[5] Two−sided Cochran-Mantel Haenszel p−value adjusted for center and genotype (1 vs. 2/3/6).

Since randomization was stratified by center and genotype (1 vs. 2/3/6) statistical analyses were also performed to adjust for these factors. The adjusted odds ratio was 5.1 (95% C.I. 1.9 to 14) and the adjusted relative risk was 2.4 (95% C.I.: 1.4 to 4.2). Using two-sided Cochran-Mantel Haenszel (CMH) statistics adjusted for center and genotype (1 vs. 2/3/6) the p-value was statistically significant (p=0.001) supporting the superiority of combination Pegasys/Copegus treatment over Pegasys monotherapy. There was no apparent interaction between center and genotype with respect to treatment effects as indicated by the non-significance of the Breslow-Day test (p=0.87). The results of these analyses are shown in Table 9.

**Table 9: Risk Differences and Exact 95% C.I. for Primary Efficacy Endpoint in Genotype 1 and non-1 subjects: Sustained Virologic Response (ITT), Protocol NV17424**

| | Pegasys / Placebo | Pegasys / Copegus |
|---|---|---|
| Genotype 1 | | |
| SVR[1] | 8/47 (17%) | 19/45 (42%) |
| Difference (95% C.I.) (Pegasys/Copegus – Pegasys/Placebo) | | 25% (6%, 43%) |
| p-value for test of superiority[2] | | 0.01 |
| Non-Genotype 1 | | |
| SVR[1] | 4/12 (33%) | 8/10 (80%) |
| Difference (95% C.I.) (Pegasys/Copegus – Pegasys/Placebo) | | 47% (4%, 74%) |
| p-value for test of superiority[2] | | 0.04 |
| | | |

[1] SVR defined as HCV RNA < LOD (10 IU/mL) at Week 72 (≥Week 68, Day 477) using TaqMan HCV Test.
[2] Fisher's exact test

In both genotype 1 and non-1 subjects, there were a significantly higher percentage of subjects treated with Pegasys / Copegus combination treatment with an SVR compared to Pegasys monotherapy, even in the small number of genotype non-1 subjects.

In addition to the analysis of SVR performed with the COBAS Taqman HCV Test, the applicant performed an analysis of SVR using another HCV RNA test, the AMPLICOR HCV test. These reported results were similar to the COBAS Taqman results with the SVR rate being 53% for both the scheduled treatment period [defined as a single last HCV RNA measurement that is not detectable on or after week 68 (study day 477)] and actual treatment period [defined as a single last HCV RNA measurement that is not detectable at least 20 weeks after treatment end (≥ study day of last dose of study medication + 140)]. In comparison, the SVR rate was 20% for the monotherapy group. The odds ratio for these responses for these two treatment groups was 5.9 (95% C.I. of 2.2, 16) and a p-value <0.001. The slightly higher SVR result was due to two patients who had undetectable AMPLICOR HCV test results, but had missing COBAS Taqman HCV test results in the time windows of concern for the primary analysis.

**Table 10: Response Rates by Visit during first 24 Weeks of Treatment, Protocol NV17424 (ITT Population)**

Group 1: Pegasys/Copegus (n=55)

| Visit | TaqMan (<=10 IU/mL) | Amplicor (<=50 IU/mL) |
|---|---|---|
| TW 1 | 2 (4%) | ----- |
| TW 3 | 4 (7%) | ----- |
| TW 5 | 12 (22%) | ----- |
| TW 12 | 29 (53%) | 32 (58%) |
| TW 24 | 36 (65%) | 40 (73%) |
| EOT[bi] | 35 (64%) | 36 (65%) |
| Week 60[bi] | 28 (51%) | 29 (53%) |
| SVR | 27 (49%) | 29 (53%) |

Group 2: Pegasys/Placebo (n=59)

| Visit | TaqMan (<=10 IU/mL) | Amplicor (<=50 IU/mL) |
|---|---|---|
| TW 1 | 1 (2%) | ----- |
| TW 3 | 3 (5%) | ----- |
| TW 5 | 6 (10%) | ----- |
| TW 12 | 11 (19%) | 15 (25%) |
| TW 24 | 23 (39%) | 26 (44%) |
| EOT[bi] | 22 (37%) | 22 (37%) |
| Week 60[bi] | 13 (22%) | 13 (22%) |
| SVR | 12 (20%) | 12 (20%) |

[bi] Backward Imputation using SVR at scheduled Week 72 visit if missing at TW 48 or TW 60.

Using backward imputation, children who achieved a virological response at the end of the follow-up period but had no HCV RNA assessment at the end of the scheduled treatment period were also considered to be virological responders at the end of treatment. Backward Imputation was also used to compute Week 60 response rates.

Interim Analysis

According to the applicant, the protocol specified that a total of up to three interim analyses of the primary efficacy variable could be performed. An adaptation of the Lan-DeMets procedure was to be used for assessing the primary efficacy variable when the interim analyses were performed.

According to the applicant, a single interim analysis was performed that included 77 patients with efficacy data. The applicant stated that while there was a provision to halt the study in the event of greater efficacy for PEG-INF alfa-2a plus ribavirin, no action was taken due to the results of the interim analysis since all of the study participants (114 patients) had already been enrolled and were in the study for at least 9 months. The FDA statistical reviewer agrees with the applicant's claim that it was highly unlikely that the reporting of these confidential results to the DSMB and Project Office introduced any operational bias into the study or had any impact on the final SVR.

*MO's Comment: Based on the submitted data and results, the efficacy of treatment with PEG-IFN alfa-2a (Pegasys) plus ribavirin (Copegus) combination therapy, as measured by SVR, was greater than with treatment with PEG-IFN alfa-2a alone.*

6.1.5 Analysis of Secondary Endpoints(s)

Secondary efficacy endpoints that were investigated included:

- Virological responses over time (weeks 1, 3, 5, 12, 24, 48, and 60)
- Maintenance of end-of-treatment virological response
- Relapse of end-of-treatment virological response
- Changes from baseline in $\log_{10}$ HCV RNA values at weeks 1, 3, 5, 12, 24, 48, and 60

Virological responses over time

Table 11 below displays the outcomes by visit for each initial treatment group including weeks 1, 3, 5, 12, 24, 48, and 60:

For each treatment group, the FDA statistical reviewer summarized outcomes at each visit by percentage of subjects with undetectable (≤10 IU/mL) HCV RNA, HCV RNA that was detectable but below the limit of quantitation (>10-25 IU/mL), quantifiable (>25 IU/mL) or missing HCV RNA data. The percentage of missing values increased dramatically from only 8% at Week 24 to 59% at Week 48 in the Pegasys monotherapy

arm. A smaller increase in the percentage of missing data was also observed for the combination therapy arm. There was a large increase in missing HCV RNA data after Week 24 because subjects with detectable HCV RNA at week 24 stopped their treatment (in the combination arm) or switched to compassionate combination treatment (in the monotherapy arm) and were considered nonresponders, as were those without measurements at or after week 68.

**Table 11: Outcomes by Visit, Protocol NV17424, TaqMan HCV Test, (ITT Population)**

Pegasys/Placebo (n=59)

| Visit | Undetectable (≤10 IU/mL) | Detectable/ BLOQ (>10-25 IU/mL) | Quantifiable (>25 IU/mL) | Missing |
|---|---|---|---|---|
| TW 1 | 1 (2%) | 2 (3%) | 53 (90%) | 3 (5%) |
| TW 3 | 3 (5%) | 1 (2%) | 50 (85%) | 5 (8%) |
| TW 5 | 6 (10%) | 0 | 51 (86%) | 2 (3%) |
| TW 12 | 11 (19%) | 2 (3%) | 35 (59%) | 11 (19%) |
| TW 24 | 23 (39%) | 1 (2%) | 30 (51%) | 5 (8%) |
| TW 48 | 22 (37%) | 1 (2%) | 1 (2%) | 35 (59%) |
| TW 60 | 12 (20%) | 0 | 6 (10%) | 41 (69%) |
| | | | | |
| TW 48[bi] | 22 (37%) | 1 (2%) | 1 (2%) | 35 (59%) |
| TW 60[bi] | 13 (22%) | 0 | 6 (10%) | 40 (68%) |
| SVR | 12 (20%) | 0 | 7 (12%) | 40 (68%) |

Pegasys/Copegus (n=55)

| Visit | Undetectable (≤10 IU/mL) | Detectable/ BLOQ (>10-25 IU/mL) | Quantifiable (>25 IU/mL) | Missing |
|---|---|---|---|---|
| TW 1 | 2 (4%) | 0 | 47 (85%) | 6 (11%) |
| TW 3 | 4 (7%) | 3 (5%) | 42 (76%) | 6 (11%) |
| TW 5 | 12 (22%) | 2 (4%) | 38 (69%) | 3 (5%) |
| TW 12 | 29 (53%) | 2 (4%) | 20 (36%) | 4 (7%) |
| TW 24 | 36 (65%) | 2 (4%) | 14 (25%) | 3 (5%) |
| TW 48 | 33 (60%) | 0 | 3 (5%) | 19 (35%) |
| TW 60 | 22 (40%) | 0 | 7 (13%) | 26 (47%) |
| | | | | |
| TW 48[bi] | 35 (64%) | 0 | 3 (5%) | 17 (59%) |
| TW 60[bi] | 28 (51%) | 0 | 7 (13%) | 20 (36%) |
| SVR | 27 (49%) | 0 | 9 (16%) | 19 (25%) |

[bi] Backward Imputation using SVR at scheduled Week 72 visit if missing at TW 48 or TW 60.

Starting at Week 12 and continuing through end of treatment and the 24 week follow-up period, virological responses were significantly higher in children who received combination therapy with Pegasys/Copegus than in children who received Pegasys monotherapy. During this time period, the odds ratio ranged from 3.1 at Week 24 to 6.5 at Week 12 while the relative risk ranged from 1.6 at Week 24 to 2.9 at Week 12. From Week 12 onwards, trends for odds ratios and relative risks were consistent with p-values in the sense that lower confidence intervals for odds ratios and relative risks exceeded 1.0.

Relapse of end-of-treatment virological response

Relapse of end-of-treatment virological response is an assessment of the loss of response after the end of treatment, and was calculated according to the scheduled treatment period. Using backward imputation, subjects who achieved a virological response at the end of the follow-up period but had no HCV RNA assessment at the end of the scheduled treatment period were also considered to be virological responders at the end of treatment.

For the intent-to-treat population, the percentage of patients who relapsed after having achieved a virologic response at the scheduled end of treatment was lower in the PEG-IFN alfa-2a plus ribavirin combination therapy group (23%) compared with the PEG-IFN alfa-2a monotherapy group (43%; see Table 23 of the Clinical Study Report).

**Table 12: Relapse of End-of-Treatment Virological Response (HPS/COBAS TaqMan HCV Test < 10 IU/mL) According to Scheduled Treatment Period Using Backward Imputation, Intent-to-Treat Population**

| Treatment Group | No. of Pts | Response at End of Trt (a) | Relapse Post-trt | Relapse Post-trt % (ab) |
|---|---|---|---|---|
| PEG-IFN alfa-2a 180 ug x BSA/1.73 sqm + Ribavirin 15 mg/kg | 55 | 35 | 8 | 23% |
| PEG-IFN alfa-2a 180 ug x BSA/1.73 sqm + Placebo | 59 | 21 | 9 | 43% |

Trt= Treatment.
(a) Patients who had an end-of-treatment virological response and did not have any HCV RNA measurement during follow-up have been excluded; these patients were not considered as having relapsed.
Patients who achieved a virological response at the end of the follow-up period (sustained virological response according to scheduled treatment period) but had no HCV RNA assessment at the end of the scheduled treatment period were also considered end-of-treatment virological responders (backward imputation).
(b) Number of patients who achieved a response at the scheduled end of treatment but had detectable HCV RNA at the last assessment posttreatment divided by the number of patients with a virological response at the scheduled end of treatment who had at least one HCV RNA assessment posttreatment.

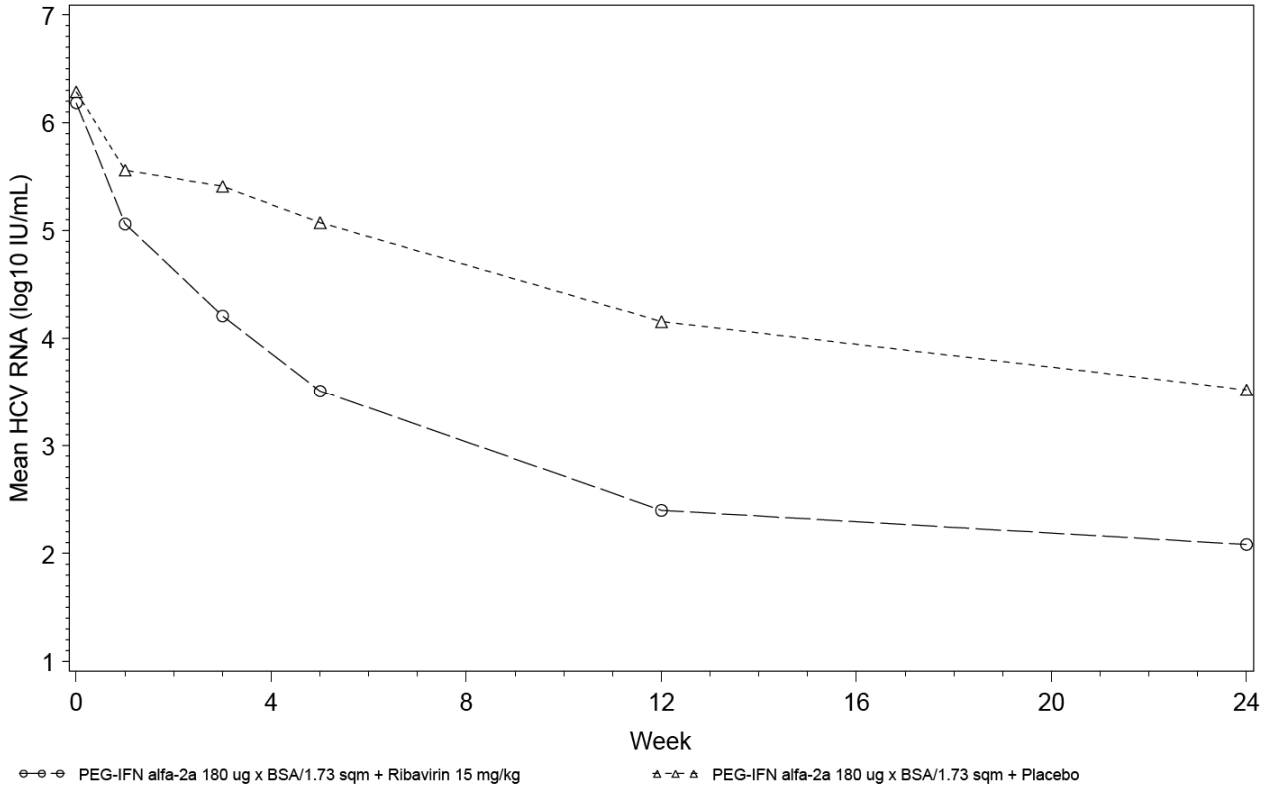
**Source: Table 23 of the Clinical Study Report for study NV17424**

When looking at the converse of relapse or maintenance of end-of-treatment virological response (HCV RNA <10 IU/mL with COBAS Taqman HCV test) at the end of the 24-week follow-up period, the initial combination therapy group had a greater proportion of subjects (77%) maintaining SVR than the proportion seen in the monotherapy group (57%).

Changes from baseline in $log_{10}$ HCV RNA values

During the first 24 weeks of treatment, when there was very little missing HCV RNA data, the applicant plotted mean $log_{10}$ HCV RNA levels at each visit. Results appeared to be consistent with other analyses with lower mean viral loads for children randomized to combination therapy than for children randomized to monotherapy.

**Figure 2: HCV RNA Level (HPS/COBAS TaqMan HCV Test) at Baseline, Week 1, 3, 5, 12, and 24, ITT Population**




**Source: Figure 2 of the Clinical Study Report for study NV17424**

*MO's Comment: Based on these secondary efficacy analyses, there appears to be a greater virologic benefit at various time points with combination therapy as compared to monotherapy.*

6.1.6 Other Endpoints

Other exploratory efficacy endpoints were investigated. They included:

- Logistic regression analyses of effects of concomitant ribavirin therapy and baseline factors on the probability of SVR
- Predictive value of virological responses of weeks 5 and 12 for SVR

Logistic regression analyses of effects of concomitant ribavirin therapy and baseline factors on the probability of SVR

The applicant's multiple logistic regression model identified baseline HCV RNA and treatment group as the only two statistically significant predictors of SVR as shown in Table 13. Higher baseline HCV RNA is a negative predictor of SVR while combination therapy is a positive predictor compared to monotherapy (odds ratio = 5.0, 95% C.I.: 1.6 to 15.5). The applicant also noted that non-genotype 1 had a non-statistically significant trend in favor of higher SVR but was probably not statistically significant due to small numbers of the non-genotype 1 subjects. Other factors like gender, race, weight, and age had no apparent influence on SVR.

**Table 13: Multiple Logistic Regression Analysis Identifying Baseline Factors Associated with Sustained Virological Response (HPS/COBAS TaqMan HCV Test < 10 IU/mL) According to Scheduled Treatment Period, Intent-to-Treat Population**

| | Parameter Estimate | Standard Error | Odds Ratio (95% CI) | P-Value |
|---|---|---|---|---|
| Gender (MALE vs FEMALE) | -0.7064 | 0.5850 | 0.493 ( 0.157, 1.553) | 0.2272 |
| Race (White vs Other) | -0.3595 | 0.7566 | 0.698 ( 0.158, 3.075) | 0.6347 |
| Genotype (Non-1 vs 1) | 0.9875 | 0.6895 | 2.684 ( 0.695, 10.369) | 0.1521 |
| Ishak fibrosis score (0-1 vs 2-6) | 0.0327 | 0.5566 | 1.033 ( 0.347, 3.076) | 0.9531 |
| Steatosis score (0 vs >=2) | -0.1983 | 1.2397 | 0.820 ( 0.072, 9.314) | 0.8729 |
| Steatosis score (1 vs >=2) | -1.0913 | 1.1908 | 0.336 ( 0.033, 3.464) | 0.3594 |
| Weight for age z-score | -0.6628 | 0.7043 | 0.515 ( 0.130, 2.050) | 0.3467 |
| Body mass index (kg/m2) | -0.0713 | 0.1573 | 0.931 ( 0.684, 1.267) | 0.6503 |
| Age (years) | -0.3619 | 0.3431 | 0.696 ( 0.355, 1.364) | 0.2915 |
| Baseline HCV RNA (log10 IU/mL) | -1.0105 | 0.3638 | 0.364 ( 0.178, 0.743) | 0.0055 |
| Baseline ALT ratio | 0.2547 | 0.3051 | 1.290 ( 0.710, 2.346) | 0.4037 |
| Initial treatment group (B vs A) | 1.6113 | 0.5778 | 5.009 ( 1.614, 15.546) | 0.0053 |
| Body surface area (sqm) | 4.2887 | 4.0207 | 72.871 ( 0.028, 192742) | 0.2861 |

Number of observations: 101 (13 observation(s) deleted due to missing values).
Sustained virological response according to scheduled treatment period is defined as a single last HCV RNA measurement that is not detectable (HPS/COBAS TaqMan HCV Test <10 IU/mL) >= week 68 (>= study day 477).
Initial treatment group: A - PEG-IFN alfa-2a+Placebo, B - PEG-IFN alfa-2a+Ribavirin.

**Source: Table 24 of the Clinical Study Report for study NV17424**

Predictive value of virological responses of weeks 5 and 12 for SVR

As an exploratory analysis, the FDA statistics and microbiology reviewers examined the effect of early treatment response, defined as undetectable HCV RNA, on the subsequent probability of obtaining an SVR (see Figure 3). For combination therapy, a very early response at Week 5 was associated with the greatest probability of an SVR; over 80% (10/12) of the subjects who responded at Week 5 had an SVR. Subjects responding at Week 48 also had a high probability (almost 80%, 27/35) of having an SVR.

Compared to Pegasys monotherapy, the chance of having an SVR was higher for Pegasys/Copegus combination therapy for responders at treatment weeks 5, 24 and 48.

For Pegasys monotherapy, a response at Week 12 was associated with the greatest chance of having an SVR; over 70% (9/11) of the subjects who responded at Week 12

had an SVR (see Figure 4). SVR rates for subjects who responded at Week 12 were approximately the same in the two treatment arms. However, since there were only a small number of children on Pegasys monotherapy who responded at Week 12, this finding should be interpreted with caution.

**Figure 3: Predictability of Early Viral Response on SVR: Pegasys/Copegus**

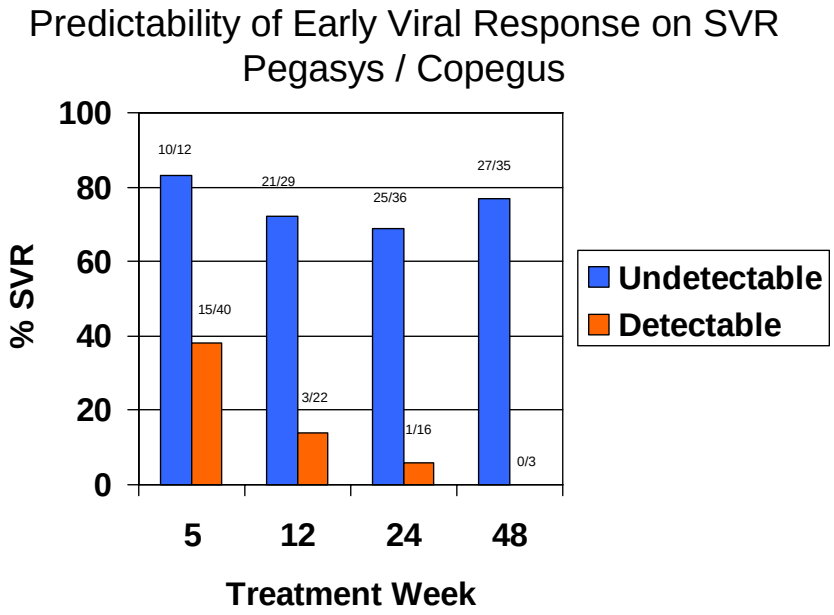
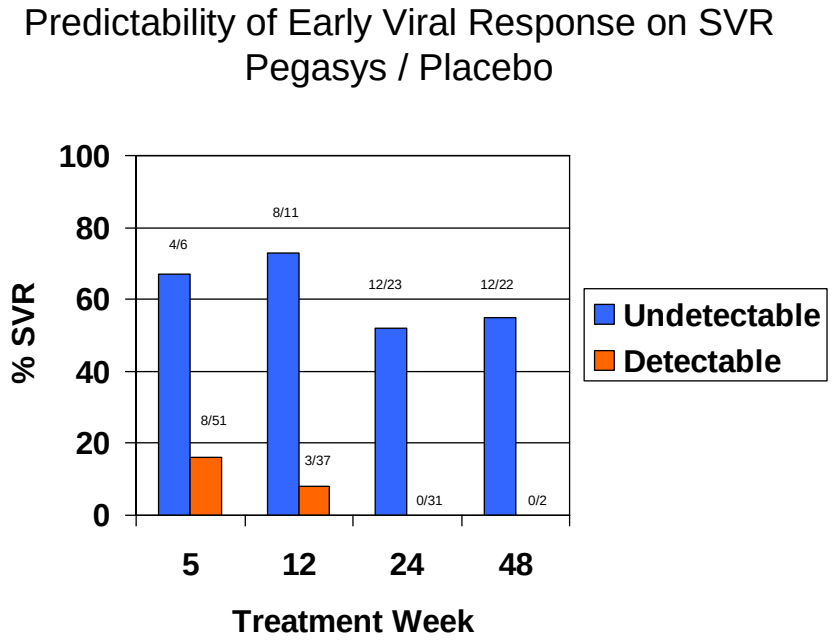


**Figure 4: Predictability of Early Viral Response on SVR: Pegasys/Placebo**




6.1.7 Subpopulations

Table 14 and Table 15 provide subgroup SVR data according to the scheduled treatment period. With the exception of baseline HCV RNA (≤600,000 and ≤800,000 copies/mL subgroups) SVR rates appeared to be consistently higher for children randomized to combination therapy than for children randomized to Pegasys monotherapy.

**Table 14: Subgroup Analyses of Sustained Virological Response (HPS/COBAS TaqMan HCV Test < 10 IU/mL) According to Scheduled Treatment Period, Intent-to-Treat Population**

| | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Ribavirin 15 mg/kg N=55 | | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Placebo N=59 | |
|---|---|---|---|---|
| | N | SVR | N | SVR |
| All Patients | 55 | 27 ( 49%) | 59 | 12 ( 20%) |
| HCV genotype | | | | |
| 1 | 45 | 19 ( 42%) | 47 | 8 ( 17%) |
| Non-1 | 10 | 8 ( 80%) | 12 | 4 ( 33%) |
| HCV genotype | | | | |
| 1 | 45 | 19 ( 42%) | 47 | 8 ( 17%) |
| 2 | 4 | 3 ( 75%) | 3 | 1 ( 33%) |
| 3 | 6 | 5 ( 83%) | 7 | 2 ( 29%) |
| Other | | | 2 | 1 ( 50%) |
| HCV RNA (COBAS TaqMan HCV Test) at baseline | | | | |
| <= 400,000 IU/mL | 10 | 8 ( 80%) | 7 | 5 ( 71%) |
| > 400,000 IU/mL | 41 | 17 ( 41%) | 52 | 7 ( 13%) |
| HCV RNA (COBAS TaqMan HCV Test) at baseline | | | | |
| <= 600,000 IU/mL | 15 | 10 ( 67%) | 10 | 7 ( 70%) |
| > 600,000 IU/mL | 36 | 15 ( 42%) | 49 | 5 ( 10%) |
| HCV RNA (COBAS TaqMan HCV Test) at baseline | | | | |
| <= 800,000 IU/mL | 17 | 12 ( 71%) | 12 | 9 ( 75%) |
| > 800,000 IU/mL | 34 | 13 ( 38%) | 47 | 3 ( 6%) |
| Geographical region (census regions) | | | | |
| Northeast | 13 | 7 ( 54%) | 14 | 4 ( 29%) |
| Midwest | 10 | 3 ( 30%) | 10 | 1 ( 10%) |
| South | 18 | 9 ( 50%) | 18 | 2 ( 11%) |
| West | 14 | 8 ( 57%) | 17 | 5 ( 29%) |
| Age | | | | |
| <= 11 years | 30 | 13 ( 43%) | 30 | 7 ( 23%) |
| >= 12 years | 25 | 14 ( 56%) | 29 | 5 ( 17%) |

Sustained virological response (SVR) according to scheduled treatment period is defined as a single last HCV RNA measurement that is not detectable (HPS/COBAS TaqMan HCV Test <10 IU/mL) >= week 68 (>= study day 477).
HCV RNA measurements after switch from monotherapy to combination therapy were not used to determine SVR.
Patients without measurements in the relevant time window are considered non-responders in the analysis.

**Source: Table 26 of the Clinical Study Report for study NV17424**

**Table 15: Subgroup Analyses of Sustained Virological Response (HPS/COBAS TaqMan HCV Test < 10 IU/mL) According to Scheduled Treatment Period, Intent-to-Treat Population**

| | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Ribavirin 15 mg/kg N=55 | | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Placebo N=59 | |
|---|---|---|---|---|
| | N | SVR | N | SVR |
| Gender | | | | |
| Male | 27 | 14 ( 52%) | 36 | 4 ( 11%) |
| Female | 28 | 13 ( 46%) | 23 | 8 ( 35%) |
| Race | | | | |
| White | 45 | 21 ( 47%) | 46 | 9 ( 20%) |
| Other | 7 | 4 ( 57%) | 11 | 3 ( 27%) |
| Weight for age z-score | | | | |
| < -1 | 5 | 3 ( 60%) | 7 | 2 ( 29%) |
| -1 to 1 | 29 | 15 ( 52%) | 31 | 7 ( 23%) |
| > 1 | 21 | 9 ( 43%) | 21 | 3 ( 14%) |
| Body surface area | | | | |
| <= 0.7 sqm | | | | |
| >0.7 to 0.9 sqm | 5 | 4 ( 80%) | 15 | 6 ( 40%) |
| >0.9 to 1.15 sqm | 13 | 3 ( 23%) | 6 | 1 ( 17%) |
| >1.15 to 1.5 sqm | 18 | 10 ( 56%) | 12 | 3 ( 25%) |
| >1.5 sqm | 19 | 10 ( 53%) | 26 | 2 ( 8%) |
| ALT at baseline | | | | |
| Elevated ALT | 31 | 13 ( 42%) | 36 | 5 ( 14%) |
| Normal ALT | 24 | 14 ( 58%) | 23 | 7 ( 30%) |
| Liver biopsy data (Ishak fibrosis score) | | | | |
| 0-1 | 31 | 16 ( 52%) | 36 | 7 ( 19%) |
| 2-4 | 23 | 10 ( 43%) | 19 | 4 ( 21%) |
| 5-6 | | | 1 | 0 ( 0%) |
| Steatosis fat score | | | | |
| 0 | 29 | 17 ( 59%) | 34 | 10 ( 29%) |
| 1 | 21 | 7 ( 33%) | 17 | 0 ( 0%) |
| >= 2 | 4 | 2 ( 50%) | 5 | 1 ( 20%) |

Sustained virological response (SVR) according to scheduled treatment period is defined as a single last HCV RNA measurement that is not detectable (HPS/COBAS TaqMan HCV Test <10 IU/mL) >= week 68 (>= study day 477).
HCV RNA measurements after switch from monotherapy to combination therapy were not used to determine SVR.
Patients without measurements in the relevant time window are considered non-responders in the analysis.

**Source: Table 26 (Cont.) of the Clinical Study Report for study NV17424**

*MO's Comment: These analyses show that the benefit of combination therapy as compared to monotherapy was consistent within the majority of analyzed subgroups..*

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

There was no clinical information or data submitted that evaluate individual dose-response or concentration-response relationships of effectiveness that significantly contributes to dosing recommendations and choice of dose interval.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The persistence of efficacy was discussed in the Section 6.1.5 which evaluated the maintenance and relapse of end-of-treatment virological response. Generally, SVR is considered a virologic "cure" and there are very few relapses seen. Once SVR is achieved, the response is usually long-lasting. Overall, there appears to be a greater persistence of efficacy with combination therapy as compared to monotherapy.

6.1.10 Additional Efficacy Issues/Analyses

In the supportive study, Study NR16141, Subjects received PEG-IFN alfa-2a subcutaneously once weekly for 48 weeks and continued to be evaluated throughout a 24-week treatment-free follow-up period. The dose for PEG-IFN alfa-2a was obtained by multiplying the BSA of the pediatric subject in $m^2$ by the $\mu g/m^2$ dose for an average adult with a BSA of 1.73 $m^2$ (180 $\mu g/1.73\ m^2$).

Nine of the 14 patients in this study completed 48 weeks of treatment and 24 weeks of treatment-free follow-up. The five other subjects were withdrawn prematurely from the treatment because of laboratory abnormalities or elevated alanine transaminase or elevated triglyceride levels.

Of the 14 subjects in this study, 6 subjects achieved SVR (43%, 95% C.I.,17.7% to 71.1%) at week 72. All six subjects had HCV genotype 1 virus.

*MO's Comment: Although the SVR rate for these patients who were treated with PEG-IFN alfa-2a monotherapy was 43%, it is difficult to draw any conclusion from this result in terms of efficacy because of the small number of subjects. In addition, it is difficult to compare and assess its contribution to support the efficacy results seen in Study NV17424.*

# 7 Review of Safety

## ***Safety Summary***

The applicant's main safety analysis incorporated results from a population (Safety-2 population, see Section 7.1.1.) consisting of not only the initial randomized treatment groups (PEG-IFN alfa-2a plus ribavirin and PEG-IFN alfa-2a plus placebo) but also the group who were initially non-responders in the monotherapy group then switched without randomization to compassionate combination therapy. This potential selection bias was taken into consideration in the interpretation of the data and analysis. In addition, results from the initially randomized groups at 24 weeks treatment (Safety-1 population) were also evaluated to have a direct comparison of combination therapy versus monotherapy. This analysis is limited because of the short period of time it covers.

The overall safety profile in NV17424 is not only similar to the safety profile previously seen in adult patients with chronic HCV infection treated with combination therapy with Pegasys and Copegus but also with the safety profile seen in pediatric patients with chronic HCV treated with other interferon/ribavirin regimens. In addition, there were no substantial differences when the data from the initial 24 week period was compared to the entire duration of the study (Safety-1 population versus Safety-2 population).

Adverse events seen were consistent with previous interferon/ribavirin clinical trials and no deaths occurred. Depression was seen in some subjects, with a higher proportion of subjects in the monotherapy group as compared to the two other combination therapy groups. However, the differences between treatment groups in terms of depression and other AEs did not appear to be clinically significant. Serious adverse events included suicidal behavior (monotherapy group), hyperglycemia (combination therapy) and cholecystectomy (combination therapy) and were considered by the investigators to be related to the study drugs. All three events resolved with treatment.

Laboratory abnormalities seen in NV17424 were similar to those previously associated with these drugs but the majority were not severe and were easily managed by dose modification.

As seen in pediatric patients on similar interferon therapy, decrease in growth parameters such as weight and height were seen during the treatment period. Although there was significant improvement of these growth changes by the 2 year post-treatment follow-up, a small proportion of subjects had not fully recovered at the end of follow-up

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary analysis for safety for PEG-IFN alfa-2a in combination with ribavirin in the treatment of chronic HCV in subjects aged 5 to 18 years was based on results from study NV17424. Safety data from study NR16141 was provided for support of the pivotal study, however, because of differences in patient population, study design, and study conduct, the data were not pooled with data from NV17424. Supportive safety data from NR 16141 will be discussed in Section 7.4.5.

The safety population for NV17424 was defined as all subjects who received at least one injection of PEG-IFN alfa-2a or one dose of ribavirin or placebo and had at least one safety assessment after baseline.

Two safety groups were assessed:

- Safety-1 population, including data from baseline through week 24 for the initial randomized treatment groups:
  - Subjects treated with PEG-IFN alfa-2a plus ribavirin
  - Subjects treated with PEG-IFN alfa-2a plus placebo (monotherapy)
- Safety-2 population, including data from baseline to end of follow-up for the following three treatment arms:
  - Subjects receiving PEG-IFN alfa-2a plus ribavirin in the first 28 weeks
  - Subjects receiving PEG-IFN alfa-2a plus placebo in the first 28 weeks and not switching to PEG-IFN alfa-2a plus ribavirin at week 28
  - Subjects receiving PEG-IFN alfa-2a plus placebo in the first 24 weeks and switching to PEG-IFN alfa-2a plus ribavirin at week 28

The main safety parameters in study NV17424 included:

- clinical adverse events (AEs)
- laboratory test results
- growth and body composition variables
- vital signs
- ophthalmologic evaluation
- quality of life assessment
- health outcomes parameters

Safety was also assessed by data regarding study drug modifications and premature withdrawals for safety reasons or intolerance.

*MO's Commnent: The sponsor has acknowledged the possible bias in examining the safety data using the Safety-2 population which incorporates the three different treatment groups since randomization was only performed initially and not when monotherapy non-responders were switched into the compassionate combination*

*therapy group. This potential selection bias should be taken into consideration when examining the data of those subjects who received combination therapy, in either the initial combination therapy group or the compassionate combination therapy group, compared to those subjects who received monotherapy with PEG-IFN alfa-2a. Although subjects in the compassionate combination group received a longer total duration of treatment, they had already shown that they tolerated PEG-IFN alfa-2a treatment. However, the Safety-2 population represents the entire time on treatment with the study drugs and is the most inclusive representation of safety data. Despite the potential bias, using the most inclusive safety data may be an appropriate method in some cases. For example, if you only looked at the two initial treatment arms, it would appear that the monotherapy group had the majority of severe AEs. This may be a consequence of the smaller number of patients as compared to the initial combination therapy group or due to the removal of the Week 24 nonresponders from the initial monotherapy group. The Safety-1 population data was also evaluated when it was provided and when appropriate.*

### 7.1.2 Categorization of Adverse Events

For Study NV17424, an adverse event was defined as a sign or symptom, including intercurrent illness, that occurred during the course of the clinical trial after treatment had started, i.e. events that were not present when the patient entered the study or events present at baseline that became worse, whether considered related to treatment or not. The Medical Dictionary for Regulatory Activities (MedDRA), version 13.0 was used for AE coding.

Clinical adverse events were categorized further into non-serious adverse events and serious adverse events. Non-serious adverse events included events considered related to PEG-IFN alfa-2a or ribavirin such as fatigue, gastrointestinal symptoms, rash, joint/muscle aches, headaches, itching, injection site reactions, and blood draw pain/bruising. They also included an additional 8 conditions common during childhood.

A serious adverse event was defined as any event that was fatal or life-threatening, required inpatient hospitalization or prolonged hospitalization, resulted in persistent or significant disability, or was a congenital anomaly or birth defect. Investigators were also advised to report an event as serious, regardless of fulfilling the previous criteria, if they considered the event to be medically significant or to jeopardize the patient and require intervention to prevent a serious adverse event.

Laboratory adverse events were defined as abnormal laboratory values that resulted in a serious adverse event, required treatment with medication or modification of an ongoing concomitant treatment, or led to premature discontinuation of treatment of any study drug. These events included events such as anemia, neutropenia, and thrombocytopenia. Laboratory abnormalities that only called for a dose reduction or a withheld dose were not recorded as an adverse event.

The Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, was used for grading of laboratory values and clinical adverse events. Revised datasets that incorporated this toxicity grading scale were submitted and reviewed.

*Medical Officer's Comments: The categorization of adverse events and safety coding for this study were appropriate and reported appropriately.*

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

There was no pooling of data for this submission. Safety data from study NR16141 was provided for support of the pivotal study however, because of the differences in subject population, study design, and study conduct, the data were not pooled with data from NV17424. Supportive safety data from NR 16141 will be discussed in Section 7.4.5.

## 7.2 Adequacy of Safety Assessments

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

In terms of extent of exposure to trial medication, greater than or equal to 65% of patients in the Safety-2 population were still receiving PEG-IFN alfa-2a therapy at week 47 when injection number 48 was to be scheduled as per the study protocol.

As shown in Table 16, the mean cumulative dose of PEG-IFN alfa-2 was 5186 µg in the monotherapy group and 5135 µg in the combination therapy group. In comparison, the mean cumulative dose (8086 µg) was higher in the compassionate combination group but was due to the longer duration of receiving two treatment courses.

The mean cumulative dose of ribavirin was similar for the combination therapy group and the compassionate combination group, 181,920 mg and 177,086 mg respectively.

**Table 16: Cumulative Dose of Study Drug by Actual Treatment Group, Safety-2 Population**

| | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Ribavirin 15 mg/kg N=55 | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Placebo Only N=31 | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Plac./Ribavirin 15 mg/kg N=28 |
|---|---|---|---|
| Cumulative PEG-IFN alfa-2a Dose (ug) | | | |
| N | 55 | 31 | 28 |
| Mean | 5135 | 5168 | 8086 |
| Std Dev | 2178 | 2314 | 2597 |
| Std Error Mean | 294 | 416 | 491 |
| Median | 4770 | 4410 | 8186 |
| Min - Max | 954 - 9000 | 990 - 9400 | 1989 - 13680 |
| Cumulative Ribavirin Dose (mg) | | | |
| N | 55 | 0 | 28 |
| Mean | 181920 | . | 177086 |
| Std Dev | 86330 | . | 67659 |
| Std Error Mean | 11641 | . | 12786 |
| Median | 170500 | . | 167200 |
| Min - Max | 70000 - 403200 | . - . | 58800 - 394200 |

**Adapted from Table 31 in Section 3.3.1 of the applicant's study report**

When the cumulative dose of the PEG-IFN alfa-2a is evaluated for only the first 24 weeks, the overall means are relatively similar between the two initially randomized therapy arms. This is shown in Table 17 below:

**Table 17: Cumulative Dose of Study Drug within the First 24 Weeks by Initial Treatment Group, Safety-1 Population**

| | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Ribavirin 15 mg/kg N=55 | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Placebo N=59 |
|---|---|---|
| Cumulative PEG-IFN alfa-2a Dose (ug) | | |
| N | 55 | 59 |
| Mean | 2909 | 2954 |
| Std Dev | 974 | 1014 |
| Std Error Mean | 131 | 132 |
| Median | 2952 | 2898 |
| Min - Max | 792 - 4320 | 990 - 4512 |
| Cumulative Ribavirin Dose (mg) | | |
| N | 55 | 0 |
| Mean | 105536 | . |
| Std Dev | 41792 | . |
| Std Error Mean | 5635 | . |
| Median | 99600 | . |
| Min - Max | 50100 - 201600 | . - . |

**Adapted from the Supporting Data Presentations section of the applicant's study report**

*MO's Comments: Overall, the exposure of subjects to the investigational drugs at established doses and durations was adequate and appropriate for this study population in order to address safety issues. The higher mean cumulative dose of PEG-IFN alfa-2a seen in the compassionate combination therapy group as compared to the other groups is due to the longer total treatment duration.*

### 7.2.2 Explorations for Dose Response

No further data was submitted to explore dose response.

### 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 assessments were performed at screening and at several designated times throughout both the treatment period and the post-treatment follow-up period. Assessments included monitoring of clinical adverse events, laboratory test parameters, vital signs, depression screening using the Child Depression Inventory (CDI), measurement of growth and body composition, ophthalmologic examinations, and documentation of study drug modifications and premature withdrawals for safety reasons or intolerance.

Subjects who were prematurely withdrawn from the study treatment had safety assessments performed at 4, 8, 12, 16, 20, and 24 weeks after their last dose of study medication.

*MO's Comments: The methodology and frequency of routine clinical and laboratory monitoring were adequate to assess safety.*

### 7.2.5 Metabolic, Clearance, and Interaction Workup

No new in vitro or in vivo assessment data was submitted regarding metabolic, clearance, or interaction work up of PEG-IFN alfa-2a or ribavirin.

As stated in the current Pegasys label, a 25% to 45% higher exposure to the drug is seen in subjects undergoing hemodialysis. For patients with impaired renal function, doses should be adjusted accordingly and caution should be used in patients with creatinine clearance less than 50mL/min. No data are available for pediatric patients with renal impairment.

Since there is limited data on renal impaired patients with Copegus, the current label recommends that patients with creatinine clearance of less than 50mL/min should not be treated with Copegus.

For Pegasys, previous adults studies have shown no effect on the pharmacokinetics of representative drugs metabolized by CYP 2C9, CYP 2C19, CYP 2D6, or CYP 3A4. In one previous study, treatment with Pegasys once weekly for 4 weeks in healthy subjects was associated with an inhibition of P450 1A2 and a 25% increase in theophylline AUC.

For Copegus, previous in vitro studies indicated that ribavirin does not inhibit CYP 2C9, CYP 2C19, CYP 2D6, or CYP 3A4.

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

Previously known adverse events associated with interferons in general include flu-like symptoms, pyrexia, bone marrow suppression, psychiatric symptoms, thyroid dysfunction, ophthalmologic disorders, hepatotoxicity, nephrotoxicity and growth delay. As previously mentioned, assessments were used throughout this study to specifically monitor for these potential AEs with PEG-IFN alfa-2a.

Hemolytic anemia is the primary toxicity associated with ribavirin use and was closely monitored with routinely scheduled complete red blood cell counts and hemoglobin.

*MO's Comments: The applicant included adequate assessments of potential adverse events known for similar drugs in the same drug class. The particular results of these assessments will be discussed further in Sections 7.3 and 7.4.*

## 7.3 Major Safety Results

Safety results were primarily based on data from 114 subjects that made up the Safety-2 population which included data from baseline to end of follow-up for the following three treatment arms:

- Subjects receiving PEG-IFN alfa-2a plus ribavirin in the first 28 weeks which represents approximately 48% of the total population (n=55)
- Subjects receiving PEG-IFN alfa-2a plus placebo in the first 28 weeks and not switching to PEG-IFN alfa-2a plus ribavirin at week 28 which represents approximately 27% of the total population (n=31)
- Subjects receiving PEG-IFN alfa-2a plus placebo in the first 24 weeks and switching to PEG-IFN alfa-2a plus ribavirin at week 28 which represents approximately 25% of the total population (n=28)

7.3.1 Deaths

There were no deaths during this study

7.3.2 Nonfatal Serious Adverse Events

Of the 114 subjects in the Safety-2 population, only 3 subjects reported nonfatal serious adverse events (SAEs) during the treatment and 24-week follow-up periods. Two subjects (4%) in the PEG-IFN alfa-2a plus ribavirin combination therapy group reported SAEs. In the PEG-IFN alfa-2a monotherapy group, there was only one reported SAE (3%). There were no SAEs reported in the compassionate combination group.

In the initial combination therapy group, SAEs of cholecystitis and hyperglycemia were reported. In the first case, a 12 year old white male with a previous history of abdominal pain and heptobiliary/pancreatic disorder not otherwise specified reported severe

abdominal pain on study day 16. Concomitant medications included ibuprofen, a laxative, and hydrocodone/paracetamol. He was admitted into the hospital and a cholecystectomy was performed. His ribavirin treatment was interrupted for one day on study day 20 but by study day 22 the event was considered resolved. The investigator considered the event as unlikely related to either PEG-IFN alfa-2a or ribavirin.

In the second case, a 10 year old white female with a history of inactive psychiatric disease initially had slightly elevated serum glucose at screening and on study day 1. At subsequent visits her serum glucose was within normal range except on study day 113 when it was elevated to 7.80 mmol/L (normal range: 3.90-6.40 mmol/L). On study day 232, the subject was found to be hyperglycemic with a serum glucose level of 19.6 mmol/L and was hospitalized. On study day 244, her PEG-IFN alfa-2 was stopped and one day later the RBV was stopped. On study day 247, she was diagnosed with Type I diabetes mellitus. At the completion of the study, she was still under treatment with insulin therapy for her diabetes. The investigator considered this event to be possibly related to both PEG-IFN alfa-2a and ribavirin.

The one subject with a reported SAE in the PEG-IFN alfa-2a monotherapy group was a 15 year old white male with a history of ENT, neurologic, psychiatric, respiratory, and skin disease that were not further specified, who had an episode of suicidal behavior. His concomitant medications included benzoyl peroxide/clindamycin, cefalexin, budesonide, montelukast, methylphenidate, ibuprofen, and paracetamol. His baseline total Child Depression Inventory (CDI) Z-score was 58 (≥65 is considered clinically significant). On study day 30, the subject developed moderate depression. On study day 36, his CDI Z-score was 60. On study day 57, he was hospitalized when he exhibited possible suicidal behavior. As per the case report form, the patient made a suicidal gesture with superficial cutting of his wrists. He was medically stable and did not meet criteria for the diagnosis of major depression. His study drug therapy was permanently discontinued on study day 56. By study day 58, the suicidal behavior was considered resolved. The investigator considered the event as possibly related to the study drug.

There was one other reported subject who was initially in the PEG-IFN alf-2a combination therapy group who had an episode of nephritis on study day 906. This 11 year old white female had been withdrawn from therapy after 173 days of treatment because of insufficient therapeutic response. When the nephritis occurred it was approximately 2 years after the discontinuation of therapy and therefore considered definitely unrelated to study drug according to the investigator.

*MO's Comments: All 4 individual case report forms were reviewed in detail for the cases of SAEs. Upon review of the case reports, the initial assessments by the investigator in regards to the SAE relation to the study drugs seemed reasonable and appropriate.*

7.3.3 Dropouts and/or Discontinuations

Table 18 shows a summary of the premature withdrawals from study treatment for AEs and laboratory abnormalities in the Safety-2 population. The main reasons for premature withdrawals for the initial combination therapy group varied from psychiatric disorders, investigational abnormalities, eye disorders, metabolism and nutrition disorders, and blood and lymphatic disorders. The premature withdrawals seen in the monotherapy group were mainly limited to psychiatric disorders and investigational abnormalities. There were no premature withdrawals in the compassionate combination therapy group.

**Table 18: Summary of Premature Withdrawals From Study Treatment for Adverse Events and Laboratory Abnormalities, Safety-2 Population**

| Body System/ Adverse Event | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Ribavirin 15 mg/kg N = 55 No. (%) | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Placebo Only N = 31 No. (%) | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Plac./Ribavirin 15 mg/kg N = 28 No. (%) |
|---|---|---|---|
| ALL BODY SYSTEMS | | | |
| Total Pts with at Least one AE | 6 ( 11) | 5 ( 16) | - |
| Total Number of AEs | 7 | 5 | - |
| PSYCHIATRIC DISORDERS | | | |
| Total Pts With at Least one AE | 1 ( 2) | 3 ( 10) | - |
| ABNORMAL BEHAVIOUR | - | 1 ( 3) | - |
| AGGRESSION | - | 1 ( 3) | - |
| DEPRESSION | 1 ( 2) | - | - |
| SUICIDAL BEHAVIOUR | - | 1 ( 3) | - |
| Total Number of AEs | 1 | 3 | - |
| INVESTIGATIONS | | | |
| Total Pts With at Least one AE | 1 ( 2) | 2 ( 6) | - |
| ALANINE AMINOTRANSFERASE INCREASED | - | 1 ( 3) | - |
| PSYCHIATRIC EVALUATION ABNORMAL | 1 ( 2) | - | - |
| TRANSAMINASES INCREASED | - | 1 ( 3) | - |
| Total Number of AEs | 1 | 2 | - |
| EYE DISORDERS | | | |
| Total Pts With at Least one AE | 2 ( 4) | - | - |
| BLINDNESS TRANSIENT | 1 ( 2) | - | - |
| RETINAL EXUDATES | 1 ( 2) | - | - |
| Total Number of AEs | 2 | - | - |

| | | | |
|---|---|---|---|
| METABOLISM AND NUTRITION DISORDERS | | | |
| Total Pts With at Least one AE | 1 ( 2) | - | - |
| HYPERGLYCAEMIA | 1 ( 2) | - | - |
| TYPE 1 DIABETES MELLITUS | 1 ( 2) | - | - |
| Total Number of AEs | 2 | - | - |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | | | |
| Total Pts With at Least one AE | 1 ( 2) | - | - |
| ANAEMIA | 1 ( 2) | - | - |
| Total Number of AEs | 1 | - | - |

**Adapted from Table 39 in Section 3.3.5 of applicant's study report**

*MO's Comment:* The *details of the AEs which caused premature withdrawal from study treatment seen in Table 18 above will be discussed in Section 7.3.4 Significant Adverse Events.*

In all cases in the combination therapy group, the AEs that led to discontinuation of treatment were considered by the investigator as possibly related to PEG-IFN alfa-2a. Four of the 6 cases were also considered possibly related to the ribavirin but the 2 other cases were considered unlikely due to the ribavirin.

In the monotherapy group, 4 out of the 5 cases were considered possibly related to PEG-IFN alfa-2a. The one other case (Patient NV17424-1-860) was considered unlikely related to PEG-IFN alfa-2a. This subject was a 13 year old white female with a history of psychiatric disease not further specified and was receiving concomitant treatment with amphetamine/dexamphetamine. On study day 123 the subject exhibited abnormal behavior which was rated as severe and treatment was prematurely discontinued. The reason for discontinuation was specified as "non-compliance and juvenile delinquent behavior." On the CRF withdrawal form, it was noted that the subject would be unable to come to follow up visits. No further information is provided regarding the AE.

*MO's Comments: All CRFs and patient narratives were reviewed. Overall, all cases were prematurely discontinued for appropriate safety reasons. However, the one case (Patient NV17424-1-860) that was considered unlikely related to the study drug probably should be included in this analysis because it is possible that this event could have been exacerbated by the study drug.*

*The proportion of subjects who were prematurely discontinued for safety in all treatment groups was relatively well matched. Those AEs and laboratory abnormalities seen with these subjects are known side effects previously associated with these drugs and to be expected.*

7.3.4 Significant Adverse Events

The most frequent types of AEs leading to premature withdrawal from treatment were psychiatric disorders. In the initial combination therapy group, 1 subject (2%) was withdrawn for AEs related to psychiatric disorders compared to 3 subjects (5%) in the monotherapy group and no subjects in the compassionate combination group. The one subject seen in the combination therapy group was due to depression. The reasons for three patients in the monotherapy included abnormal behavior, aggressive behavior, and suicidal behavior.

The proportion of all reported depression including those considered by investigators as clinical adverse events of depression on CRFs and those identified using the Childhood Depression Inventory, was higher among subjects in the monotherapy group (19%) as compared to the subjects in the initial combination therapy group (9%) and the compassionate combination therapy group (7%).

Eye disorders were seen in 2 subjects (4%) of subjects prematurely withdrawn from treatment in the PEG-IFN alfa-2a plus ribavirin group. These two cases included an episode of transient blindness and retinal exudates that were considered by the investigator to be probably related to PEG-IFN alfa-2a. No eye disorders were seen in either the monotherapy group or the compassionate combination group.

The proportion of all reported eye disorders was higher in the monotherapy group (23%) as compared to the patient in the initial combination therapy group (15%) and the compassionate combination therapy group (18%). Conjunctivitis was commonly reported in all treatment groups.

Significant laboratory abnormalities will be discussed in Section 7.4.2.

*MO's Comment: The significant adverse events seen in this trial are AEs previously reported with interferon drugs. Although not statistically significant, higher proportions of psychiatric and eye disorders were seen in the monotherapy group as compared to the combination therapy groups, making it unlikely that the combination of PEG-IFN alfa-2a and ribavirin caused an increase in incidence of these AEs.*

7.3.5 Submission Specific Primary Safety Concerns

Changes in growth and body composition in pediatric patients with the use of interferon are previously known and are a safety concern not identified in the adult clinical trials. The findings of Study NV17424 will be discussed in Section 7.6.3.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

All patients in the Safety-2 population reported at least one AE. Overall, the most frequently reported types of AEs included general disorders, administration site conditions, infections and infestations, skin and subcutaneous tissues disorders, gastrointestinal disorders, and nervous system conditions. Table 19 shows a summary of the most frequent AEs with an incidence of at least 5% during treatment and the follow-up period. These results were confirmed by review of submitted CRFs, datasets and other data provided.

**Table 19: Summary of the Most Frequent AEs with an Incidence of At Least 5% During Treatment and Follow-up, Safety-2 Population**

| Adverse Event | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Ribavirin 15 mg/kg N = 55 No. (%) | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Placebo Only N = 31 No. (%) | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Plac./Ribavirin 15 mg/kg N = 28 No. (%) |
|---|---|---|---|
| INFLUENZA LIKE ILLNESS | 50 ( 91) | 28 ( 90) | 22 ( 79) |
| UPPER RESPIRATORY TRACT INFECTION | 33 ( 60) | 20 ( 65) | 23 ( 82) |
| HEADACHE | 35 ( 64) | 15 ( 48) | 19 ( 68) |
| GASTROINTESTINAL DISORDER | 31 ( 56) | 21 ( 68) | 16 ( 57) |
| SKIN DISORDER | 26 ( 47) | 20 ( 65) | 19 ( 68) |
| INJECTION SITE REACTION | 25 ( 45) | 15 ( 48) | 12 ( 43) |
| MUSCULOSKELETAL PAIN | 20 ( 36) | 11 ( 35) | 10 ( 36) |
| FATIGUE | 16 ( 29) | 10 ( 32) | 6 ( 21) |
| IRRITABILITY | 18 ( 33) | 8 ( 26) | 6 ( 21) |
| EAR INFECTION | 10 ( 18) | 10 ( 32) | 8 ( 29) |
| SINUSITIS | 10 ( 18) | 8 ( 26) | 8 ( 29) |
| RASH | 11 ( 20) | 9 ( 29) | 5 ( 18) |
| DECREASED APPETITE | 7 ( 13) | 5 ( 16) | 6 ( 21) |
| INSOMNIA | 7 ( 13) | 6 ( 19) | 5 ( 18) |
| PRURITUS | 8 ( 15) | 4 ( 13) | 5 ( 18) |
| MEDICAL DEVICE COMPLICATION | 11 ( 20) | 3 ( 10) | 2 ( 7) |
| ALOPECIA | 6 ( 11) | 2 ( 6) | 4 ( 14) |
| DEPRESSION | 4 ( 7) | 5 ( 16) | 2 ( 7) |
| ABDOMINAL PAIN UPPER | 4 ( 7) | 4 ( 13) | 2 ( 7) |
| EPISTAXIS | 8 ( 15) | - | 2 ( 7) |
| PYREXIA | 3 ( 5) | 5 ( 16) | 2 ( 7) |
| CONJUNCTIVITIS | 2 ( 4) | 6 ( 19) | 1 ( 4) |
| PHARYNGITIS STREPTOCOCCAL | 5 ( 9) | 2 ( 6) | 2 ( 7) |
| CONSTIPATION | 4 ( 7) | 1 ( 3) | 3 ( 11) |
| VESSEL PUNCTURE SITE HAEMATOMA | 3 ( 5) | 2 ( 6) | 2 ( 7) |
| VOMITING | 3 ( 5) | 2 ( 6) | 2 ( 7) |
| DYSMENORRHOEA | 4 ( 7) | - | 2 ( 7) |

**(continued)**

| | | | |
|---|---|---|---|
| PAIN IN EXTREMITY | 2 ( 4) | 2 ( 6) | 2 ( 7) |
| DIZZINESS | 3 ( 5) | 1 ( 3) | 1 ( 4) |
| DIARRHOEA | - | 3 ( 10) | 1 ( 4) |
| EYE PAIN | 1 ( 2) | 1 ( 3) | 2 ( 7) |
| GASTROENTERITIS VIRAL | 3 ( 5) | 1 ( 3) | - |
| HYPERSENSITIVITY | 1 ( 2) | 3 ( 10) | - |
| INFLUENZA | 1 ( 2) | 2 ( 6) | 1 ( 4) |
| ORAL HERPES | 1 ( 2) | 2 ( 6) | 1 ( 4) |
| STOMATITIS | 3 ( 5) | - | 1 ( 4) |
| TOOTH ABSCESS | 4 ( 7) | - | - |
| TOOTH EXTRACTION | 4 ( 7) | - | - |
| LIMB INJURY | 1 ( 2) | 2 ( 6) | - |
| MUSCLE STRAIN | 1 ( 2) | - | 2 ( 7) |
| CHEST PAIN | - | 2 ( 6) | - |
| CONTUSION | - | - | 2 ( 7) |
| HYPOTHYROIDISM | - | 2 ( 6) | - |
| TINEA INFECTION | - | 2 ( 6) | - |

**Adapted from Table 33 from Section 3.3.2.2 in applicant's study report**

The most frequent clinical AEs through the entire study period were influenza-like illness, upper respiratory tract infection, headache, gastrointestinal disorder, skin disorder, and injection site reaction.

Specifically, in the PEG-IFN alfa-2a plus ribavirin treatment group, influenza-like illness was reported in 91%, upper respiratory tract infections were reported in 60%, gastrointestinal disorders were reported in 56%, skin disorders were reported in 47%, and injection site reactions were reported in 45% of subjects.

When the incidence of adverse events of at least 5% is evaluated in the Safety-1 population which only encompasses the first 24 weeks of randomized treatment, the results are relatively similar to the results seen in Safety-2 population. Table 20 provides a summary of the AEs in this population.

**Table 20: Summary of Adverse Events with an Incidence Rate of at Least 5% within the First 24 Weeks, Safety-1 Population**

| Adverse Event | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Ribavirin 15 mg/kg N = 55 No. (%) | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Placebo N = 59 No. (%) |
|---|---|---|
| INFLUENZA LIKE ILLNESS | 50 ( 91) | 48 ( 81) |
| GASTROINTESTINAL DISORDER | 27 ( 49) | 26 ( 44) |
| HEADACHE | 28 ( 51) | 23 ( 39) |
| INJECTION SITE REACTION | 24 ( 44) | 25 ( 42) |
| UPPER RESPIRATORY TRACT INFECTION | 16 ( 29) | 27 ( 46) |
| MUSCULOSKELETAL PAIN | 19 ( 35) | 17 ( 29) |
| SKIN DISORDER | 17 ( 31) | 17 ( 29) |
| FATIGUE | 14 ( 25) | 12 ( 20) |
| IRRITABILITY | 13 ( 24) | 8 ( 14) |
| SINUSITIS | 7 ( 13) | 9 ( 15) |
| EAR INFECTION | 6 ( 11) | 9 ( 15) |
| DECREASED APPETITE | 6 ( 11) | 8 ( 14) |
| RASH | 8 ( 15) | 6 ( 10) |
| PRURITUS | 6 ( 11) | 7 ( 12) |
| INSOMNIA | 5 ( 9) | 7 ( 12) |
| MEDICAL DEVICE COMPLICATION | 7 ( 13) | 3 ( 5) |
| EPISTAXIS | 7 ( 13) | 2 ( 3) |
| ALOPECIA | 5 ( 9) | 3 ( 5) |
| VESSEL PUNCTURE SITE HAEMATOMA | 2 ( 4) | 4 ( 7) |
| DEPRESSION | 1 ( 2) | 4 ( 7) |
| CONJUNCTIVITIS | 1 ( 2) | 3 ( 5) |
| CONSTIPATION | 3 ( 5) | 1 ( 2) |
| STOMATITIS | 3 ( 5) | 1 ( 2) |

Investigator text for Adverse Events encoded using MedDRA version 13.0.
Percentages are based on N.

**Adapted from the Supporting Data Presentations section of the applicant's study report**

*MO's Comment: Overall, the most frequently reported types of AEs seen in study NV17424 were AEs known to be associated with peginterferon and ribavirin and are similar to those seen in adult patients.*

*In the Safety-2 population, the prevalence of influenza-like illness was higher in the initial combination group (91%) and monotherapy group (90%) compared to the compassionate combination group (79%). In the Safety-1 population, this trend was similarly seen where the prevalence of influenza-like illness was higher in the initial combination therapy group (91%) compared to the monotherapy group (81%). In*

*addition, headache was more prominent in the initial combination therapy group (64%) and the compassionate combination therapy group (68%) as compared to the monotherapy group. This trend is also seen in the Safety-1 population, where headache was seen in 51% of the patients in the initial combination group and 39% in the monotherapy group, suggesting that ribavirin may contribute to these events.*

*However, among other common AEs seen in this study, upper respiratory tract infections and skin disorders were seen more in the monotherapy group (65% and 65%, respectively) as compared to the initial combination group (60% and 47% respectively) but less than the compassionate combination therapy group (82% and 68% respectively). Again, during the first 24 weeks of treatment the combination therapy group had only 29% of subjects with upper respiratory tract infections as compared to 46% in the monotherapy group. Skin disorders in the first 24 weeks were observed in similar proportions; 31% of the combination therapy group compared to 29% of the monotherapy group.*

*The monotherapy group had the largest proportion of subjects with gastrointestinal disorders (68%) and injection site reactions (48%) in comparison to the other two groups when looking throughout the duration of the study. All subjects received the same dose and injection schedule of PEG-IFN alfa-2a, and the small difference in rates of injection site reactions was not considered clinically meaningful. During the first 24 weeks, the proportion of subjects with gastrointestinal disorders in both the combination therapy group and the monotherapy group was relatively similar (49% versus 44%, respectively).*

*Overall, there did not seem to be any clinically meaningful differences in safety profile when comparing data from the first 24 weeks of randomized treatment to the total duration of the study.*

Laboratory Findings

Overall, across all three treatment groups, the most common laboratory abnormalities with one or more values outside the laboratory normal range were decreases in white blood cell (WBC) count and increases in triglyceride, AST, and ALT levels. In the groups treated with RBV, the most common laboratory abnormalities were a decrease in total neutrophils, low T3 uptake, hemoglobin, hematocrit, and monocyte levels. The most common laboratory abnormality seen in the PEG-IFN alfa-2a monotherapy group was low glucose levels.

Neutropenia

In all three treatment groups, the median absolute neutrophil count decreased in the first 12 weeks of treatment. In the monotherapy group, median neutrophil counts increased slightly from weeks 12 to 48 and then steadily approached baseline levels by the Year 1 post-treatment follow-up. In the other two groups who received ribavirin,

median neutrophil counts remained lower until the end of treatment but also returned to baseline levels by Year 1 post-treatment follow-up.

No case of neutropenia was considered serious and thus neutropenia was not considered an AE in any subject. No case of neutropenia was a cause for premature discontinuation and most were handled with dose modification of PEG-INF alfa-2a. Nineteen subjects (35%) in the initial combination therapy group and 11 subjects (39%) in the compassionate combination therapy group had dose modification of PEG-IFN alfa-2a for their neutropenia. In the monotherapy group, 7 subjects (23%) required PEG-IFN dose modification. No subjects had modification of their ribavirin dose. When neutropenia was evaluated in the first 24 weeks (Safety-1 population) the results were similar to the analysis of the Safety-2 population.

*MO's Comment: As seen in previous studies with interferon, neutrophil counts decreased initially with therapy but recovered at the end of therapy. The neutrophil count seemed to recover slightly quicker in the monotherapy group*

Lymphopenia

Median lymphocyte counts decreased during the first 12 weeks of treatment across all three treatment groups with the largest decrease seen in the initial combination therapy group, falling from a baseline of 2.72 $x10^9$/L to the lowest median value of 1.21 $x10^9$/L at week 40. However, all three treatment groups' values rose after the end of treatment and remained slight below baseline between 24 weeks and 2 years post-treatment. When lymphopenia was evaluated in Safety-1 population, the results were similar to the analysis of the Safety-2 population.

Thrombocytopenia

Median platelet counts decreased over the first 12 weeks of treatment for all three therapy groups. For all treatment groups, median platelet counts remained decreased until end of treatment and returned to baseline by the Year 1 post-treatment follow-up. Despite decreases in platelet counts overall, most values remained in the normal range. No cases of thrombocytopenia were considered serious or an adverse event, thus, did not result in premature discontinuation of therapy. Overall, only one patient in the initial combination therapy group, required dose modification of PEG-IFN alfa-2a for thrombocytopenia. No dose medication of RBV was required in any patient. When thrombocytopenia was evaluated in Safety-1 population, the results were similar to the analysis of the Safety-2 population.

Anemia

Median hemoglobin counts decreased over the first 12 weeks of treatment across all three treatment groups with the largest decrease seen in the initial combination therapy group. In this group, baseline hemoglobin of 13.2 g/dL decreased to the lowest median value of 11.5 g/dL at week 32. However, all three treatment groups' values rose after the end of treatment and returned to baseline by 24 weeks to 1 year post-treatment.

One subject in the initial combination therapy group had anemia that was considered to be an adverse event and treatment was prematurely discontinued. However, it did not meet criteria to be considered a serious AE. No subjects required dose modification of PEG-IFN alfa-2a but dose modification of ribavirin was performed in 11 subjects. When anemia was evaluated in Safety-1 population, the results were similar between treatment groups.

*MO's Comment: The findings of the one subject on ribavirin therapy having anemia severe enough to prematurely discontinue therapy and 11 subjects needing ribavirin dose modification is consistent with ribavirin's known potential to cause anemia.*

Elevation in Serum ALT

The distribution of subjects by highest ALT level throughout the duration of the study was similar between all three treatment groups and is illustrated in Table 21 below.

**Table 21: Summary of Highest ALT level During Treatment and Follow-up, Safety-2 Population**

| | | ALT Levels | | | | |
|---|---|---|---|---|---|---|
| Treatment Group | N | Normal <1.25 (xULN) | 1.25 - 2.5 (xULN) | >2.5 - 5 (xULN) | >5 - 10 (xULN) | >10 (xULN) |
| PEG-IFN alfa-2a 180 ug x BSA/1.73 sqm + Ribavirin 15 mg/kg | 55 | 17 31% | 21 38% | 14 25% | 3 5% | 0 0% |
| PEG-IFN alfa-2a 180 ug x BSA/1.73 sqm + Placebo Only | 31 | 8 26% | 10 32% | 8 26% | 4 13% | 1 3% |
| PEG-IFN alfa-2a 180 ug x BSA/1.73 sqm + Plac./Ribavirin 15 mg/kg | 28 | 5 18% | 12 43% | 10 36% | 1 4% | 0 0% |

**Adapted from Table 49 in Section 3.3.8.5 in the sponsor's study report**

At baseline, most subjects had Grade 0 or 1 baseline ALT levels (<2.5 x ULN) and no patients had Grade 3 or 4 (>5 x ULN). Baseline ALT was relatively similarly distributed between the three treatment groups. When highest values during treatment were compared to baseline values, the patterns of change were also similar between treatment groups.

However, an ALT level of Grade 3 was seen in a higher proportion of the monotherapy group (13%) as compared to the initial combination therapy group (5%) and the compassionate combination therapy group (4%). One subject, from the monotherapy group, reportedly had an ALT level of Grade 4.

Two subjects in the monotherapy group were prematurely withdrawn from treatment for increases in transaminases and three subjects in this group required PEG-IFN alfa-2a dose modifications. No subjects required ribavirin dose modification.

Triglycerides

Overall, only one subject did not have a triglyceride level greater than1.13 mmol/L during the study. In the highest category (greater than or equal to 4.52 mmol/L) the proportion of patients was relatively similar between the initial combination therapy group (22%) and the monotherapy group (26%), however the compassionate combination therapy group was much lower (4%)

Abnormal Thyroid Function Tests

There were no consistent changes seen in thyroid laboratory measurements. Two subjects in the monotherapy group had AEs related to hypothyroidism.

*MO's Comment: Overall, the laboratory abnormalities seen in this study were consistent with laboratory abnormalities known to occur with the use of interferon and ribavirin. These laboratory abnormalities were relatively easily managed with dose modification or appropriate discontinuation of therapy.*

7.4.3 Vital Signs

Overall, no vital sign abnormalities were reported as AEs. A higher proportion of subjects in the compassionate combination therapy group had abnormal vital signs as compared to the other two therapy groups. This is shown in Table 22 below:

**Table 22: Summary of Abnormal Vital Signs During Treatment and Follow-up, Safety-2 Population**

| | | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Ribavirin 15 mg/kg N = 55 | | | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Placebo Only N = 31 | | | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Plac./Ribavirin 15 mg/kg N = 28 | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | N | Abnormal | | N | Abnormal | | N | Abnormal | |
| Diastolic BP | High | 55 | 6 | 11% | 31 | 4 | 13% | 28 | 5 | 18% |
| Systolic BP | High | 55 | 10 | 18% | 31 | 3 | 10% | 28 | 8 | 29% |
| Pulse Rate | High | 55 | 1 | 2% | 31 | 1 | 3% | 28 | 3 | 11% |
| | Low | 55 | 3 | 5% | 31 | 3 | 10% | 28 | 5 | 18% |

High diastolic and systolic blood pressure is defined as above an age-dependent upper reference value and >20% increase from baseline.
High pulse rate is defined as above an age-dependent upper reference value and >20% increase from baseline.
Low pulse rate is defined as below an age-dependent lower reference value and >20% decrease from baseline.

**Adapted from Table 58 in Section 3.3.10 in the sponsor's study report**

When the vital sign abnormalities were evaluated within the first 24 weeks of randomized treatment, there was no apparent difference except with pulse rates; a greater number of the monotherapy group had both high and low pulse rates as seen in Table 23 below:

**Table 23: Summary of Abnormal Vital Signs within the First 24 Weeks, Safety-1 Population**

| | | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Ribavirin 15 mg/kg N = 55 | | | PEG-IFN alfa-2a 180 ug x BSA /1.73 sqm Placebo N = 59 | | |
|---|---|---|---|---|---|---|---|
| | | N | Abnormal | | N | Abnormal | |
| Diastolic BP | High | 55 | 6 | 11% | 59 | 6 | 10% |
| Systolic BP | High | 55 | 6 | 11% | 59 | 6 | 10% |
| Pulse Rate | High | 55 | 0 | 0% | 59 | 2 | 3% |
| | Low | 55 | 2 | 4% | 59 | 7 | 12% |

High diastolic and systolic blood pressure is defined as above an age-dependent upper reference value and >20% increase from baseline.
High pulse rate is defined as above an age-dependent upper reference value and >20% increase from baseline.
Low pulse rate is defined as below an age-dependent lower reference value and >20% decrease from baseline.

**Adapted from the Supporting Data Presentations section of the sponsor's study report**

Elevated temperature is a known side effect of interferon therapy. Temperature was obtained at each clinical study visit. Review of the tables provided in the study report that showed a summary of temperatures at each visit revealed no apparent trend in any treatment group. In addition, the highest temperature recorded in any group was 38.1 degrees Celsius which occurred at Week 32 in the compassionate combination therapy group.

*MO's Comment: The higher proportion of abnormal vital signs may be due to the longer duration of therapy (72 weeks) for the patients in the compassionate combination therapy group. However, between the two initial treatment groups there appears to be no clinically meaningful difference.*

### 7.4.4 Electrocardiograms (ECGs)

No data regarding ECGs was submitted.

### 7.4.5 Special Safety Studies/Clinical Trials

Safety data from study NR16141 was provided for support of the pivotal study, however because of the differences in patient population, study design, and study conduct, the data were not pooled with data from NV17424.

The safety population consisted for this study of all subjects who received at least one dose of the study drug and had at least one post-baseline safety assessment, whether or not they had withdrawn prematurely.

The main safety parameters for this study were:

- clinical AEs
- laboratory test results
- vital signs

In terms of clinical AEs, all 14 subjects in this study experienced an AE and all 14 subjects had one or more treatment-related AEs. The most common AE was pyrexia (86%). Five subjects (36%) had severe AEs including severe headache, but no subject had an SAE or died. Three patients (21%) were withdrawn from treatment because of laboratory abnormalities and six subjects had dose modifications because of laboratory abnormalities. There were no reports of depression in Study NR 16141.

Laboratory abnormalities were common in this study. The following abnormalities were seen at one or more times during the study in almost every subject: decreased creatinine, elevated ALT, decreased neutrophil count, and elevated triglyceride level. Other abnormalities seen during this study included low hematocrit, decreased WBC count, elevated AST, elevated total cholesterol, elevated glucose, and decreased uric acid.

In terms of vital signs, 13 of the 14 subjects had at least one blood pressure value above normal for their age during the study but no subjects had hypertension as an AE. Most of the recorded body temperatures were not elevated and the highest recorded value was 38.1 degrees Celsius observed when a subject had a concurrent cough and ear infection.

*MO's Comment: Although the safety results seen in Study NR16141 are relatively similar to those seen in the pivotal study NV17424, the overall number of subjects is small and it is difficult to fully interpret because of this.*

### 7.4.6 Immunogenicity

There are no specific immunogenicity issues. Serious hypersensitivity to the study drugs were not seen in Study NV17424. There was one subject (2%) in the initial combination therapy group who had a hypersensitivity adverse event and three patients (10%) in the monotherapy group with reported hypersensitivity adverse events. None of these events warranted discontinuation of therapy. No hypersensitivity reactions were seen in the compassionate combination therapy group. Overall, hypersensitivity is known to be rarely seen with use of interferon therapy.

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Events

No dose dependency information or data was submitted pertaining to adverse events. Only a single dose and regimen for both study drugs was evaluated.

### 7.5.2 Time Dependency for Adverse Events

No time dependency information or data was submitted pertaining to adverse events. Only a single dose and regimen for both study drugs was evaluated.

### 7.5.3 Drug-Demographic Interactions

No specific drug-demographic interaction information was submitted.

### 7.5.4 Drug-Disease Interactions

All subjects in these studies submitted had some degree of liver disease but none had significant renal disease.

### 7.5.5 Drug-Drug Interactions

No new information or data was submitted regarding drug interactions.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

No new information or data was submitted regarding carcinogenicity. Pegasys has not been tested for its carcinogenic potential. For ribavirin, previous carcinogenicity studies were negative and ribavirin is considered not to be oncogenic. However, ribavirin did demonstrate mutagenic activity in previous in vitro mouse lymphoma assay studies thus ribavirin has possible mutagenic potential and, as stated in the current label for Copegus, the potential carcinogenic risk to humans cannot be excluded.

### 7.6.2 Human Reproduction and Pregnancy Data

No new information or data was submitted regarding pregnancy or lactation. Pegasys has not been studied for its teratogenic effect and should be assumed to have abortifacient potential. Currently, Pegasys is recommended for use during pregnancy

only if the potential benefit justifies the potential risk to the fetus and in women of childbearing potential who are using effective contraception during therapy. Copegus has been shown to have significant teratogenic and embryocidal effects in animals and is contraindicated in women who are pregnant and in the male partners of women who are pregnant.

The effect of orally ingested drug from breast milk on the nursing infant has not been evaluated.

7.6.3 Pediatrics and Assessment of Effects on Growth

Across all three treatment groups, a decrease was observed in the height, weight, and body mass index (BMI) as expressed as percentiles of the U.S. normative population growth curves during treatment. In addition, weight for age Z-scores and height for age Z-scores showed significant decline from baseline during treatment but increased significantly from the end of therapy and to the 1 year 2 years post-treatment periods.

At baseline, in all three treatment groups, the mean weights were higher than the normative population growth curve 50$^{th}$ percentile but showed a decrease in percentile over the treatment period. However, at the end of 2 years after treatment follow-up, all three treatment groups were near or above their mean baseline normative growth curve percentiles. The following table illustrates the trend seen in weight.

**Table 24: Changes in Weight for Age as Percentile of US Pediatric Population**

| Treatment | Baseline | Mean Decrease from Baseline On Treatment | At the 2 Year End of Treatment Follow-up |
|---|---|---|---|
| **PEG-IFN alfa-2a + RBV** | 64.2% | -13.0% | 60.4% |
| **PEG-IFN alfa-2a monotherapy** | 58.8% | -10.9% | 59.0% |
| **Compassionate combination therapy** | 70.4% | -9.9% | 75.4% |

In addition, 43% of subjects in the initial combination therapy group had percentile decrease of greater than 15% from baseline to end of treatment but only 16% of patients in this group had a percentile decrease of greater than 15% at 2 years post-treatment.

At baseline, in all three treatment groups, the mean heights were higher than the normative population growth curve 50$^{th}$ percentile but showed a decrease in percentile over the treatment period. However, at the end of 2 years after treatment follow-up, all three treatment groups were near or above their mean baseline normative growth curve percentiles. The following table illustrates the trend seen in height.

**Table 25: Changes in Height for Age as Percentile of US Pediatric Population**

| Treatment | Baseline | Mean Decrease from Baseline On Treatment | At the 2 Year End of Treatment Follow-up |
|---|---|---|---|
| **PEG-IFN alfa-2a + RBV** | 53.7% | -9.0% | 56.0% |
| **PEG-IFN alfa-2a monotherapy** | 51.5% | -8.6% | 45.6% |
| **Compassionate combination therapy** | 60.2% | -6.0% | 61.1% |

In addition, 25% of subjects in the initial combination therapy group had a height percentile decreases of greater than 15% from baseline to end of treatment but only 11% of patients in this group had a percentile decrease of greater than 15 % at 2 years post-treatment.

Since BMI is dependent on height and weight, similar changes were observed in BMI percentiles.

*MO's Comment: Growth changes (decrease in weight and height) have previously been seen in pediatric patients treated with combination therapy of interferon and ribavirin. Although by the 2 year follow up, mean weight and height percentiles appear to have improved to baseline or close to baseline, there were a significant number of subjects who had not recovered from these changes in growth parameters.*

The applicant also evaluated z-scores for weight and height. These z-scores were calculated using gender-specific CDC growth charts as reference. Table 26 shows a summary of Analysis of Covariance (ANCOVA) results for growth and body composition variables for Safety-1 population including z-scores for weight and height.

**Table 26: Summary of ANCOVA Results for Growth and Body Composition Variables at Week 24 (adjusted Means and 95% CI), Safety-1 Population**

| Group | N | n | Baseline Value | LSM (95% CI) | Comparison | Difference in LSM (95% CI) | p-value (a) |
|---|---|---|---|---|---|---|---|
| Change of Weight for Age z-Score from Baseline | | | | | | | |
| (1) PEG-IFN alfa-2a + Ribavirin | 55 | 50 | 0.60 | -0.43 ( -0.52 to -0.35) | | | |
| (2) PEG-IFN alfa-2a + Placebo | 59 | 56 | 0.54 | -0.19 ( -0.27 to -0.11) | (2) minus (1) | 0.24 ( 0.14 to 0.34) | <.0001 |
| Change of Height for Age z-Score from Baseline | | | | | | | |
| (1) PEG-IFN alfa-2a + Ribavirin | 55 | 50 | 0.13 | -0.22 ( -0.27 to -0.16) | | | |
| (2) PEG-IFN alfa-2a + Placebo | 59 | 56 | 0.21 | -0.11 ( -0.16 to -0.06) | (2) minus (1) | 0.11 ( 0.04 to 0.18) | 0.0024 |
| Change of BMI for Age z-Score from Baseline | | | | | | | |
| (1) PEG-IFN alfa-2a + Ribavirin | 55 | 50 | 0.71 | -0.44 ( -0.55 to -0.32) | | | |
| (2) PEG-IFN alfa-2a + Placebo | 59 | 56 | 0.52 | -0.19 ( -0.30 to -0.08) | (2) minus (1) | 0.25 ( 0.11 to 0.39) | 0.0008 |
| Change of Lean Body Mass from Baseline | | | | | | | |
| (1) PEG-IFN alfa-2a + Ribavirin | 55 | 46 | 30254 | -602 ( -1193 to -12) | | | |
| (2) PEG-IFN alfa-2a + Placebo | 59 | 49 | 33006 | 454 ( -116 to 1024) | (2) minus (1) | 1056 ( 332 to 1781) | 0.0048 |
| Change of Percentage of Body Fat from Baseline | | | | | | | |
| (1) PEG-IFN alfa-2a + Ribavirin | 55 | 29 | 28.18 | -1.21 ( -2.07 to -0.34) | | | |
| (2) PEG-IFN alfa-2a + Placebo | 59 | 31 | 26.14 | -0.01 ( -0.85 to 0.82) | (2) minus (1) | 1.19 ( 0.15 to 2.24) | 0.0262 |

n= Patients used in analysis, LSM= Least square mean, CI= Confidence interval.
(a) P-value from the analysis of covariance with gender, genotype as factors and age, baseline log10 HCV RNA and baseline value of the dependent endpoint as covariates.

**Adapted from Table 52 in Section 3.3.9 of applicant's study report**

In both treatment groups there was a statistically significant decrease in weight z-scores from baseline to Week 24, however the decrease was significantly larger in the combination group (mean, -0.43) as compared to the monotherapy group (mean, -0.19).

Similarly, in both treatment group there was a statistically significant decrease in height z-scores from baseline to Week 24, however the decrease was significantly larger in the combination group mean, -0.22) as compared to the monotherapy group (mean, -0.11)

However, for both weight and height, the mean change in z-scores from baseline improved at the 1 year and 2 year posttreatment period.

*MO's Comment: As seen in the analysis of percentile growth parameters, z-scores for weight and height were significantly decreased in both initial treatment groups. In addition the inclusion of ribavirin in subject's regimen may have contributed to a greater decrease in the combination therapy group. Overall, these changes seem to improve in over time and by the 2 year posttreatment mark.*

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There has been no new information or data submitted to assess the abuse, overdosing or withdrawal potential of either PEG-IFN alfa-2a or ribavirin. In previous studies, no rebound signals were detected which warranted further follow-up.

### 7.7 Additional Submissions / Safety Issues

There are no additional submissions or safety issues.

# 8 Postmarket Experience

As of September 21, 2010, the applicant has conducted a cumulative search of the global Roche Drug Safety database (ADVENT) to identify relevant cases of reported AEs associated with Pegasys alone or in combination with ribavirin involving patients less than 18 years of age. Both serious and non-serious events were reported from clinical trials, literature, and spontaneous reports.

Forty-six pediatric cases involving non-serious AEs were identified. Thirty-four of these patients were greater than 5 years of age. The majority of these patients were treated for chronic hepatitis C. Ninety-four non-serious AEs were associated with these 46 patients. These AEs were reported in the following system organ classes (SOCs):

- General, which included events such as pyrexia, fatigue, malaise, irritability, and “no adverse event” reported in association with a medication error or accidental exposure
- Investigations, which consisted mainly of laboratory and hematologic abnormalities
- Skin, such as rash and pruritus
- Gastrointestinal, such as nausea and vomiting
- Injury and Poisoning, such as accidental exposure, drug administration error, and drug exposure via breast milk

Review of individual non-serious AEs showed that the most frequently reported events were decreased WBC counts, decreased appetite, nausea, pyrexia, and rash. All other non-serious AEs were reported in no more than two cases.

In terms of serious AEs (SAEs), most of the 44 patients were being treated for CHC. These SAEs were reported in the following SOCs:

- Investigations, which consisted of neutrophil and WBC count decreases and hepatic enzyme abnormalities
- Blood Disorders, such as neutropenia and anemia

Review of the individual SAEs revealed none were reported in more than one case other than laboratory and hematological abnormalities.

Nine cases reported both serious and non-serious AEs.

*MO's Comment: Based on these post-marketing data, the applicant states there is no suggestion that the safety risk in pediatric patients is significantly different from the safety profile seen in adults.*

# 9 Appendices

## 9.1 Literature Review/References

1. Mohan P, Colvin C, Glymph C, et al. Clincal spectrum and histopathologic features of chronic hepatitis C infection in children. J Pediatr. 2007; 150 (2): 168-174.

2. Sherman KE, Fleischer R, Laessig K, Murray J, Tauber J, Tauber W, Birnkrant D. Development of novel agents for the treatment of chronic hepatitis C infection: summary of the FDA antiviral products advisory committee recommendations. Hepatology 2007. 46(6): 2014-2020.

3. Pegasys® label
http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103964s5184lbl.pdf

4. Copegus® label
http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021511s021lbl.pdf

5. Pegintron® label
http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/103949s5172lbl.pdf

6. Rebetol® label
http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020903s046,021546s002lbl.pdf

## 9.2 Labeling Recommendations

Labeling negotiations are in progress at the time of this review. However, for both the Pegasys and Copegus labels, the following sections will likely have information from this pediatric supplement included: Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, and Clinical Studies.

## 9.3 Advisory Committee Meeting

There was no Advisory Committee Meeting for this submission.

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/s/

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