ANTIVIRAL DRUGS ADVISORY COMMITTEE
BRIEFING DOCUMENT

FOR

PEGASYS® IN COMBINATION WITH COPEGUS™

TREATMENT OF CHRONIC HEPATITIS C

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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TABLE OF CONTENTS

Page

LIST OF TABLES

Page

LIST OF FIGURES

Page

LIST OF APPENDICES

Page

EXECUTIVE SUMMARY

This briefing document summarizes the Pegasys® and Copegus™ (Roche ribavirin) clinical development program for the treatment of chronic hepatitis C (CHC). Although CHC had been viewed as a single disease, it is now recognized to be a complex and heterogeneous disease. Many factors, including genotype and liver histology, affect the pathophysiology, prognosis, and likelihood of response to treatment. Hoffmann-La Roche has designed a multifaceted, comprehensive clinical development program for Pegasys and Copegus combination therapy for the treatment of CHC.

The Pegasys and Copegus combination clinical development program for CHC consisted of an initial pilot safety study (NV15800) and two phase III international registration trials, NV15801 and NV15942, with complementary objectives. Study NV15801 was a comparative trial vs Rebetron designed to show the superiority of Pegasys and Copegus combination therapy over Rebetron. Patients were stratified according to genotype and treated for 48 weeks with Pegasys or Intron A in combination with 1000 or 1200 mg of Copegus or Rebetol, respectively, or with Pegasys plus placebo. Study NV15942 was designed to build on the results of NV15801 by using the Pegasys and Copegus combination therapy arm from study NV15801 as the control arm and assessing the benefits and risks of lower exposures in patient subgroups.

Study NV15942 used a matrix design to assess the effects of either a shorter duration of treatment (ie, 24 weeks vs 48 weeks) or a lower daily dose of Copegus (ie, 800 mg fixed dose vs 1000 or 1200 mg by body weight category), or both, on safety and efficacy. The primary objective was to determine if baseline disease factors can be used to prospectively optimize therapy. Patients were stratified in this study according to HCV genotype and viral load to assess if patients who have previously been shown to be more responsive to treatment, ie, patients with genotype non-1 infection or low baseline viral load, can be treated successfully for a shorter period of time and with a lower ribavirin dose than patients who have previously been shown to be less likely to respond, ie, patients infected with genotype 1 or high baseline viral load.

The efficacy end point used in this briefing document for both NV15801 and NV15942 is sustained virological response (no detectable virus) assessed 6 months after the end of treatment. For the primary analysis, sustained virological response was based on two measurements of HCV RNA as specified in the protocols. Patients with only a single undetectable value were considered nonresponders in this analysis. The population analyzed is all treated patients.

The principal efficacy findings from the two phase III combination therapy studies were the following:

- Sustained virological response in patients treated for 48 weeks with 180 μg of Pegasys and 1000 or 1200 mg of Copegus combination therapy (52%) in study

NV15801 was statistically significantly higher (p = 0.005) than in patients treated for 48 weeks with Rebetron (43%).

- Statistically significant improvement in sustained virological response of Pegasys and Copegus combination therapy over Rebetron was seen in patients infected with genotype 1 (43% vs 35%, p = 0.046) as well as in patients infected with genotype non-1 (predominantly genotypes 2 and 3) (68% vs 57%, p = 0.044).

- Improvement in sustained virological response of Pegasys and Copegus combination therapy over Rebetron was seen in patients with genotype 1 infection regardless of viral load (high or low) and in patients with genotype non-1 infection regardless of viral load.

- In study NV15942, patients infected with genotype 1, irrespective of baseline viral load, achieved the highest sustained virological response when treated for 48 weeks with Pegasys and 1000 or 1200 mg of Copegus (50%).

- In patients infected with genotype non-1 (predominantly genotype 2 or 3) in study NV15942, irrespective of baseline viral load, similar sustained virological responses were achieved after treatment for 24 weeks with Pegasys and 800 mg of ribavirin (78%) and after treatment for 48 weeks with Pegasys and 1000 or 1200 mg of Copegus (75%).

- Pegasys and Copegus combination therapy provided substantial efficacy in the subgroup of patients with compensated cirrhosis or bridging fibrosis. Cirrhotic patients treated for 48 weeks with Pegasys and 1000 or 1200 mg of Copegus achieved sustained virological responses of 41% vs 52% for the overall population in study NV15801 and 52% vs 59% for the overall population in study NV15942. Sustained virological responses in patients with cirrhosis treated with Pegasys and Copegus in study NV15801 were numerically higher than those in cirrhotic patients treated with Rebetron (41% vs 33%). In study NV15942, the effects of genotype and ribavirin dose in cirrhotic patients were consistent with the findings in the overall population.

- An analysis based on quantitative HCV RNA testing to assess whether it is possible to identify by week 12 of treatment those patients with little chance of achieving a sustained virological response after the full course of therapy was performed. This analysis used the 889 patients from studies NV15801 and NV15942 treated for 48 weeks with Pegasys and 1000 or 1200 mg of Copegus. Of the 113 patients who failed to achieve an early virological response (ie, undetectable HCV RNA or a 2-$\log_{10}$ decrease from baseline HCV RNA) by week 12 of treatment, 108 failed to achieve a sustained virological response, resulting in a negative predictive value (probability of nonresponse) of 96%. The negative predictive value of not achieving an early virological response by week 12 for sustained virological response in the 569 patients with genotype 1 infection was also 96%.

The principal safety findings from the two phase III combination therapy studies were the following:

- Based on a large safety data base, the safety profile of Pegasys and Copegus combination therapy has been well characterized in CHC patients, including those with compensated cirrhosis.
- Overall safety profile of 180 μg of Pegasys and 1000 or 1200 mg of Copegus combination therapy for 48 weeks is similar to Rebetron; no new clinical adverse events were observed with Pegasys and Copegus combination therapy that would not have been expected from combination therapy with interferon alfa and ribavirin. Most common clinical adverse events were reported at a similar frequency with Pegasys and Copegus combination therapy and Rebetron therapy.
- Frequency of serious adverse events was comparable with Pegasys and Copegus combination therapy and Rebetron therapy. Some differences in the point estimates for serious adverse events grouped by body system were observed between Pegasys and Copegus combination therapy and Rebetron therapy, respectively, in study NV15801 that included
    - Serious infections (4% vs 2%)
    - Serious psychiatric disorders (1% vs 3%)
- Similar frequency of anemia but higher frequencies of neutropenia and thrombocytopenia were observed with Pegasys and Copegus combination therapy than with Rebetron therapy in study NV15801.
    - Hemoglobin concentration <10 g/dL (11% vs 11%, for Pegasys and Copegus combination therapy and Rebetron therapy, respectively)
    - Neutrophil counts 0.5 to <0.75 x 10^9/L (22% vs 7%) and neutrophil counts <0.5 x 10^9/L (5% vs 1%)
    - Platelet counts <50 x 10^9/L (5% vs <1%). No patient experienced a platelet count of <20 x 10^9/L.
- Similar frequency of modification of the interferon dose for adverse events with Pegasys and Copegus combination therapy (11%) and Rebetron therapy (11%). However, modification of the interferon dose for neutropenia and thrombocytopenia occurred more frequently with Pegasys and Copegus combination therapy (20% and 4%) than with Rebetron therapy (5% and <1%). Modification of the ribavirin dose for anemia occurred with a similar frequency with Pegasys and Copegus combination therapy (22%) and with Rebetron therapy (19%).
- Majority of laboratory abnormalities were managed with dose modification and did not require withdrawal of patients from treatment. Treatment discontinuation

for safety reasons occurred at similar frequency with Pegasys and Copegus combination therapy (10%) and with Rebetron therapy (11%). With both combination therapies, clinical adverse events were the most common safety reasons for treatment discontinuation (7% vs 10%, respectively).

- In study NV15942 treatment-limiting events, including serious adverse events (3%), hemoglobin levels <10 g/dL (3%), and premature withdrawal for clinical adverse events and laboratory abnormalities (5%), occurred with the lowest frequency in patients receiving the lowest exposure regimen (ie, 24 weeks of treatment and the 800 mg daily dose of Copegus). Shorter duration of Pegasys and Copegus combination therapy and administration of a lower daily ribavirin dose offer a safety advantage over 48 weeks of treatment with Pegasys and the higher dose (1000 or 1200 mg) of Copegus.

- Overall safety profile of Pegasys and Copegus combination therapy in patients with compensated cirrhosis was similar to that in the overall patient population. Differences observed were a higher frequency of platelet counts decreasing to between 20 and 50 x 10^9/L and a higher frequency of dose modification of Pegasys for thrombocytopenia.

Data from the literature and Roche preclinical studies indicate that ribavirin is teratogenic and a reproductive toxicant. A pregnancy risk management program for Copegus has been developed and includes provider and patient labeling (including a medication guide), pregnancy prevention education, and a pregnancy registry to collect and track information on pregnancies, fetal exposures, and all associated outcomes.

Pegassist, a comprehensive patient education program, has also been developed to educate patients on the safe and appropriate use of Pegasys and Copegus combination therapy as well as to provide important general hepatitis C and pregnancy information. This program includes a variety of patient and provider support materials including educational brochures on hepatitis C and a self-injection video.

Based on an evaluation of the efficacy, safety, and exposure data from the two phase III studies NV15801 and NV15942, the recommended dosing regimens for Pegasys and Copegus combination therapy are:

- *For patients with genotype non-1 infection:* 180 µg of Pegasys given once weekly plus 800 mg of Copegus given daily for 24 weeks.

- *For patients with genotype 1 infection:* 180 µg of Pegasys given once weekly plus 1000 or 1200 mg of Copegus given daily for 48 weeks.

The data generated from the clinical development program demonstrate that the combination of Pegasys and Copegus represents an advance in the treatment of CHC over Rebetron. The efficacy and safety results from the two pivotal phase III Pegasys and Copegus combination studies also provide further evidence to support a treatment

paradigm based on baseline disease characteristics that has been evolving for the treatment of CHC patients, including patients with cirrhosis. In this paradigm, HCV genotype is the determining factor in the selection of the appropriate treatment duration and Copegus dose to achieve a balance of efficacy and safety in the treatment of patients with this serious and life-threatening disease. The Pegasys and Copegus clinical development program has not only established the safety and efficacy of Pegasys and Copegus therapy for the overall population of patients with CHC but has also established the benefits of therapy in patients with cirrhosis, as well as the benefits of shorter duration of therapy and lower daily Copegus dose for certain patient subpopulations.

LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase (SGPT)
AUC	area under the concentration vs time curve
C_{max}	maximum concentration
CHC	chronic hepatitis C
CL/F	apparent total body clearance
CRTN	clinical research task number, unique number identifying protocol, center, and investigator
HCV	hepatitis C virus
IFN alfa	interferon alfa
IFN alfa-2a	interferon alfa-2a (Roferon®-A)
IFN alfa-2b	interferon alfa-2b (Intron A)
iv	intravenous
MIU	million international units
2′,5′-OAS	2′, 5′-oligoadenylate synthetase
PCR	polymerase chain reaction
PEG	polyethylene glycol
PEG-IFN alfa-2a	peginterferon alfa-2a (Pegasys®, Ro 25-8310)
po	orally
qw	once per week
RNA	ribonucleic acid
sc	subcutaneous
$t_{1/2}$	terminal phase half-life
T_{max}	time to maximum concentration
U/L	units per liter

1. INTRODUCTION

This briefing document summarizes the Pegasys and Copegus clinical development program for the treatment of chronic hepatitis C (CHC). Because CHC is a complex, heterogeneous disease and many factors affect the pathophysiology, prognosis, and likelihood of response to treatment, Hoffmann-La Roche designed a multifaceted, comprehensive clinical development program for Pegasys and Copegus combination therapy for the treatment of CHC. This program not only established the safety and efficacy of Pegasys and Copegus therapy for the overall population of patients with CHC but also established the benefits of therapy in patients with cirrhosis, as well as the benefits of shorter duration of therapy and lower daily Copegus dose for certain patient subpopulations.

1.1 Chronic Hepatitis C

Infection with the hepatitis C virus (HCV) is a leading cause of chronic liver disease in the United States. An estimated 2.7 million Americans suffer from chronic HCV infection. Approximately 85% of those with acute HCV infection progress to chronic infection. Progression to cirrhosis is expected in about 20% of patients with CHC within 20 years and in about 30% within 30 years. Approximately 25% of the patients who develop cirrhosis will die from hepatic failure, develop liver cancer, or require liver transplantation. In the United States, CHC is responsible for an estimated 8000 to 10,000 deaths per year and is the leading cause of liver transplantation. Because the majority of those infected with HCV are currently under 50 years of age, deaths from HCV-associated disease are expected to triple during the next 10 to 20 years as the infected cohort reaches an age at which complications of liver disease typically occur.

Although CHC has been viewed in the past as a single disease, it is now recognized to be a complex and heterogeneous disease. CHC occurs in various subgroups of patients. Each of these patient subgroups has a different likelihood of responding to therapy and requires a particular treatment and dosing regimen to optimize treatment response. A number of prognostic factors that affect response to anti-HCV therapy have been reported in the literature including HCV genotype, histological status of the liver, pretreatment HCV RNA viral load, age, gender, and race [1-4]. The clinical development plan for Pegasys includes studies that prospectively examined all these important factors as likely predictors of response to treatment and dose optimization.

HCV genotype, in particular, has been identified as a key prognostic factor in determining response to IFN alfa-based therapies. HCV is an RNA virus of the Flaviviridae family and is generally classified into six major genotypes, with some of the genotypes distributed worldwide (1a, 1b, 2, and 3) and others (4, 5, and 6) geographically restricted [5]. Of the six genotypes, genotype 1, the most common genotype in the United States, is considered the most resistant to therapy. Of the non-1 genotypes, genotypes 2 and 3 have been the most responsive to IFN alfa-based therapies. Similar to patients with genotype 1 infection, patients with genotype 4 infection have been relatively resistant to therapy [6,7]. Pretreatment viral load has also been found to be a

prognostic factor; patients with a low viral load are more likely to respond to therapy than patients with a high viral load. The cutoff used for distinguishing high and low viral load has been 2 million copies/mL. Patients infected with genotype 1 and having a high viral load have been found to be one of the subgroups most resistant to therapy.

Histological status of the liver, that is whether a patient is noncirrhotic and has minimal fibrosis or has progressed to cirrhosis and has more extensive fibrosis, is another important prognostic factor associated with response to anti-HCV therapies. Less than 10% of CHC patients with cirrhosis who are treated with IFN alfa monotherapy are reported to achieve a sustained virological response compared with responses of 10% to 20% in the general CHC patient population. Patients with cirrhosis are also perceived to be more likely to experience adverse effects from IFN alfa-based therapies, and safety concerns have been raised about treating patients with cirrhosis with these therapies.

Patients who are older, male, or Black are also less likely than other patients to have a favorable response to IFN alfa-based therapy.

The Pegasys clinical development program was designed to address a number of these complexities and issues affecting the optimal treatment of patients with CHC. The goal of Roche's clinical development program was to maximize the benefits and minimize the risks of Pegasys monotherapy and Pegasys and Copegus combination therapy for individual patient subgroups.

Data are provided in this application that address the following areas:

- Relationship of genotype, viral load, duration of treatment, and ribavirin dose and sustained virological response to therapy
- Relationship between cirrhosis and the safety of interferon therapy and between cirrhosis and sustained virological response to therapy
- Relationship between important patient subgroups and response to combination therapy with pegylated interferons vs response to interferon combination therapy

1.2 Rationale for Pegylated Interferons

The first available therapy approved for the treatment of CHC was interferon (IFN) alfa monotherapy. IFN alfa-2a (Roferon-A), IFN alfa-2b (Intron A), and IFN alfa con-1 (Infergen) were all approved in the early-to-mid 1990s for the treatment of this disease. IFN alfa monotherapy administered three times weekly results in sustained virological responses in only 10% to 20% of patients; less than 10% of patients with genotype 1 infection and/or cirrhosis will achieve a sustained virological response. Addition of ribavirin to IFN alfa significantly increased the number of sustained virological responses, and combination therapy has replaced IFN alfa monotherapy as the standard of treatment for patients with CHC.

IFN alfa is quickly absorbed after subcutaneous administration but, unfortunately, has a short terminal half-life of approximately 4 to 10 hours. Serum concentrations of IFN alfa therefore almost always rise rapidly and then decline rapidly, resulting in little or no detectable IFN alfa in serum by 24 hours after administration. Because of this pharmacokinetic profile (1) frequent dosing, typically three times weekly, is necessary to maintain a sustained antiviral effect, (2) efficacy may be limited by the lack of circulating IFN alfa for substantial periods between doses, and (3) the rapid fluctuations in IFN alfa concentrations, including the peaks following dosing and the rapid decline in IFN alfa concentrations, may contribute toward intolerance to therapy.

Different, longer-acting pegylated interferons, including PEG-Intron and Pegasys, were developed to address the shortcomings of IFN alfa and to potentially improve the efficacy and tolerability of treatment. Pegasys (Ro 25-8310, peginterferon alfa-2a) is made by conjugating a single branched polyethylene glycol chain (PEG) of approximate molecular weight of 40,000 daltons to a molecule of IFN alfa-2a (19,237 daltons) in a 1:1 molar ratio via a stable amide bond. Peginterferon alfa-2a (PEG-IFN alfa-2a) has an approximate molecular weight of 60,000 daltons. PEG-Intron, which consists of a 12,000 dalton single PEG chain conjugated to IFN alfa-2b, is approved in the United States as monotherapy and as combination therapy for the treatment of CHC.

PEG-IFN alfa-2a exhibits sustained absorption from the injection site and reduced clearance compared with nonpegylated IFN alfa-2a. The pharmacokinetic properties result in a consistent serum concentration for 7 days (168 hours) and allow for once weekly administration, thus avoiding the high peaks, low troughs, and repeated peak-trough cycling of IFN alfa concentrations.

The pharmacokinetic profile of Pegasys was associated with a significant improvement in the benefit-risk relationship over IFN alfa monotherapy, the standard of care for the treatment of CHC at the time the Pegasys monotherapy studies were started. During the conduct of the Pegasys monotherapy studies, another interferon-alfa-based therapy, IFN alfa-2b (Intron A) in combination with ribavirin (Rebetol), was approved. As noted earlier, the addition of ribavirin to IFN alfa-2b significantly increased sustained virological responses compared with IFN alfa-2b monotherapy. Since Pegasys monotherapy was shown to be more effective than IFN alfa monotherapy in the Pegasys monotherapy pivotal trials, Hoffmann-La Roche postulated that the combination of ribavirin and Pegasys might result in even greater efficacy than that seen with Rebetron (IFN alfa-2b and ribavirin).

1.3 Overview of Clinical Development Program

1.3.1 Pegasys Monotherapy Studies

Pegasys was initially developed as monotherapy for the treatment of previously untreated patients chronically infected with HCV. The monotherapy clinical development program consisted of four studies enrolling 1600 patients; 996 were treated with Pegasys (Figure 1). The four monotherapy studies included a phase II dose-finding study in

noncirrhotic patients (NV15489), a phase II/III study in patients with cirrhosis or bridging fibrosis (transition to cirrhosis) (NV15495), and two phase III studies in a general population of cirrhotic and noncirrhotic patients (NV15496 and NV15497).

The principal findings of the Pegasys monotherapy studies are summarized below:

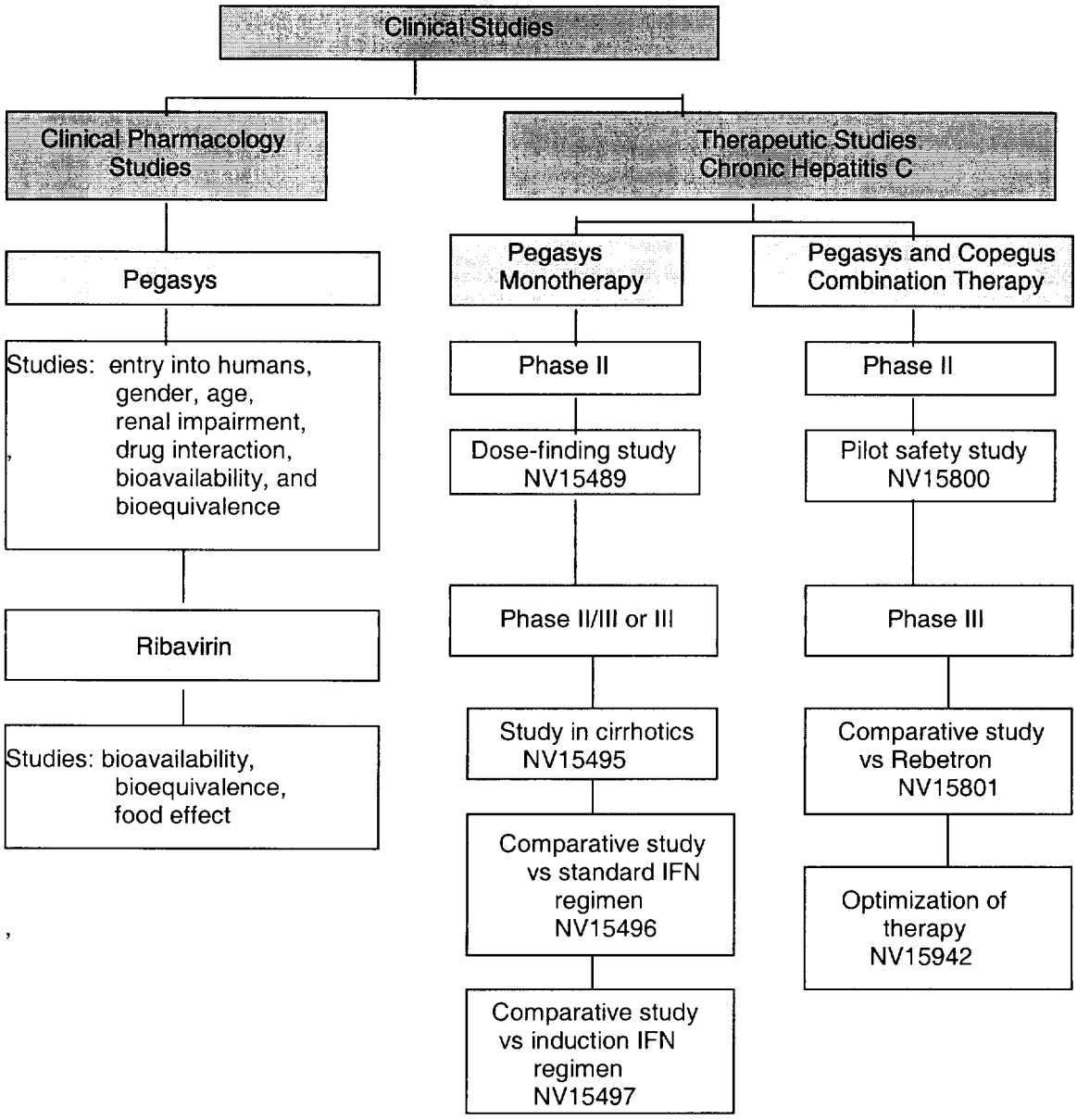
- The 180 μg dose of Pegasys resulted in the highest sustained virological response in the phase II dose-finding study and the best balance between efficacy and safety, results that were confirmed by the phase III monotherapy studies.
- Administration of a once weekly dose of 180 μg of Pegasys for 48 weeks resulted in significant improvement in sustained virological response as compared with either standard or induction regimens of Roferon-A.
- The 180 μg dose of Pegasys substantially improved sustained virological responses over responses observed with Roferon-A treatment in the most difficult-to-treat populations, those infected with genotype 1 or those with accompanying cirrhosis.
- Histological improvement at the end of follow-up was also significantly higher with 180 μg of Pegasys for 48 weeks than with the standard regimen of Roferon-A, including histological improvement in patients with cirrhosis or bridging fibrosis.
- The adverse event profile of 180 μg of Pegasys was similar to that of Roferon-A, and no new or unique adverse events clearly related to Pegasys were observed.
- An increase in the incidence of some other known interferon side effects was observed that included neutropenia and thrombocytopenia. The increase in incidence of these laboratory abnormalities was not associated with clinical symptoms and could be managed clinically in most cases by temporary or permanent dose reduction and only infrequently required discontinuation of treatment.

1.3.2 Pegasys and Copegus Combination Studies

Copegus is the Roche formulation of ribavirin. An NDA for the use of Copegus in combination with Pegasys was filed jointly with the BLA for Pegasys as combination therapy with Copegus. The Pegasys and Copegus combination clinical development program for the treatment of CHC consisted of an initial pilot safety study (NV15800) and two phase III international registration trials, NV15801 and NV15942, with complementary objectives (Figure 1). Study NV15801, the comparative trial vs Rebetron, was a randomized, multicenter, partially blinded, active-controlled and placebo-controlled trial designed to show the superiority of Pegasys and Copegus combination therapy over Rebetron. Patients were stratified according to genotype and treated for 48 weeks with Pegasys or Intron A in combination with 1000 or 1200 mg of Copegus or Rebetol, respectively, or with Pegasys plus placebo. Study NV15942, the

optimization of therapy trial, was a randomized, multicenter, double-blind trial designed to assess the effects on response to treatment of a shorter duration of treatment (24 vs 48 weeks) and a lower Copegus dose (800 mg fixed dose vs 1000 or 1200 mg by body weight category). Patients were stratified in this study according to HCV genotype and viral load.

Figure 1 Overview of Clinical Development Program for Pegasys and Copegus in Chronic Hepatitis C



1.3.3 Ongoing Studies in Special Populations

CHC is now recognized to be a complex and heterogeneous disease that occurs in various patient subgroups who have a different likelihood of responding to therapy. The Pegasys monotherapy and Pegasys and Copegus combination therapy clinical development programs were prospectively designed to address these complexities and include studies in the following HCV-infected special populations:

- HCV and HIV coinfected patients
- African-American patients
- Patients with cirrhosis
- Patients with persistently normal ALT activity
- Liver transplant patients
- Pediatric patients

A list of some of the ongoing Pegasys studies in these special populations is provided in Appendix 1. Drug interaction studies in patients with CHC are also being conducted examining the potential interaction between the following drugs:

- Pegasys and methadone
- Ribavirin and HIV reverse transcriptase inhibitors

A list of ongoing drug interaction studies is provided in Appendix 2.

2. NONCLINICAL DEVELOPMENT

Data from the preclinical studies performed, combined with a review of the extensive literature on ribavirin, provide nonclinical support for the combination of Pegasys with Copegus for the treatment of CHC. Nonclinical studies with Pegasys in combination with ribavirin have shown in an in vitro model of hepatitis C viral replication that the combination was more effective than either compound alone. No evidence of pharmacokinetic interactions between the two drugs has been observed, and no additional or unexpected toxicity was seen with this combination above that observed for each drug alone.

2.1 Key Findings from Nonclinical Pharmacology Program

Pegasys qualitatively retains those properties that define IFN alfa. Pegasys binds to the IFN alfa receptor, transduces a signal, and stimulates expression of known IFN alfa inducible genes, leading to antiviral, immunomodulatory, and antiproliferative activities characteristic of most interferons.

Pegasys demonstrates similar biological activity to IFN alfa-2a in the monkey, using induction of 2′,5′-oligoadenylate synthetase activity in serum as a pharmacodynamic marker of antiviral activity.

Ribavirin inhibits HCV subgenomic RNA replication in vitro in human hepatoma cells (HCV replicon assay). Ribavirin and Pegasys in combination were found to be more effective than either agent alone in inhibiting HCV subgenomic RNA replication in this in vitro model. Ribavirin also increases T helper 1 cytokine and decreases T helper 2 cytokine secretion from stimulated human T cells in vitro, in addition to inhibiting T cell proliferation. The mechanism by which ribavirin in combination with Pegasys exerts its effects against HCV is unknown, although it is likely to involve both direct antiviral and immunomodulatory activities. No appropriate in vivo pharmacology models are currently available for assessing the combination of Pegasys with ribavirin in hepatitis C.

2.2 Key Findings from Nonclinical Pharmacokinetics Program

Pegasys has a pharmacokinetic profile in animals that is superior to that of IFN alfa-2a. The absorption of Pegasys is sustained from the subcutaneous site, the clearance is reduced, and the volume of distribution is more restricted to interstitial fluids and the blood. Compared with IFN alfa-2a, the half-life of Pegasys was about sevenfold longer in rats and 20-fold longer in cynomolgus monkeys. These pharmacokinetic findings supported by the findings with a pharmacodynamic marker in monkeys provide a basis for once weekly dosing of Pegasys.

A single-dose pharmacokinetic study in dogs demonstrated that Roche ribavirin administered as a tablet (Copegus) displayed similar pharmacokinetic attributes as ribavirin administered as a capsule (Rebetol). The absorption, distribution, metabolism, and excretion of ribavirin after single doses in animals have been well characterized and are reported in the literature. No pharmacokinetic interactions were noted in a 4-week combination toxicology study of Pegasys and ribavirin in cynomolgus monkeys.

The results from multiple-dose toxicokinetic studies of ribavirin in rats, dogs, and monkeys showed that serum ribavirin $AUC_{0\text{-}24\ h}$ was approximately dose proportional in these species, while C_{max} showed inconsistent linearity with increases in dose of ribavirin. This phenomenon has also been reported in humans [8]. The results from these studies also indicated species differences in the accumulation of ribavirin in red blood cells (RBCs). The differences observed among the monkey, rat, and dog in the accumulation of ribavirin are consistent with findings reported in the literature and may be due to the equilibrium between RBCs and plasma, which is rapid in rats and slow in monkey and human. This observation is consistent with the theory that ribavirin accumulates in RBCs and thus promotes their removal by the reticuloendothelial system (ie, decreases the life span of RBCs), leading to anemia [9].

2.3 Key Findings from Toxicology Program

Studies with Pegasys alone showed that Pegasys did not induce any additional or unexpected toxicity beyond those previously seen with IFN alfa. Toxicities observed

with Copegus alone are similar to those reported in the literature for ribavirin and are consistent with ribavirin's inhibitory effects on rapidly proliferating cells or tissues.

Dosing in toxicology studies was at high multiples of the proposed human dose (ie, doses up to 1400-fold the proposed clinical dose of Pegasys and up to 20-fold the proposed clinical dose of Copegus). Since IFN alfa activity is species-specific (no pharmacological activity is seen in rodents or dogs and nonhuman primates show the most response to human interferons), all nonclinical safety assessments of Pegasys alone and of the combination of Pegasys and ribavirin were conducted in cynomolgus monkeys. Ribavirin monotherapy studies were performed in dogs and rodents.

The nonclinical toxicity studies with Pegasys and ribavirin, Pegasys alone, or ribavirin alone have characterized the untoward effects of the Pegasys and Copegus combination therapy that have been observed in some humans taking these therapies. These untoward effects include anemia, alterations in other clinical pathology parameters (platelet counts, WBCs, total protein concentration, ALT and/or AST activity), gastrointestinal irritation, lymphoid depletion, and reproductive and teratogenic effects. All the findings are expected and have been associated with alpha IFNs or with compounds such as ribavirin that interfere with cellular proliferation. The treatment of monkeys with the combination of Pegasys and Copegus results in only a slight increase in expected toxicities (ie, anemia) with no new or unexpected toxicities.

Data from the literature indicate that ribavirin is teratogenic and a reproductive toxicant. The Roche-sponsored fertility study in rats confirmed ribavirin's embryotoxic effect and showed slight effects on sperm counts at a daily Copegus dose of 100 mg/kg. Importantly, all effects on reproductive parameters were reversible following treatment withdrawal.

The reported mean multiple-dose terminal half-life for ribavirin in patients receiving Intron A and Rebetol is approximately 298 hours (12 days) [10]. This value is longer than the mean terminal half-life for ribavirin (both Copegus and Rebetol) of 180 hours obtained from a multiple-dose pharmacokinetic substudy in patients receiving Pegasys and Copegus or Intron A and Rebetol [11]. While the mean terminal half-life of ribavirin after 48 weeks of treatment in this Roche clinical study is about 180 hours for both Copegus and Rebetol, the half-life in some patients is greater than 180 hours. Because ribavirin is teratogenic and is extensively distributed to tissues, an extended washout period of 15 times the terminal half-life of 300 hours for ribavirin, approximately 6 months, is recommended for both men and women. Fifteen half-life estimations, or approximately 6 months, which is based on the most conservative mean terminal half-life reported (300 hours), ensures that ribavirin is adequately cleared from the systemic circulation and tissues before patients discard effective contraception.

Although the literature and Roche-sponsored studies indicate ribavirin is genotoxic, results from the 6-month carcinogenicity study in p53 (+/-) knockout mice revealed no evidence of treatment-related neoplasia.

3. CLINICAL PHARMACOLOGY AND PHARMACOKINETIC PROFILE

Clinical pharmacology data were collected in 19 clinical pharmacology studies (14 with Pegasys and 5 with ribavirin) and seven clinical trials in CHC patients (Figure 1).

The clinical pharmacology data for Pegasys were derived from 950 healthy subjects, 48 subjects with renal impairment or end-stage renal disease requiring hemodialysis, 146 patients with CHC receiving monotherapy, and 304 patients with CHC receiving combination therapy. Of the 450 patients with CHC, 103 patients had cirrhosis or bridging fibrosis. All CHC patients and all but 21 subjects in the clinical pharmacology studies received subcutaneous (sc) doses of Pegasys.

The clinical pharmacology data for ribavirin were derived from 305 patients with CHC who received single oral doses of 600 mg of ribavirin alone in clinical pharmacology studies, 302 patients with CHC who received multiple oral doses of ribavirin in combination with Pegasys, and 66 patients with CHC who received multiple oral doses of ribavirin in combination with Intron A.

3.1 Pegasys

3.1.1 Pharmacodynamics of Pegasys

HCV RNA levels decline in a biphasic manner in patients with CHC who have received Pegasys and respond to therapy. In patients who achieve a sustained virological response, the first phase of decline occurs within 24 to 36 hours after the first dose of Pegasys and the second phase of decline occurs over the next 4 to 16 weeks. Compared with treatment with standard alpha interferons, the administration of 180 μg of Pegasys once weekly enhances viral clearance and improves virological end-of-treatment responses.

Pegasys stimulates the production of effector proteins such as serum neopterin and 2',5'-oligoadenylate synthetase (2',5'-OAS) in a dose-dependent manner. The stimulation of 2',5'-OAS activity is maximal after single doses of 135 to 180 μg of Pegasys and stays maximal throughout the 1-week dosing interval. The magnitude and duration of Pegasys-induced 2',5'-OAS activity were reduced in subjects older than 62 years. The clinical relevance of these findings with pharmacodynamic markers of Pegasys is not known.

3.1.2 Pharmacokinetics of Pegasys

The structure of the PEG moiety directly affects the clinical pharmacology of Pegasys. The size and branching of the 40,000 dalton PEG moiety define the absorption, distribution, and elimination of Pegasys. The pharmacokinetics of Pegasys were studied in healthy subjects and CHC patients. Absorption is sustained, peak PEG-IFN alfa-2a serum concentrations are reached 72 to 96 hours after dosing, and concentrations are detectable within 3 to 6 hours after a single dose. Within 24 hours, 80% of peak serum concentrations are reached. Dose-proportional increases in AUC and C_{max} are seen in patients who received once weekly doses of Pegasys. The absolute bioavailability is 84% and is similar to that seen with IFN alfa-2a.

The systemic clearance is about 100 mL/h, which is 100-fold lower than that of IFN alfa-2a. After an intravenous dose, the terminal half-life is about 60 to 80 hours compared with 3 to 4 hours for standard IFN. The terminal half-life after subcutaneous dosing is longer (range, 50 to 130 hours). PEG-IFN alfa-2a is found mainly in the bloodstream and extracellular fluids, as the volume of distribution after intravenous dosing in humans is 6 to 14 L. Based on studies in rats, the drug is distributed to the liver, kidney, and bone marrow as well as being highly concentrated in the blood.

Metabolism by the liver is the main clearance mechanism for Pegasys; however the metabolic profile has not been fully characterized. Studies in rats show that the kidney is the main organ for excretion of radiolabeled material. The kidneys eliminate less than 10% of a dose as the intact PEG-IFN alfa-2a. The metabolic products are excreted in both the urine and bile. In the rat, the half-life of radiolabeled PEG moiety is about 10 days, and thus within 50 to 60 days the PEG moiety is eliminated from the body.

In CHC patients, steady-state serum concentrations increase twofold to threefold compared with single-dose values and reach steady state within 6 to 8 weeks of once weekly dosing. The peak-to-trough ratio during treatment and at the end of 48 weeks of treatment is between 1.5 and 2.0. PEG-IFN alfa-2a serum concentrations are sustained throughout the dose interval of 1 full week (168 hours).

The pharmacokinetics of Pegasys were comparable in male and female healthy subjects. The AUC was modestly increased in subjects older than 62 years taking 180 μg of Pegasys, but peak concentrations were similar in those older and younger than 62 years. Based on drug exposure, pharmacodynamic response, and tolerability, a lower starting dose of Pegasys is not needed in geriatric patients.

The pharmacokinetics of Pegasys were similar between healthy subjects and CHC patients. Comparable exposure and pharmacokinetic profiles were seen in patients having cirrhosis with compensated liver disease and patients without cirrhosis. Pegasys has not been evaluated in patients with decompensated cirrhosis (eg, Child-Pugh B/C or bleeding esophageal varices).

No significant relationship between Pegasys's pharmacokinetics and creatinine clearance was seen in 23 subjects with normal renal function to significant renal impairment (creatinine clearance of 20 to >100 mL/min). In patients with end-stage renal disease undergoing hemodialysis, there is a 25% to 45% reduction in the clearance of Pegasys and doses of 135 μg provide exposure similar to those observed in patients with normal renal function receiving 180 μg doses.

3.1.3 Pegasys Drug-Drug Interactions

Administration of 180 μg of Pegasys once weekly for 4 weeks to healthy male subjects had no effect on the pharmacokinetic profiles of tolbutamide (cytochrome P450 2C9), mephenytoin (cytochrome P450 2C19), debrisoquine (cytochrome P450 2D6), and dapsone (cytochrome P450 3A4). PEG-IFN alfa-2a is a modest inhibitor of cytochrome

P450 1A2, as a 25% increase in the AUC of theophylline was seen in the same study. Comparable effects on theophylline's pharmacokinetics have been seen after treatment with standard alpha interferons. Alpha interferons have been shown to affect the oxidative metabolism of some drugs by reducing the activity of hepatic microsomal cytochrome P450 isoenzymes. It is recommended for patients taking theophylline and Pegasys concomitantly that theophylline serum concentrations be monitored and appropriate dose adjustments of theophylline be made.

Week 12 and week 48 results from a pharmacokinetic substudy of the phase III trial NV15801 in CHC patients showed that ribavirin did not affect the pharmacokinetic parameters of PEG-IFN alfa-2a and that PEG-IFN alfa-2a did not affect the pharmacokinetic parameters of ribavirin.

3.2 Ribavirin

3.2.1 Pharmacokinetics of Ribavirin

Orally administered ribavirin is absorbed rapidly, reaching maximal plasma concentrations within 1 to 2 hours. Absorption is extensive; about 10% to 15% of a radiolabeled dose is excreted in the feces. The absolute bioavailability, however, is between 45% and 65%, probably as the result of extensive first-pass metabolism. Ribavirin is absorbed from the gastrointestinal tract via an active sodium-dependent nucleoside transport process. Since this process is saturable, less than proportional increases in C_{max} were observed for doses above 800 mg. However, the exposure as measured by $AUC_{0\text{-}inf}$ was proportional up to a 2400-mg dose.

Ribavirin partitions into all cells rapidly and extensively, and a very large steady-state volume of distribution of about 850 L is seen after intravenous dosing. This distribution is facilitated by the sodium-independent *es* nucleoside transporter that is present in all types of cells, and thus ribavirin accumulates in erythrocytes, ova, and spermatozoa. Ribavirin sequesters in erythrocytes extensively, with a ratio of 60:1 between whole blood and plasma concentrations. Ribavirin does not bind to plasma proteins.

Both metabolism and renal excretion are major routes of elimination of ribavirin in humans and animals. Clearance after intravenous dosing was about 20 to 25 L/h, with about 30% accounted for by renal clearance. In humans, about 61% of the radioactivity of a 600-mg oral dose was eliminated in the urine within 336 hours, of which unchanged ribavirin accounted for 17%. Ribavirin is metabolized via two major pathways: (1) a reversible phosphorylation in nucleated cells that forms monophosphate, diphosphate, and triphosphate metabolites and (2) deribosylation and amide hydrolysis, forming the triazole carboxylic acid metabolite. The triazole carboxylic acid and triazole carboxamide are the principal metabolites. The cytochrome P450 enzyme system is not involved in the metabolism of ribavirin.

Because of extensive distribution, the terminal half-life of a single oral or intravenous dose is about 120 to 170 hours. This half-life may be longer in some patients after multiple dosing (ie, 180 to 300 hours). Extensive accumulation of ribavirin was seen

after multiple dosing (twice daily) such that the AUC at steady state was sixfold higher than that of a single dose.

Bioavailability of a single oral dose of ribavirin was increased by coadministration of a high-fat meal. The absorption was slowed (T_{max} was doubled), and the $AUC_{0\text{-}192h}$ and C_{max} increased by 42% and 66%, respectively, when the Copegus film-coated tablet was taken with a high-fat meal compared with fasting conditions. In the phase III combination studies NV15801 and NV15942, CHC patients were instructed to take their twice daily doses of ribavirin with food.

Single-dose ribavirin pharmacokinetics were altered (increased AUC_{last} and C_{max}) in patients with renal dysfunction compared with control subjects whose creatinine clearance was greater than 90 mL/min. The oral clearance of ribavirin is substantially reduced in CHC patients with renal dysfunction. Ribavirin has been used in dialysis patients with CHC at substantially reduced doses of 100 to 300 mg daily. The use of ribavirin in patients with severe renal impairment requires special facilities and expertise in order to ensure that ribavirin plasma concentrations and hemoglobin are closely monitored and appropriate dose adjustments are made. Ribavirin concentrations are essentially unchanged by dialysis, and thus ribavirin cannot be removed from the circulation by dialysis. Ribavirin should be used with caution in patients with severe renal impairment.

Specific pharmacokinetic evaluations for ribavirin in the elderly have not been performed. In a population pharmacokinetic study, age alone was not a key factor; however, the declining renal function in the elderly will result in higher exposure to ribavirin.

No clinically significant differences in the pharmacokinetics of ribavirin were observed between male and female subjects in a population pharmacokinetic analysis of 3600 sparsely collected serum concentration data from 138 patients.

3.2.2 Ribavirin Drug-Drug Interactions

Week 12 and week 48 results from a pharmacokinetic substudy of the phase III trial NV15801 in CHC patients showed that PEG-IFN alfa-2a did not affect the pharmacokinetic parameters of ribavirin and that ribavirin did not affect the pharmacokinetic parameters of PEG-IFN alfa-2a.

Results of in vitro studies using both human and rat liver microsomal preparations indicated no cytochrome P450-mediated metabolism of ribavirin. Ribavirin does not inhibit cytochrome P450 isoenzymes. No evidence was found from toxicity studies that ribavirin induces liver enzymes. Therefore, the potential for cytochrome P450-mediated interactions is minimal.

The bioavailability of a 600-mg oral dose of ribavirin was decreased by coadministration with an antacid containing magnesium, aluminum, and simethicone; AUC_{last} decreased 14%. It is possible that the decreased bioavailability in this study resulted from delayed

transit of ribavirin or from a modified pH. This interaction is not considered to be clinically relevant.

Ribavirin has been shown in vitro to interact with selected HIV reverse transcriptase inhibitors (zidovudine, stavudine, and didanosine). The clinical significance of these findings is not fully understood. However, concurrent use of ribavirin with these HIV reverse transcriptase inhibitors might result in drug-drug interactions that affect response to either HIV or HCV therapies or result in an increased risk of adverse events.

3.2.3 Bioavailability and Bioequivalence of Ribavirin

The Copegus tablet was demonstrated to be bioequivalent to the ribavirin capsule (Rebetol).

4. PIVOTAL PHASE III STUDIES

4.1 Pegasys and Copegus Combination Clinical Program

The Pegasys and Copegus combination clinical development program for the treatment of CHC consisted of two phase III international registration trials, NV15801 and NV15942, that were complementary in their objectives. The comparative trial vs Rebetron, study NV15801, was designed to show the superiority of Pegasys and Copegus combination therapy to Rebetron. Study NV15942 was designed to build on the results of NV15801 by using the Pegasys and Copegus combination therapy arm from study NV15801 as the control arm and assessing the benefits and risks of lower exposures in patient subgroups. Study NV15942 used a matrix design to assess the effects of either a shorter duration of treatment (ie, 24 weeks vs 48 weeks) or a lower daily dose of Copegus (ie, 800 mg fixed dose vs 1000 or 1200 mg by body weight category), or both, on safety and efficacy. The primary objective was to determine if baseline disease factors can be used to prospectively optimize therapy. Patients were stratified in this study according to HCV genotype and viral load to assess if patients who have previously been shown to be more responsive to treatment, ie, patients with genotype non-1 infection or low baseline viral load, can be treated successfully for a shorter period of time and with a lower ribavirin dose than patients who have previously been shown to be less likely to respond, ie, patients infected with genotype 1 or high baseline viral load.

The two studies were both randomized, multicenter trials in patients with previously untreated CHC, without or with accompanying cirrhosis or bridging fibrosis. Inclusion and exclusion criteria were the same for both studies and are provided in Appendix 3. Dose adjustment guidelines for patients who developed adverse events and laboratory abnormalities were also the same for both studies; a summary of these guidelines is provided in Appendix 4. The studies were conducted in a similar patient population and had a common treatment arm. The studies were conducted at sites in the United States, Canada (NV15942 only), Europe, South America, Australia, and Taiwan. A total of 2405 patients were treated in the two studies, and 1737 received Pegasys in combination with Copegus.

4.1.1 Overall Study Design

4.1.1.1 Comparative Trial vs Rebetron (Study NV15801)

Patients were stratified by genotype within each country and randomized to one of three treatment arms in a ratio of 2:2:1:

- 180 μg of Pegasys administered sc once weekly plus 1000 mg (patients weighing <75 kg) or 1200 mg (patients weighing ≥ 75 kg) of Copegus given orally daily in split doses
- 3 MIU of Intron A sc three times a week plus 1000 mg (patients weighing <75 kg) or 1200 mg (patients weighing ≥ 75 kg) of Rebetol given orally daily in split doses
- 180 μg of Pegasys sc once weekly plus placebo given orally daily in split doses

The study was blinded with respect to use of ribavirin, but Pegasys and Intron A were administered open-label. Patients were treated for 48 weeks and then followed for an additional 24 weeks. Patients who did not demonstrate a response at week 24 (response defined as either HCV RNA < 100 copies/mL or normal ALT) were discontinued from treatment as nonresponders. Patients prematurely withdrawn from treatment for nonresponse were followed for safety for at least 12 weeks following their last dose of study medication. Patients who were responding to treatment but who were prematurely withdrawn from treatment for other reasons were to be followed for efficacy to week 72, but between 5% and 9% of these patients were not followed beyond 12 weeks posttreatment.

4.1.1.2 Optimization of Therapy (Study NV15942)

Patients were stratified by genotype and viral load within each geographical region and randomized following a preplanned unbalanced stratification plan described in the next section to one of four treatment arms:

Group A: 180 μg of Pegasys administered sc once weekly plus 800 mg of Copegus given orally daily in split doses for 24 weeks

Group B: 180 μg of Pegasys administered sc once weekly plus 1000 mg (for patients weighing <75 kg) or 1200 mg (for patients weighing ≥ 75 kg) of Copegus given orally daily in split doses for 24 weeks

Group C: 180 μg of Pegasys administered sc once weekly plus 800 mg of Copegus given orally daily in split doses for 48 weeks

Group D: 180 μg of Pegasys administered sc once weekly plus 1000 mg (for patients weighing <75 kg) or 1200 mg (for patients weighing ≥ 75 kg) of Copegus given orally daily in split doses for 48 weeks

Studies NV15801 and NV15942 had a common treatment arm, which was the group receiving 48 weeks of treatment with 180 µg of Pegasys and 1000 or 1200 mg of Copegus. As in NV15801, patients who completed treatment were followed for an additional 24 weeks. Patients randomized to receive 48 weeks of treatment who did not respond to treatment by week 24 were discontinued from treatment as nonresponders. Patients who prematurely discontinued treatment were followed for safety for at least 12 weeks following their last dose of study medication. Patients who had received at least 12 weeks of treatment and were responding to treatment but were prematurely withdrawn for other reasons were followed for efficacy to the end of their scheduled treatment (24 or 48 weeks) and follow-up period (week 48 or week 72) in order to accurately assess patients' response status at the end of the scheduled follow-up period.

4.1.2 Selection of Dose of Pegasys and Copegus for Combination Trials

4.1.2.1 Pegasys Dose

The dose of Pegasys used in both phase III combination studies was 180 µg once weekly subcutaneously and was chosen for the combination studies based on the following data:

1. Results from the phase II dose-finding monotherapy study NV15489 in which doses of 45, 90, 180, and 270 µg of Pegasys were evaluated. In this study, the best balance of efficacy and safety was achieved with a dose of 180 µg. As shown in Table 1, the highest sustained virological response was seen in the group treated with 180 µg of Pegasys, particularly in patients with genotype 1 infection, the most common genotype in the US patient population. The 270-µg dose did not result in increased efficacy and was less well tolerated than the 180-µg dose, a larger percentage of patients in the 270-µg group having their dose modified for safety reasons.

Table 1 Sustained Virological Response in Phase II Monotherapy Dose-Finding Study NV15489, Intent-to-Treat Population

	Roferon A 3 MIU	Pegasys 45 µg	Pegasys 90 µg	Pegasys 180 µg	Pegasys 270 µg
Overall SVR	1/33 (3%)	2/20 (10%)	6/20 (30%)	16/45 (36%)	12/41 (29%)

Note: SVR = sustained virological response.

2. Efficacy and safety results from a prospectively planned administrative look of data obtained from the phase III monotherapy study NV15496 supported the use of 180 µg of Pegasys over 135 µg using HCV RNA titer at week 4 as a surrogate marker of efficacy.

The final results from the four Pegasys monotherapy studies support the 180 µg dose of Pegasys as the recommended dose for Pegasys as monotherapy as well as in combination with Copegus.

4.1.2.2 Copegus Dose

The dose of Copegus used in study NV15801, 1000 mg for patients weighing < 75 kg and 1200 mg for patients weighing ≥ 75 kg given orally daily in split doses, was the standard ribavirin dose approved in combination with Intron A for the treatment of CHC at the time study NV15801 was started and thus was the dose of Rebetol used in the Rebetron comparator arm. A pilot safety study (NV15800) investigating the safety and tolerability of the combination of 180 μg of Pegasys in combination with 1000 or 1200 mg of ribavirin was conducted, and safety data were reviewed by an external safety review board. Patients in study NV15801 were treated after a review of week 12 safety data from study NV15800 demonstrated no safety concerns with this combination.

In study NV15942, the higher dose of Copegus used, 1000 mg for patients weighing < 75 kg and 1200 mg for patients weighing ≥ 75 kg given orally daily in split doses, is the currently approved dose of ribavirin in the United States and Europe for combination therapy with Intron A. The lower dose of Copegus, 800 mg given orally daily in split doses, was chosen for study because it has been shown that a starting dose of 1000 or 1200 mg reduced to 600 mg daily to manage decreases in hemoglobin concentrations does not appear to affect the ability of patients who completed treatment at this dose to achieve a sustained virological response [12]. The 800 mg dose was chosen as the lower ribavirin dose because of concern that lower starting doses, ie, 600 mg, were likely to be too low to achieve reasonable clinical efficacy.

4.1.3 Sample Size, Stratification, and Power

In study NV15801, patients were stratified by genotype within each country. In study NV15942, patients were stratified by genotype and viral load within each geographical region.

4.1.3.1 Study NV15801

The planned sample size was 1125 patients who were randomized in a ratio of 2:2:1 to Pegasys and Copegus vs Intron A and Rebetol vs Pegasys and placebo. Randomization was by HCV genotype (type 1 and non-1) within each country.

A global test of no treatment differences and three pairwise comparisons were conducted under a "closed testing procedure" using the Cochran-Mantel-Haenszel test stratified by country and genotype. First, the global test was conducted at a significance level of 0.05. Next, since the global hypothesis of no treatment difference was rejected, each of the three pairwise treatment comparisons was conducted at a significance level of 0.05. Since the simulated significance level for each pairwise treatment comparison under the closed testing procedure is approximately 0.025, the two-sided 97.5% confidence interval for the odds ratios were reported in addition to hypotheses testing.

4.1.3.2 Study NV15942

The study was a factorial design investigating Pegasys and Copegus combination therapy with respect to two important factors in order to optimize treatment benefits and risks: treatment duration (24 and 48 weeks) and ribavirin dosing (800 mg and 1000 or 1200 mg daily). The primary objective was to compare the benefits and risks of treatment regimens administered for 24 weeks versus 48 weeks. The secondary objective was to compare ribavirin doses of 800 mg versus 1000 or 1200 mg.

Each comparison was first made with data from the overall population and then analyzed further as a function of genotype and baseline viral load. Formal statistical testing of clinical efficacy was planned in only the overall population; it was not practical or feasible to conduct a study of sufficient size to show a statistically significant difference between treatment regimens in patients grouped by genotype and viral load. A study designed to detect statistically significant differences among four treatment regimens in patients grouped by genotype and viral load would have required a much larger sample size than that in NV15942 (in order to accommodate the multiple pairwise comparisons by genotype and viral load) and would have taken several more years to conduct. However, because of the clinical importance of assessing these important variables (treatment duration and ribavirin dose) on response to treatment (in patients grouped by HCV genotype and baseline viral load), prospective plans were made to collect these data and summarize them descriptively.

Since formal tests for statistically significant differences between the different treatment regimens were to be carried out in only the overall population, the sample size calculation was based on assumptions for this population. A total of 1280 patients were planned to be enrolled. Randomization to the four treatment groups was stratified by genotype (1 vs non-1) and baseline viral load (low versus high defined as $\leq$ and $>$ 2 million copies/mL, respectively) within each geographical region.

The original randomization scheme was amended, in consultation with FDA, after 3 months of recruitment, when it became apparent that the planned number of patients infected with genotype non-1 and low viral load could not be recruited within a reasonable time frame. In the amended scheme, the total sample size was to remain the same at 1280 patients. The objective of the amended protocol was to reallocate patients across the four strata so that (1) minimally 35 to 40 patients would be randomized to each treatment group within each stratum and (2) the relative sizes of the four strata would mimic their relative sizes in the general patient population. (See Appendix 5 for the final randomization scheme.) Consequently, more patients than were originally planned were to be randomized to the genotype 1 high viral load stratum, which was the fastest recruiting stratum. The randomization ratio was changed to 1:1:5:5 (groups A:B:C:D) among patients with genotype 1 and high baseline viral load and to 1:1:1:1 (groups A:B:C:D) among all other patients.

More patients with genotype 1 and high baseline viral load were allocated to 48 weeks of treatment than to 24 weeks of treatment because of growing concerns that shorter

treatment would not be sufficient in this group of patients. The intent of the amended protocol was to achieve a balance between allocating the maximum number of patients with genotype 1 infection to the potentially more efficacious 48 weeks of treatment while still allocating a sufficient number of patients with genotype 1 infection to 24 weeks of treatment to test the hypothesis that longer duration of therapy for patients infected with genotype 1 result in higher sustained virological responses. Provision was made to provide an additional course of treatment to patients treated for 24 weeks who relapsed by offering them the opportunity to enroll in a separate re-treatment protocol after they completed study NV15942.

4.1.4 Assessment of Efficacy

Sustained virological response assessed 6 months after the end of treatment is used as the efficacy end point for both NV15801 and NV15942 in the proposed label and in this briefing document. This efficacy end point is being used in agreement with FDA and in accordance with current clinical practice and regulatory criteria for assessing patient response to CHC therapy as well as for consistency in assessing response in the two phase III Pegasys and Copegus combination trials.

The original protocol-defined primary efficacy end point in study NV15801, based on the recommendation of FDA, was a combined end point of both sustained virological response and sustained biochemical response at the conclusion of the 6-month untreated follow-up period (week 72). Sustained virological response was a secondary end point in study NV15801. At the time study NV15801 was designed, the use of sustained virological response as a single efficacy end point was not universally accepted, since an approved validated test for measuring serum HCV RNA was not yet available. In addition, serum ALT activity was still considered by some as the appropriate primary measure of response to treatment with interferon.

During the conduct of the combination studies a validated test for detecting serum HCV RNA was approved. As a result, the protocol-defined primary efficacy end point in study NV15942 was changed by protocol amendment during the study to a sustained virological response at the end of the untreated follow-up period.

The population presented in this document is all treated patients, which is consistent with current regulatory criteria. In both studies NV15801 and NV15942, no major differences in safety or efficacy are seen when treatment effects are compared between all randomized patients and all treated patients. The number of patients in each of these populations is similar, and any differences between the two populations appear to be random. No imbalance is apparent across the treatment arms.

A patient was considered to have responded to therapy (achieved a sustained virological response) if no virus was detected 6 months after the end of treatment. For the primary analyses specified in the two protocols, sustained virological response was based on two measurements of HCV RNA and was defined as two undetectable HCV RNA measurements ≥ 21 days apart measured on or after week 36 (for patients assigned to 24

weeks of treatment) or on or after week 60 (for patients assigned to 48 weeks of treatment). These windows were based on the scheduled assessments after the end of treatment for HCV RNA, which were at weeks 36 and 48 for patients treated for 24 weeks and at weeks 60 and 72 for patients treated for 48 weeks. Patients with only a single undetectable value were considered nonresponders in this analysis. The COBAS Amplicor HCV Test, version 2.0, which has a lower limit of detection of 100 copies/mL, was used to detect the presence of HCV RNA.

For exploratory secondary analyses, sustained virological response was based on one measurement of HCV RNA 6 months after the end of treatment and was defined as a single undetectable HCV RNA measurement on or after week 68 for patients treated for 48 weeks or on or after week 44 for patients treated for 24 weeks. One HCV RNA measurement to detect virus 6 months after the end of treatment is used in other published trials in the literature to assess response to anti-HCV therapies. This way of assessing sustained virological response is also more likely to reflect current clinical practice.

4.2 Efficacy Results

4.2.1 Principal Efficacy Findings

- Sustained virological response in patients treated for 48 weeks with Pegasys and Copegus combination therapy (52%) in study NV15801 was significantly higher ($p = 0.005$) than in patients treated for 48 weeks with Rebetron (43%).

- Statistically significant improvement over Rebetron was seen in patients infected with genotype 1 (43% vs 35%, $p = 0.046$) as well as in patients infected with genotype non-1 (predominantly genotypes 2 and 3) (68% vs 57%, $p = 0.044$).

- Improvement over Rebetron was seen in patients with genotype 1 infection regardless of viral load (high or low) and in patients with genotype non-1 infection regardless of viral load.

- In study NV15942, patients infected with genotype 1, irrespective of baseline viral load, achieved the highest sustained virological response when treated for 48 weeks with Pegasys and 1000 or 1200 mg of Copegus (50%).

- In patients infected with genotype non-1 (predominantly genotype 2 or 3) in study NV15942, irrespective of baseline viral load, similar sustained virological responses were achieved after treatment for 24 weeks with Pegasys and 800 mg of ribavirin (78%) and after treatment for 48 weeks with Pegasys and 1000 or 1200 mg of Copegus (75%).

- Pegasys and Copegus combination therapy provided substantial efficacy in the subgroup of patients with compensated cirrhosis or bridging fibrosis. Cirrhotic patients treated for 48 weeks with Pegasys and 1000 or 1200 mg of Copegus achieved sustained virological responses of 41% vs 52% for the overall population in study

NV15801 and 52% vs 59% for the overall population in study NV15942. Sustained virological responses in patients with cirrhosis treated with Pegasys and Copegus in study NV15801 were numerically higher than those in cirrhotic patients treated with Rebetron (41% vs 33%). In study NV15942, the effects of genotype and ribavirin dose in cirrhotic patients were consistent with the findings in the overall population.

- An analysis based on quantitative HCV RNA testing to assess whether it is possible to identify by week 12 of treatment those patients with little chance of achieving a sustained virological response after the full course of therapy was performed. This analysis used the 889 patients from studies NV15801 and NV15942 treated for 48 weeks with Pegasys and 1000 or 1200 mg of Copegus. Of the 113 patients who failed to achieve an early virological response (ie, undetectable HCV RNA or a 2-$\log_{10}$ decrease from baseline HCV RNA) by week 12 of treatment, 108 failed to achieve a sustained virological response, resulting in a negative predictive value (probability of nonresponse) of 96%. The negative predictive value of not achieving an early virological response by week 12 for sustained virological response in the 569 patients with genotype 1 infection was also 96%.

4.2.2 Study NV15801

4.2.2.1 Study Population

The three treatment groups were well-balanced with respect to demographic and baseline disease characteristics (Appendix 6). The majority of the patients were Caucasian men, and the median age was between 42 and 43 years. Between 12% and 15% of the patients had cirrhosis. Approximately two thirds of the patients were infected with genotype 1.

A total of 28 of the 1149 patients randomized to treatment did not receive study drug. The percentage of patients randomized but not treated in the Pegasys and Copegus combination therapy group (3%) was the same as in the Rebetron group (3%) (Appendix 7).

A similar percentage of patients in the three treatment groups completed 12 weeks of treatment (93% to 96%) and 24 weeks of treatment (87% to 89%) (Appendix 7). A higher percentage of patients in the Pegasys and Copegus combination group (76%) completed 48 weeks of treatment than in the Rebetron (67%) and Pegasys monotherapy groups (67%) (Appendix 7). This difference in the proportion of patients completing the full 48 weeks of treatment is related to the study design, which required patients who were not responding to treatment by week 24 to be withdrawn, since they were highly unlikely to respond to further treatment. The most frequent reason for discontinuation of treatment was an insufficient therapeutic response, and the percentage of patients who discontinued treatment for this reason was lowest in the Pegasys and Copegus combination group (Appendix 8). Other reasons for discontinuation of treatment occurred with a similar frequency in the three groups (Appendix 8).

4.2.2.2 Sustained Virological Response

Sustained virological response in patients treated with Pegasys and Copegus combination therapy was significantly higher than in patients treated with Rebetron (p = 0.005). Superiority over Rebetron was seen in patients infected with genotype 1 as well as in patients infected with genotype non-1 (predominantly genotypes 2 and 3) (Table 2). As per the statistical analysis plan in the protocol, the global test of treatment differences was shown to be significant for the overall population (p = 0.001) as well as for patients infected with genotype 1 (p = 0.001) or genotype non-1 (p = 0.004), thus allowing the pairwise comparisons.

Table 2 Sustained Virological Response in Study NV15801, All Treated Patients

	Pegasys + Placebo 48 Weeks		Pegasys + Copegus 1000 or 1200 mg 48 Weeks		Intron A + Rebetol 1000 or 1200 mg 48 Weeks	
	N	SVR	N	SVR	N	SVR
All Patients	224	62 (28%)	453	234 (52%)	444	190 (43%)
Treatment Difference[a]				8.9%		
Odds ratio[b]				1.493 (1.083, 2.057)		
P value[c]				0.005		
Genotype 1 Patients	145	27 (19%)	298	129 (43%)	285	100 (35%)
Treatment Difference[a]				8.2%		
Odds ratio[b]				1.420 (0.957, 2.108)		
P value				0.046		
Genotype Non-1 Patients	79	35 (44%)	155	105 (68%)	159	90 (57%)
Treatment Difference[a]				11.1%		
Odds ratio[b]				1.640 (0.945, 2.846)		
P value				0.044		

Note: SVR = sustained virological response. SVR is determined based on two HCV RNA measurements <100 copies/mL measured ≥21 days apart using a lower time window of week 60.

[a] Difference in SVR between Pegasys + Copegus group and Intron A + Rebetol group.

[b] The ratio of the odds of a response in the Pegasys + Copegus group to the odds of a response in the Intron A + Rebetol group. 97.5% confidence intervals are included in parentheses.

[c] Assessed by Cochran-Mantel-Haenszel test stratified by country and HCV genotype.

Improvement over Rebetron was seen in patients with genotype 1 infection irrespective of viral load (Table 3). Genotype 1 patients with a high viral load appear to have disease that is the least responsive to treatment and represent more than half the CHC population in the United States. Improvement over Rebetron was also seen in genotype non-1 patients who had either a high viral load or a low viral load (Table 3).

As was seen in patients infected with genotypes 2 and 3, sustained virological response in the small number of patients in this study infected with genotype 4 was higher in patients treated with Pegasys and Copegus combination therapy (77%, 10 of 13 patients) than in patients treated with Rebetron (27%, 3 of 11 patients) (Appendix 9).

Table 3 Sustained Virological Response as a Function of Genotype and Baseline Viral Load in Study NV15801, All Treated Patients

	Pegasys (N = 224)		Pegasys + Copegus 1000 or 1200 mg (N = 453)		Intron A + Rebetol 1000 or 1200 mg (N = 444)	
	N	SVR	N	SVR	N	SVR
Genotype 1 Patients	145	27 (19%)	298[a]	129 (43%)	285[a]	100 (35%)
Low viral load	44	15 (34%)	115	58 (50%)	94	39 (41%)
High viral load	101	12 (12%)	182	71 (39%)	189	61 (32%)
Genotype Non-1 Patients	79	35 (44%)	155	105 (68%)	159	90 (57%)
Low viral load	25	15 (60%)	44	31 (70%)	56	36 (64%)
High viral load	54	20 (37%)	111	74 (67%)	103	54 (52%)

Note: High viral load = >2 x 10^6 copies/mL, low viral load = ≤2 x 10^6 copies/mL, SVR = sustained virological response. SVR is determined based on two HCV RNA measurements <100 copies/mL measured ≥21 days apart using a lower time window of week 60.

[a] The viral load was not available for two patients in the Intron A + Rebetol group and for one patient in the Pegasys + Copegus group.

Pegasys Monotherapy vs Combination Therapy:

Pegasys and Copegus combination therapy was superior to Pegasys monotherapy in the overall population (52% vs 28%, p = 0.001), in patients infected with genotype 1 (43% vs 19%, P = 0.001), and in patients infected with genotype non-1 (68% vs 44%, p = 0.002). Rebetron was also superior to Pegasys monotherapy in the overall population (43% vs 28%, p = 0.001) and in patients infected with genotype 1 (35% vs 19%, p = 0.001). In patients infected with genotype non-1, sustained virological response was numerically higher with Rebetron than with Pegasys monotherapy but the difference was not statistically significant (57% vs 44%, p= 0.125).

4.2.2.3 Sustained Biochemical Response

As was seen with sustained virological response, sustained biochemical response in patients treated with Pegasys and Copegus combination therapy was significantly higher than in patients treated with Rebetron (p = 0.025) (Table 4).

Table 4 Sustained Biochemical Response in Study NV15801, All Treated Patients

	Pegasys + Placebo 48 Weeks		Pegasys + Copegus 1000 or 1200 mg 48 Weeks		Intron A + Rebetol 1000 or 1200 mg 48 Weeks	
	N	SBR	N	SBR	N	SBR
Sustained Biochemical Response	224	72 (32%)	453	233 (51%)	444	197 (44%)
Treatment Difference[a]				7.0%		
Odds ratio[b]				1.37 (1.00, 1.87)		
P value[c]				0.025		

Note: SBR = sustained biochemical response. SBR is defined as two consecutive normal ALT levels measured ≥21 days apart using a lower time window of week 60.

[a] Difference in sustained biochemical response between Pegasys + Copegus & Intron A + Rebetol groups.

[b] The ratio of the odds of a response in the Pegasys + Copegus group to the odds of a response in the Intron A + Rebetol group. 97.5% confidence intervals are included in parentheses.

[c] Assessed by Cochran-Mantel-Haenszel test stratified by country and HCV genotype.

4.2.2.4 Combined Sustained Virological and Biochemical Response

Combined sustained virological and biochemical response in all randomized patients, the primary end point in this study, was highest in the group receiving the combination of Pegasys and Copegus and showed borderline statistical superiority to Rebetron (45% vs 39%, p = 0.057). Individually, sustained virological response (50% vs 42%, p = 0.004) and sustained biochemical response (50% vs 43%, p = 0.022) were each statistically significantly higher in patients receiving the combination of Pegasys and Copegus than in patients receiving Rebetron.

As specified in the protocol, the assessment of the combined sustained virological and biochemical response is based on four measurements, two measurements of HCV RNA and two measurements of ALT activity. In most of the patients with a sustained virological response who were not considered to be sustained biochemical responders, one or both ALT measurements were slightly above the upper limit of normal, although considerably lower than baseline pretreatment ALT values. With the recent availability of well-characterized assays for measuring virological response and because of the low sensitivity and specificity of serum ALT activity, elimination of the virus is now considered a more reliable measure of response to therapy.

4.2.2.5 Histological Response

By protocol design, approximately 20% of patients were to have a liver biopsy at the end of the 24-week untreated follow-up period in order to assess histological response in this study. In this subgroup of 198 patients, which was about 17% of the patients in this study, between 72% and 80% of patients had a histological response (defined as 2-point decrease or greater in total HAI score) (Table 5).

Since the protocol stipulated that patients not responding to treatment by week 24 be withdrawn from treatment, the majority of patients with paired biopsies were virological responders at week 24. Four of the five patients whose total HAI score worsened did not achieve a sustained virological response.

Table 5 Histological Response in Study NV15801, Patients with Paired Liver Biopsies

	Pegasys	Pegasys + Copegus 1000 or 1200 mg	Intron A + Rebetol 1000 or 1200 mg
No. of patients with paired biopsies	39	80	79
No. of histological responders[a]	28 (72%)	64 (80%)	60 (76%)
No. of histological nonresponders	11 (28%)	16 (20%)	19 (24%)
No change[b]	10	16	15
Worsening[c]	1	0	4

[a]Histological response = decrease of at least 2 points in total HAI score.
[b]Change in total HAI score of +1, 0, or -1.
[c]Increase in total HAI score of ≥2 points.

4.2.3 Study NV15942

4.2.3.1 Study Population

The four treatment groups were well balanced with respect to demographic and baseline characteristics (Appendix 11). Two thirds of the patients were men, and most were Caucasian. The median age was between 41 and 42 years. The proportion of patients with cirrhosis or bridging fibrosis ranged between 21% and 26%. Because of the randomization scheme of the study, which planned to allocate more patients with genotype 1 infection and high viral load to the 48 week treatment groups than to the 24 week treatment groups, pretreatment viral load and the proportion of patients with genotype 1 infection were higher in the 48 week treatment groups than in the 24 week treatment groups.

A total of 27 of the 1311 patients (2%) randomized to treatment did not receive study drug. The percentage of patients randomized but not treated in the four Pegasys and Copegus combination therapy groups ranged from 1% to 3% (Appendix 12).

A similar percentage of patients in the four treatment groups completed 12 weeks of treatment (93% to 97%) and 24 weeks of treatment (89% to 90%) (Appendix 12). The percentage of patients in the groups assigned to 24 weeks of treatment who completed their assigned duration of treatment (24 weeks) was higher (90%) than the percentage of patients assigned to 48 weeks of treatment who completed their assigned duration of treatment (48 weeks, 67% to 72%) (Appendix 12). This difference in the proportion of patients completing the 24-week treatment regimen vs the 48-week treatment regimen is partially related to the study design, which required patients assigned to 48 weeks of treatment who were not responding to treatment by week 24 to be withdrawn, since they were highly unlikely to respond to further treatment. The most common reasons for discontinuation of treatment in the two groups assigned to 48 weeks of treatment were clinical adverse events, insufficient therapeutic response, and refusal of treatment (Appendix 13).

4.2.3.2 Sustained Virological Response

The results of the formal statistical testing in study NV15942 showed that:

- Patients treated for 48 weeks were more likely to achieve a sustained virological response than patients treated for 24 weeks. The difference between the two groups was statistically significant ($p = 0.039$) (Appendix 14).
- The likelihood of achieving a sustained virological response was greater among patients receiving 1000 or 1200 mg of Copegus than among patients receiving 800 mg of Copegus, a difference that was also statistically significant ($p = 0.018$) (Appendix 14).

In addition, the study was prospectively designed to examine the effect of treatment duration and Copegus dose on sustained virological response in patients stratified by genotype and viral load (descriptive analyses).

Patients Infected with Genotype 1:

The highest sustained virological response in patients infected with genotype 1 was achieved with the most intensive regimen, 48 weeks of treatment and 1000 or 1200 mg of Copegus (50%) (Table 6). This was the case whether patients had a high pretreatment viral load or a low pretreatment viral load (46% and 60%, respectively). A reduction in either the Copegus dose or duration of treatment was associated with a substantial loss of efficacy in both patient subgroups. The statistically significant results for treatment duration and Copegus dose described above for the pooled overall population can be attributed in large part to the results obtained in patients infected with genotype 1, the group making up the majority of patients in this study (58%).

Patients Infected with Genotype Non-1:

In patients infected with genotype non-1, similar sustained virological responses were achieved after treatment for 24 weeks with 800 mg of Copegus and after treatment for a longer duration or with a higher dose of Copegus (Table 6). This was the case whether patients had a high pretreatment viral load or a low pretreatment viral load.

Table 6 Sustained Virological Response as a Function of Genotype and Baseline Viral Load in Study NV15942, All Treated Patients

	24 Weeks Treatment				48 Weeks Treatment			
	Pegasys + Copegus 800 mg (N = 207)		Pegasys + Copegus 1000 or 1200 mg (N = 280)		Pegasys + Copegus 800 mg (N = 361)		Pegasys + Copegus 1000 or 1200 mg (N = 436)	
	N	SVR	N	SVR	N	SVR	N	SVR
Genotype 1	101	29 (29%)	118	48 (41%)	250	97 (39%)	271	136 (50%)
Low viral load	51	21 (41%)	71	36 (51%)	60	31 (52%)	85	51 (60%)
High viral load	50	8 (16%)	47	12 (26%)	190	66 (35%)	186	85 (46%)
Genotype non-1	106	83 (78%)	162	129 (80%)	111	83 (75%)	165	123 (75%)
Low viral load	39	28 (72%)	61	48 (79%)	41	33 (80%)	57	45 (79%)
High viral load	67	55 (82%)	101	81 (80%)	70	50 (71%)	108	78 (72%)

Note: High viral load = $>2 \times 10^6$ copies/mL, low viral load = $\leq 2 \times 10^6$ copies/mL, SVR = sustained virological response. SVR is determined based on two HCV RNA measurements <100 copies/mL measured ≥ 21 days apart using a lower time window of week 60.

The genotype non-1 patients in this study were predominantly infected with genotype 2 or 3 (90% of patients), which to a large extent account for the results observed in genotype non-1 patients in this study (Table 7). In the small number of patients infected with genotype 4 in this study (36 patients), sustained virological response was highest after 48 weeks of treatment with 1000 or 1200 mg of Copegus, suggesting that these patients respond similarly to patients infected with genotype 1.

Table 7 **Sustained Virological Response in Genotype Non-1 Patients by Genotype and Baseline Viral Load in Study NV15942, All Treated Patients**

	24 Weeks Treatment				48 Weeks Treatment			
	Pegasys + Copegus 800 mg (N = 207)		Pegasys + Copegus 1000 or 1200 mg (N = 280)		Pegasys + Copegus 800 mg (N = 361)		Pegasys + Copegus 1000 or 1200 mg (N = 436)	
	N	SVR	N	SVR	N	SVR	N	SVR
Genotype non-1	106	83 (78%)	162	129 (80%)	111	83 (75%)	165	123 (75%)
Low viral load	39	28 (72%)	61	48 (79%)	41	33 (80%)	57	45 (79%)
High viral load	67	55 (82%)	101	81 (80%)	70	50 (71%)	108	78 (72%)
Genotypes 2 & 3	96	79 (82%)	144	117 (81%)	99	77 (78%)	153	113 (74%)
Low viral load	34	27 (79%)	47	39 (83%)	33	28 (85%)	48	37 (77%)
High viral load	62	52 (84%)	97	78 (80%)	66	49 (74%)	105	76 (72%)
Genotype 4	5	0 (0%)	12	8 (67%)	8	5 (63%)	11	9 (82%)
Low viral load	4	0 (0%)	11	8 (73%)	7	5 (71%)	9	8 (89%)
High viral load	1	0 (0%)	1	0 (0%)	1	0 (0%)	2	1 (50%)
Genotype 5	2	1 (50%)	4	2 (50%)	0		1	1 (100%)
Low viral load	0		2	0 (0%)	0		0	
High viral load	2	1 (50%)	2	2 (100%)	0		1	1 (100%)
Genotype 6	3	3 (100%)	2	2 (100%)	4	1 (25%)	0	
Low viral load	1	1 (100%)	1	1 (100%)	1	0 (0%)	0	
High viral load	2	2 (100%)	1	1 (100%)	3	1 (33%)	0	

Note: High viral load = >2 x 10^6 copies/mL, low viral load = ≤2 x 10^6 copies/mL, SVR = sustained virological response. SVR is determined based on two HCV RNA measurements <100 copies/mL measured ≥21 days apart using a lower time window of week 60.

4.2.3.3 Sustained Biochemical Response

As with sustained virological response, sustained biochemical response in patients with genotype 1 infection was higher after 48 weeks of treatment than after 24 weeks of treatment, irrespective of baseline viral load (Table 8). Also, sustained biochemical response was higher in patients with genotype 1 receiving 1000 or 1200 mg of Copegus than in patients receiving 800 mg of Copegus.

In patients with genotype non-1 infection, irrespective of high or a low baseline viral load, sustained biochemical response was similar in patients treated for either 24 or 48

weeks and in patients treated with either 1000 or 1200 mg of Copegus or 800 mg of Copegus. These results are also in agreement with those for sustained virological response in patients infected with genotype non-1, which showed that treatment for 24 weeks with 800 mg of Copegus was as efficacious as treatment for 48 weeks with 1000 or 1200 mg of Copegus.

Table 8 Sustained Biochemical Response as a Function of Genotype and Baseline Viral Load in Study NV15942, All Treated Patients

	24 Weeks Treatment				48 Weeks Treatment			
	Pegasys + Copegus 800 mg (N = 207)		Pegasys + Copegus 1000 or 1200 mg (N = 280)		Pegasys + Copegus 800 mg (N = 361)		Pegasys + Copegus 1000 or 1200 mg (N = 436)	
	N	SBR	N	SBR	N	SBR	N	SBR
Genotype 1	101	32 (32%)	118	52 (44%)	250	96 (38%)	271	138 (51%)
Low viral load	51	20 (39%)	71	37 (52%)	60	27 (45%)	85	50 (59%)
High viral load	50	12 (24%)	47	15 (32%)	190	69 (36%)	186	88 (47%)
Genotype non-1	106	72 (68%)	162	119 (73%)	111	75 (68%)	165	119 (72%)
Low viral load	39	22 (56%)	61	42 (69%)	41	26 (63%)	57	39 (68%)
High viral load	67	50 (75%)	101	77 (76%)	70	49 (70%)	108	80 (74%)

Note: High viral load = $>2 \times 10^6$ copies/mL, low viral load = $\leq 2 \times 10^6$ copies/mL, SBR = sustained biochemical response. SBR is defined as two consecutive normal ALT levels measured ≥ 21 days apart using a lower time window of week 60.

4.2.3.4 Histological Response

By protocol design, approximately 20% of patients were to have a liver biopsy at the end of the 24-week untreated follow-up period in order to assess histological response in this study. In this subgroup of 260patients, which was about 20% of the patients in this study, between 72% and 78% of patients had a histological response (defined as 2-point decrease or greater in total HAI score) (Table 9).

Since the protocol stipulated that patients not responding to treatment by week 24 be withdrawn from treatment, the majority of patients with paired biopsies were virological responders at week 24. None of the nine patients whose total HAI score worsened achieved a sustained virological response.

Table 9 Histological Response in Study NV15942, Patients with Paired Liver Biopsies

	24 Weeks Treatment		48 Weeks Treatment	
	Pegasys + Copegus 800 mg	Pegasys + Copegus 1000 or 1200 mg	Pegasys + Copegus 800 mg	Pegasys + Copegus 1000 or 1200 mg
No. of patients with paired biopsies	48	51	68	93
No. histological responders[a]	35 (73%)	40 (78%)	52 (76%)	67 (72%)
No. histological nonresponders	13 (27%)	11 (22%)	16 (24%)	26 (28%
No change[b]	7	10	15	25
Worsening[c]	6	1	1	1

[a]Histological response = decrease of at least 2 points in total HAI score.
[b]Change in total HAI score of +1, 0, or -1.
[c]Increase in total HAI score of ≥ 2 points.

4.2.4 Predictability of Sustained Virological Response

The product information for some currently available interferon-based therapies for HCV infection suggests that all patients should be treated for a minimum of 24 weeks before considering the discontinuation of therapy because the patient is unlikely to achieve a sustained virological response with further treatment. The availability of quantitative HCV RNA testing may allow such decisions to be made earlier in the course of treatment by determining how much a patient's pretreatment HCV RNA titer has decreased during therapy rather than using interim undetectability as a measure of response to therapy. An assessment with a high negative predictive value at a time point earlier than 24 weeks of therapy could be used clinically to identify patients with little chance of responding to continued therapy, thereby sparing these patients unnecessary treatment.

An analysis of the predictability of sustained virological response based on response by week 12 in patients treated for 48 weeks with Pegasys and 1000 or 1200 mg of Copegus combination therapy is presented in Table 10. The data from the common arm of studies NV15801 and NV15942 have been pooled for this exploratory analysis. In this analysis, patients who have either undetectable HCV RNA, unquantifiable HCV RNA, or at least a 2-$\log_{10}$ drop from their baseline HCV RNA titer at any time during the initial 12 weeks of treatment were considered to have demonstrated an early virological response by week 12. The negative predictive value of not achieving an early virological response by week 12 for a sustained virological response is calculated by dividing the number of patients who had neither a response by week 12 nor a sustained virological response by the number of patients who did not have a response by week 12.

In the overall population, 87% of patients being treated for 48 weeks with Pegasys and 1000 or 1200 mg of Copegus combination therapy had an early virological response by week 12. Of the 113 patients in the overall population who failed to achieve a virological

response by week 12 of treatment, 108 failed to achieve a sustained virological response, resulting in a negative predictive value of 96% in the overall population.

The percentage of patients with genotype 1 infection being treated for 48 weeks with Pegasys and 1000 or 1200 mg of Copegus combination therapy who had an early virological response was similar to that of the overall population (82%). The negative predictive value of not achieving an early virological response by week 12 for sustained virological response in patients with genotype 1 infection was 96%.

In contrast to patients with genotype 1 infection, almost all patients with genotype non-1 infection being treated with Pegasys and Copegus combination therapy (97%) had an early virological response by week 12; only a small number of patients (11 patients) did not achieve an early virological response. Of the 11 patients with genotype non-1 infection who failed to achieve a virological response by week 12 of treatment, 10 also failed to achieve a sustained virological response.

Table 10 Negative Predictive Value of a Virological Response by Week 12 for Sustained Virological Response, All Treated Patients

	Overall Population (N = 889)		Genotype 1 Patients (N = 569)		Genotype Non-1 Patients (N = 320)	
	SVR	No SVR	SVR	No SVR	SVR	No SVR
HCV RNA unquantifiable or $\geq 2\log_{10}$ drop by week12						
Yes	488	288	261	206	227	82
No	5	108	4	98	1	10
Week 12 response	87%		82%		97%	
Negative predictive value	108/(5 + 108) = 96%		98/(4 + 98) = 96%		10/(1 + 10) = 91%	

Note: The analysis population is patients treated for 48 weeks with Pegasys and 1000 or 1200 mg of Copegus from the common arm of studies NV15801 and NV15942. SVR = sustained virological response. SVR is determined based on two HCV RNA measurements <100 copies/mL measured ≥21 days apart using a lower time window of week 60.

4.2.5 Efficacy in Patients with Cirrhosis

Sustained virological response in the subset of patients with compensated cirrhosis in study NV15801 who were treated with Pegasys and Copegus combination therapy was numerically higher than that in patients with compensated cirrhosis who were treated with Rebetron (41% vs 33%, Table 11). The same trends were seen in cirrhotic patients with genotype 1 infections and in cirrhotic patients with genotype non-1 infection (predominantly genotypes 2 and 3) (Table 11 and Appendix 16). The patterns of response in cirrhotic patients were similar to those in the overall population.

Table 11 Sustained Virological Response in Patients with Cirrhosis in Study NV15801, All Treated Patients

	Pegasys (N = 34)		Pegasys + Copegus 1000 or 1200 mg (N = 56)		Intron A + Rebetol 1000 or 1200 mg (N = 54)	
Patients with Cirrhosis	N	SVR	N	SVR	N	SVR
All patients	34	6 (18%)	56	23 (41%)	54	18 (33%)
Genotype 1 patients	24	3 (13%)	38	11 (29%)	32	8 (25%)
Genotype non-1 patients	10	3 (30%)	18	12 (67%)	22	10 (45%)

Note: SVR = sustained virological response. SVR is determined based on two HCV RNA measurements <100 copies/mL measured ≥21 days apart using a lower time window of week 60.

Sustained virological responses in the subgroup of patients with cirrhosis in this study were numerically lower than those in the overall population (Table 12). Patients with cirrhosis have more difficult-to-treat disease, and cirrhosis has been found to be a significant independent prognostic factor affecting the probability of achieving a sustained virological response in patients with genotype 1 and in patients with genotype non-1 infection treated with the combination of Pegasys and Copegus.

Table 12 Sustained Virological Response with Combination Therapy in Cirrhotic Patients vs Overall Population in Study NV15801, All Treated Patients

	Cirrhotic Patients				Overall Population			
	Pegasys + Copegus 1000 or 1200 mg (N = 56)		Intron A + Rebetol 1000 or 1200 mg (N = 54)		Pegasys + Copegus 1000 or 1200 mg (N = 453)		Intron A + Rebetol 1000 or 1200 mg (N = 444)	
	N	SVR	N	SVR	N	SVR	N	SVR
All patients	56	23 (41%)	54	18 (33%)	453	234 (52%)	444	190 (43%)
Genotype 1 patients	38	11 (29%)	32	8 (25%)	298	129 (43%)	285	100 (35%)
Genotype non-1 patients	18	12 (67%)	22	10 (45%)	155	105 (68%)	159	90 (57%)

Note: SVR = sustained virological response. SVR is determined based on two HCV RNA measurements <100 copies/mL measured ≥21 days apart using a lower time window of week 60.

In study NV15942, the relationship among treatment duration, dose of ribavirin, and genotype in patients with cirrhosis was the same as that seen in the overall noncirrhotic and cirrhotic population. In patients with cirrhosis who were infected with genotype 1 and had either a low or high viral load, sustained virological response was highest in patients treated for 48 weeks with Pegasys and 1000 or 1200 mg of Copegus (Table 13).

A shorter treatment duration (24 weeks) or a lower Copegus dose (800 mg) resulted in lower sustained virological responses in patients infected with genotype 1.

These data also suggest that 24 weeks of treatment with Pegasys and 800 mg of Copegus is sufficient for patients with compensated cirrhosis infected with HCV genotype non-1. Examination of responses among the different non-1 genotypes suggests that cirrhotic patients infected with genotypes 2 and 3, which account for most of the genotype non-1 population in this study, do not receive any additional benefit from treatment with more than an 800-mg daily dose of Copegus or from treatment for more than 24 weeks (Appendix 17).

Table 13 Sustained Virological Response in Cirrhotic Patients as a Function of Genotype and Baseline Viral Load in Study NV15942, All Treated Patients

	24 Weeks Treatment				48 Weeks Treatment			
	Pegasys + Copegus 800 mg (N = 44)		Pegasys + Copegus 1000 or 1200 mg (N = 71)		Pegasys + Copegus 800 mg (N = 91)		Pegasys + Copegus 1000 or 1200 mg (N = 115)	
	N	SVR	N	SVR	N	SVR	N	SVR
Genotype 1	23	6 (26%)	27	7 (26%)	67	19 (28%)	78	32 (41%)
Low viral load	9	3 (33%)	12	6 (50%)	9	3 (33%)	21	12 (57%)
High viral load	14	3 (21%)	15	1 (7%)	58	16 (28%)	57	20 (35%)
Genotype non-1	21	14 (67%)	44	33 (75%)	24	15 (63%)	37	28 (76%)
Low viral load	4	2 (50%)	13	11 (85%)	10	8 (80%)	10	8 (80%)
High viral load	17	12 (71%)	31	22 (71%)	14	7 (50%)	27	20 (74%)

Note: High viral load = $>2 \times 10^6$ copies/mL, low viral load = $\leq 2 \times 10^6$ copies/mL, SVR = sustained virological response. SVR is determined based on two HCV RNA measurements <100 copies/mL measured ≥ 21 days apart using a lower time window of week 60.

Similar to study NV15801, sustained virological response in patients with cirrhosis who were treated for 48 weeks with Pegasys and 1000 or 1200 mg of Copegus was lower than that in the overall population of noncirrhotic and cirrhotic patients (52% vs 59%) (Table 14). Sustained virological responses in cirrhotic patients in this study infected with genotype non-1 were very similar to those in the overall population. In contrast, sustained virological response in cirrhotic patients infected with genotype 1 were lower than that in the overall population (41% vs 50%).

Table 14 Sustained Virological Response in Cirrhotic Patients vs Overall Population Treated with Pegasys and 1000 or 1200 mg of Copegus for 48 Weeks in Study NV15942, All Treated Patients

	Cirrhotic Patients		Overall Population	
	Pegasys + Copegus 1000 or 1200 mg (N = 115)		Pegasys + Copegus 1000 or 1200 mg (N = 436)	
	N	SVR	N	SVR
All Patients	115	60 (52%)	436	259 (59%)
Genotype 1	78	32 (41%)	271	136 (50%)
Low viral load	21	12 (57%)	85	51 (60%)
High viral load	57	20 (35%)	186	85 (46%)
Genotype non-1	37	28 (76%)	165	123 (75%)
Low viral load	10	8 (80%)	57	45 (79%)
High viral load	27	20 (74%)	108	78 (72%)

Note: Low viral load = $\leq 2 \times 10^6$ copies/mL, high viral load = $>2 \times 10^6$ copies/mL, SVR = sustained virological response. SVR is determined based on two HCV RNA measurements <100 copies/mL measured ≥ 21 days apart using a lower time window of week 60.

4.2.6 Exploratory Analyses of Sustained Virological Response

Analysis of sustained virological response based on one measurement of HCV RNA 6 months after the end of treatment is used in other published trials in the literature to assess response to anti-HCV therapies. This way of assessing sustained virological response is also more likely to reflect current clinical practice.

This section provides efficacy results from the two combination trials, the comparative trial vs Rebetron (NV15801) and the optimization of therapy trial (NV15942), based on a single measurement of HCV RNA at the end of 6 months of follow-up. The results of these analyses are very similar to those using two measurements of HCV RNA to assess sustained virological response. The same statistically significant improvement of Pegasys and Copegus combination therapy over Rebetron and the same effects of genotype on Copegus dose and treatment duration are seen.

4.2.6.1 Study NV15801

As was shown using an assessment of sustained virological response based on two HCV RNA measurements, sustained virological response in patients treated with Pegasys and Copegus combination therapy was significantly higher than in patients treated with Rebetron ($p = 0.0058$). Superiority over Rebetron was seen in patients infected with genotype 1 as well as in patients infected with genotype non-1 (predominantly genotypes 2 and 3) (Table 15).

Table 15 Sustained Virological Response in Study NV15801, All Treated Patients

One HCV RNA Measurement 24 Weeks Posttreatment

	Pegasys + Placebo 48 Weeks		Pegasys + Copegus 1000 or 1200 mg 48 Weeks		Intron A + Rebetol 1000 or 1200 mg 48 Weeks	
	N	SVR	N	SVR	N	SVR
All Patients	224	65 (29%)	453	241 (53%)	444	197 (44%)
Treatment Difference[a]				8.8%		
Odds ratio[b]				1.49 (1.08, 2.05)		
P value[c]				0.0058		
Genotype 1 Patients	145	29 (20%)	298	132 (44%)	285	103 (36%)
Treatment Difference[a]				8.2%		
Odds ratio[b]				1.42 (0.95, 2.11)		
P value				0.0478		
Genotype Non-1 Patients	79	36 (46%)	155	109 (70%)	159	94 (59%)
Treatment Difference[a]				11.2%		
Odds ratio[b]				1.62 (0.93, 2.82)		
P value				0.0495		

Note: SVR = sustained virological response. SVR is determined based on one HCV RNA measurement <100 copies/mL measured on or after week 68..

[a] Difference in SVR between Pegasys + Copegus group and Intron A + Rebetol group.

[b] The ratio of the odds of a response in the Pegasys + Copegus group to the odds of a response in the Intron A + Rebetol group. 97.5% confidence intervals are included in parentheses.

[c] Assessed by Cochran-Mantel-Haenszel test stratified by country and HCV genotype.

Improvement over Rebetron was seen in patients with genotype 1 infection irrespective of viral load and in genotype non-1 patients irrespective of viral load (Table 16). As was seen in patients infected with genotypes 2 and 3, sustained virological response in the small number of patients in this study infected with genotype 4 was higher in patients treated with Pegasys and Copegus combination therapy (77%, 10 of 13 patients) than in patients treated with Rebetron (36%, 4 of 11 patients) (Appendix 10).

Table 16 Sustained Virological Response as a Function of Genotype and Baseline Viral Load in Study NV15801, All Treated Patients
One HCV RNA Measurement 24 Weeks Posttreatment

	Pegasys (N = 224)		Pegasys + Copegus 1000 or 1200 mg (N = 453)		Intron A + Rebetol 1000 or 1200 mg (N = 444)	
	N	SVR	N	SVR	N	SVR
Genotype 1 Patients	145	29 (20%)	298[a]	132 (44%)	285[a]	103 (36%)
Low viral load	44	16 (36%)	115	60 (52%)	94	41 (44%)
High viral load	101	13 (13%)	182	72 (40%)	189	62 (33%)
Genotype Non-1 Patients	79	36 (46%)	155	109 (70%)	159	94 (59%)
Low viral load	25	15 (60%)	44	31 (70%)	56	38 (68%)
High viral load	54	21 (39%)	111	78 (70%)	103	56 (54%)

Note: High viral load = >2 x 10^6 copies/mL, low viral load = ≤2 x 10^6 copies/mL, SVR = sustained virological response. SVR is determined based on one HCV RNA measurement <100 copies/mL measured on or after week 68.

[a] The viral load was not available for two patients in the Intron A + Rebetol group and for one patient in the Pegasys + Copegus group.

4.2.6.2 Study NV15942

The results of the formal statistical testing in study NV15942 based on one HCV RNA measurement to assess sustained virological response were similar to those based on two measurements of HCV RNA. Patients treated for 48 weeks were more likely to achieve a sustained virological response than patients treated for 24 weeks (p = 0.015) (Appendix 15). The likelihood of achieving a sustained virological response was greater among patients receiving 1000 or 1200 mg of Copegus than among patients receiving 800 mg of Copegus (p = 0.010) (Appendix 15).

Patients Infected with Genotype 1:

As was shown using an assessment of sustained virological response based on two HCV RNA measurements, the highest sustained virological response in patients infected with genotype 1, irrespective of viral load, was achieved with the most intensive regimen, 48 weeks of treatment and 1000 or 1200 mg of Copegus (51%) (Table 17). A reduction in either the Copegus dose or duration of treatment was associated with a substantial loss of efficacy in both patient subgroups.

Patients Infected with Genotype Non-1:

In patients infected with genotype non-1, similar sustained virological responses were achieved after treatment for 24 weeks with 800 mg of Copegus and after treatment for a longer duration or with a higher dose of Copegus (Table 17). This was the case whether patients had a high pretreatment viral load or a low pretreatment viral load.

Table 17 **Sustained Virological Response as a Function of Genotype and Baseline Viral Load in Study NV15942, All Treated Patients**

One HCV RNA Measurement 24 Weeks Posttreatment

	24 Weeks Treatment				48 Weeks Treatment			
	Pegasys + Copegus 800 mg (N = 207)		Pegasys + Copegus 1000 or 1200 mg (N = 280)		Pegasys + Copegus 800 mg (N = 361)		Pegasys + Copegus 1000 or 1200 mg (N = 436)	
	N	SVR	N	SVR	N	SVR	N	SVR
Genotype 1	101	29 (29%)	118	48 (41%)	250	99 (40%)	271	138 (51%)
Low viral load	51	21 (41%)	71	36 (51%)	60	32 (53%)	85	52 (61%)
High viral load	50	8 (16%)	47	12 (26%)	190	67 (35%)	186	86 (46%)
Genotype non-1	106	83 (78%)	162	127 (78%)	111	81 (73%)	165	127 (77%)
Low viral load	39	28 (72%)	61	47 (77%)	41	32 (78%)	57	44 (77%)
High viral load	67	55 (82%)	101	80 (79%)	70	49 (70%)	108	83 (77%)

Note: High viral load = $>2 \times 10^6$ copies/mL, low viral load = $\leq 2 \times 10^6$ copies/mL, SVR = sustained virological response. SVR is determined based on one HCV RNA measurement <100 copies/mL measured on or after week 44 for patients treated for 24 weeks and on or after week 68 for patients treated for 48 weeks.

The genotype non-1 patients in this study were predominantly infected with genotype 2 or 3 (90% of patients), which to a large extent account for the results observed in genotype non-1 patients in this study (Table 18). In the small number of patients infected with genotype 4 in this study (36 patients), sustained virological response was highest after 48 weeks of treatment with 1000 or 1200 mg of Copegus, suggesting that these patients respond similarly to patients infected with genotype 1.

Table 18 **Sustained Virological Response in Genotype Non-1 Patients by Genotype and Baseline Viral Load in Study NV15942, All Treated Patients**
One HCV RNA Measurement 24 Weeks Posttreatment

	24 Weeks Treatment				48 Weeks Treatment			
	Pegasys + Copegus 800 mg (N = 207)		Pegasys + Copegus 1000 or 1200 mg (N = 280)		Pegasys + Copegus 800 mg (N = 361)		Pegasys + Copegus 1000 or 1200 mg (N = 436)	
	N	SVR	N	SVR	N	SVR	N	SVR
Genotypes 2 & 3	96	79 (82%)	144	116 (81%)	99	75 (76%)	153	117 (76%)
Low viral load	34	27 (79%)	47	39 (83%)	33	27 (82%)	48	36 (75%)
High viral load	62	52 (84%)	97	77 (79%)	66	48 (73%)	105	81 (77%)
Genotype 4	5	0 (0%)	12	7 (58%)	8	5 (63%)	11	9 (82%)
Low viral load	4	0 (0%)	11	7 (64%)	7	5 (71%)	9	8 (89%)
High viral load	1	0 (0%)	1	0 (0%)	1	0 (0%)	2	1 (50%)
Genotype 5	2	1 (50%)	4	2 (50%)	0		1	1 (100%)
Low viral load	0		2	0 (0%)	0		0	
High viral load	2	1 (50%)	2	2 (100%)	0		1	1 (100%)
Genotype 6	3	3 (100%)	2	2 (100%)	4	1 (25%)	0	
Low viral load	1	1 (100%)	1	1 (100%)	1	0 (0%)	0	
High viral load	2	2 (100%)	1	1 (100%)	3	1 (33%)	0	

Note: High viral load = >2 x 10^6 copies/mL, low viral load = ≤2 x 10^6 copies/mL, SVR = sustained virological response. SVR is determined based on one HCV RNA measurement <100 copies/mL measured on or after week 44 for patients treated for 24 weeks and on or after week 68 for patients treated for 48 weeks.

4.2.6.3 Predictability of Sustained Virological Response

An analysis of the predictability of sustained virological response based on response by week 12 in patients treated for 48 weeks with Pegasys and 1000 or 1200 mg of Copegus combination therapy is presented in Table 19. The data from the common arm of studies NV15801 and NV15942 have been pooled for this exploratory analysis. Sustained virological response is assessed using one HCV RNA measurement at the end of 24 weeks of follow-up.

The negative predictive value of not achieving an early virological response by week 12 based on sustained virological response assessed using one HCV RNA measurement was very similar or unchanged compared with the negative predictive value based on

sustained virological response assessed using two HCV RNA measurements. Of the 113 patients in the overall population who failed to achieve a virological response by week 12 of treatment, 107 failed to achieve a sustained virological response, resulting in a negative predictive value of 95% in the overall population. The negative predictive value of not achieving an early virological response by week 12 for sustained virological response in patients with genotype 1 infection was 95%.

Table 19 Negative Predictive Value of a Virological Response by Week 12 for Sustained Virological Response, All Treated Patients
One HCV RNA Measurement 24 Weeks Posttreatment

	Overall Population (N = 889)		Genotype 1 Patients (N = 569)		Genotype Non-1 Patients (N = 320)	
	SVR	No SVR	SVR	No SVR	SVR	No SVR
HCV RNA unquantifiable or $\geq 2\log_{10}$ drop by week12						
Yes	500	276	265	202	235	74
No	6	107	5	97	1	10
Week 12 response	87%		82%		97%	
Negative predictive value	107/(6 + 107) = 95%		97/(5 + 97) = 95%		10/(1 + 10) = 91%	

Note: The analysis population is patients treated for 48 weeks with Pegasys and 1000 or 1200 mg of Copegus from the common arm of studies NV15801 and NV15942. SVR = sustained virological response. SVR is determined based on one HCV RNA measurement <100 copies/mL measured on or after week 68.

4.2.6.4 Efficacy in Patients with Cirrhosis

The efficacy results in patients with cirrhosis using one measurement of HCV RNA to assess sustained virological response are very similar to the results using two measurements of HCV RNA to assess sustained virological response. The same numerical improvement of Pegasys and Copegus combination therapy over Rebetron and the same effects of genotype on Copegus dose and treatment duration are seen.

Sustained virological response in the subset of patients with compensated cirrhosis in study NV15801 who were treated with Pegasys and Copegus combination therapy was numerically higher than that in patients with compensated cirrhosis who were treated with Rebetron (41% vs 33%, Table 20). The same trends were seen in cirrhotic patients with genotype 1 infections and in cirrhotic patients with genotype non-1 infection (predominantly genotypes 2 and 3) (Table 20 and Appendix 18).

Sustained virological responses in the subgroup of patients with cirrhosis in this study were numerically lower than those in the overall population (Table 21).

Table 20 **Sustained Virological Response in Patients with Cirrhosis in Study NV15801, All Treated Patients**
One HCV RNA Measurement 24 Weeks Posttreatment

	Pegasys (N = 34)		Pegasys + Copegus 1000 or 1200 mg (N = 56)		Intron A + Rebetol 1000 or 1200 mg (N = 54)	
Patients with Cirrhosis	N	SVR	N	SVR	N	SVR
All patients	34	7 (21%)	56	23 (41%)	54	18 (33%)
Genotype 1 patients	24	3 (13%)	38	11 (29%)	32	8 (25%)
Genotype non-1 patients	10	4 (40%)	18	12 (67%)	22	10 (45%)

Note: SVR = sustained virological response. SVR is determined based on one HCV RNA measurement <100 copies/mL measured on or after week 68.

Table 21 **Sustained Virological Response with Combination Therapy in Cirrhotic Patients vs Overall Population in Study NV15801, All Treated Patients**
One HCV RNA Measurement 24 Weeks Posttreatment

	Cirrhotic Patients				Overall Population			
	Pegasys + Copegus 1000 or 1200 mg (N = 56)		Intron A + Rebetol 1000 or 1200 mg (N = 54)		Pegasys + Copegus 1000 or 1200 mg (N = 453)		Intron A + Rebetol 1000 or 1200 mg (N = 444)	
	N	SVR	N	SVR	N	SVR	N	SVR
All patients	56	23 (41%)	54	18 (33%)	453	241 (53%)	444	197 (44%)
Genotype 1 patients	38	11 (29%)	32	8 (25%)	298	132 (44%)	285	103 (36%)
Genotype non-1 patients	18	12 (67%)	22	10 (45%)	155	109 (70%)	159	94 (59%)

Note: SVR = sustained virological response. SVR is determined based on one HCV RNA measurement <100 copies/mL measured on or after week 68.

In study NV15942, the relationship among treatment duration, dose of ribavirin, and genotype in patients with cirrhosis was the same as that seen in the overall noncirrhotic and cirrhotic population. In patients with cirrhosis who were infected with genotype 1 and had either a low or high viral load, sustained virological response was highest in patients treated for 48 weeks with Pegasys and 1000 or 1200 mg of Copegus (Table 22). In cirrhotic patients infected with genotype non-1, similar sustained virological responses were achieved after treatment for 24 weeks with an 800 mg daily dose of Copegus and after treatment for a longer duration or with a higher dose of Copegus (Table 22).

Table 22 **Sustained Virological Response in Cirrhotic Patients as a Function of Genotype and Baseline Viral Load in Study NV15942, All Treated Patients**
One HCV RNA Measurement 24 Weeks Posttreatment

	24 Weeks Treatment				48 Weeks Treatment			
	Pegasys + Copegus 800 mg (N = 44)		Pegasys + Copegus 1000 or 1200 mg (N = 71)		Pegasys + Copegus 800 mg (N = 91)		Pegasys + Copegus 1000 or 1200 mg (N = 115)	
	N	SVR	N	SVR	N	SVR	N	SVR
Genotype 1	23	6 (26%)	27	7 (26%)	67	18 (27%)	78	32 (41%)
Low viral load	9	3 (33%)	12	6 (50%)	9	2 (22%)	21	12 (57%)
High viral load	14	3 (21%)	15	1 (7%)	58	16 (28%)	57	20 (35%)
Genotype non-1	21	14 (67%)	44	33 (75%)	24	13 (54%)	37	26 (70%)
Low viral load	4	2 (50%)	13	11 (85%)	10	7 (70%)	10	8 (80%)
High viral load	17	12 (71%)	31	22 (71%)	14	6 (43%)	27	18 (67%)

Note: High viral load = >2 x 10^6 copies/mL, low viral load = ≤2 x 10^6 copies/mL, SVR = sustained virological response. SVR is determined based on one HCV RNA measurement <100 copies/mL measured on or after week 44 for patients treated for 24 weeks and on or after week 68 for patients treated for 48 weeks.

In study NV15942, sustained virological response in patients with cirrhosis who were treated for 48 weeks with Pegasys and 1000 or 1200 mg of Copegus was numerically lower than that in the overall population of noncirrhotic and cirrhotic patients (50% vs 61%) (Table 23). Sustained virological responses in cirrhotic patients in this study infected with genotype 1 or with genotype non-1 were also numerically lower than responses in the overall genotype 1 and genotype non-1 populations.

Table 23 Sustained Virological Response in Cirrhotic Patients vs Overall Population Treated with Pegasys and 1000 or 1200 mg of Copegus for 48 Weeks in Study NV15942, All Treated Patients

One HCV RNA Measurement 24 Weeks Posttreatment

	Cirrhotic Patients		Overall Population	
	Pegasys + Copegus 1000 or 1200 mg (N = 115)		Pegasys + Copegus 1000 or 1200 mg (N = 436)	
	N	SVR	N	SVR
All Patients	115	58 (50%)	436	265 (61%)
Genotype 1	78	32 (41%)	271	138 (51%)
Low viral load	21	12 (57%)	85	52 (61%)
High viral load	57	20 (35%)	186	86 (46%)
Genotype non-1	37	26 (70%)	165	127 (77%)
Low viral load	10	8 (80%)	57	44 (77%)
High viral load	27	18 (67%)	108	83 (77%)

Note: Low viral load = $\leq 2 \times 10^6$ copies/mL, high viral load = $>2 \times 10^6$ copies/mL, SVR = sustained virological response. SVR is determined based on two HCV RNA measurements <100 copies/mL measured ≥ 21 days apart using a lower time window of week 60.

4.3 Safety Results

4.3.1 Principal Safety Findings

- Based on a large safety data base, the safety profile of Pegasys and Copegus combination therapy has been well characterized in CHC patients, including those with compensated cirrhosis.

- Overall safety profile of 180 µg of Pegasys and 1000 or 1200 mg of Copegus combination therapy for 48 weeks is similar to Rebetron; no new clinical adverse events were observed with Pegasys and Copegus combination therapy that would not have been expected from combination therapy with interferon alfa and ribavirin. Most common clinical adverse events were reported at a similar frequency with Pegasys and Copegus combination therapy and Rebetron therapy.

- Frequency of serious adverse events was comparable with Pegasys and Copegus combination therapy and Rebetron therapy. Some differences in the point estimates for serious adverse events grouped by body system were observed between Pegasys and Copegus combination therapy and Rebetron therapy, respectively, in study NV15801 that included

    - Serious infections (4% vs 2%)

    - Serious psychiatric disorders (1% vs 3%)

- Similar frequency of anemia but higher frequencies of neutropenia and thrombocytopenia were observed with Pegasys and Copegus combination therapy than with Rebetron therapy in study NV15801.
    - Hemoglobin concentration <10 g/dL (11% vs 11%, for Pegasys and Copegus combination therapy and Rebetron therapy, respectively)
    - Neutrophil counts 0.5 to <0.75 x 10^9/L (22% vs 7%) and neutrophil counts <0.5 x 10^9/L (5% vs 1%)
    - Platelet counts <50 x 10^9/L (5% vs <1%). No patient experienced a platelet count of <20 x 10^9/L.
- Similar frequency of modification of the interferon dose for adverse events with Pegasys and Copegus combination therapy (11%) and Rebetron therapy (11%). However, modification of the interferon dose for neutropenia and thrombocytopenia occurred more frequently with Pegasys and Copegus combination therapy (20% and 4%) than with Rebetron therapy (5% and <1%). Modification of the ribavirin dose for anemia occurred with a similar frequency with Pegasys and Copegus combination therapy (22%) and with Rebetron therapy (19%).
- Majority of laboratory abnormalities were managed with dose modification and did not require withdrawal of patients from treatment. Treatment discontinuation for safety reasons occurred at similar frequency with Pegasys and Copegus combination therapy (10%) and with Rebetron therapy (11%). With both combination therapies, clinical adverse events were the most common safety reasons for treatment discontinuation (7% vs 10%, respectively).
- In study NV15942 treatment-limiting events, including serious adverse events (3%), hemoglobin levels <10 g/dL (3%), and premature withdrawal for clinical adverse events and laboratory abnormalities (5%), occurred with the lowest frequency in patients receiving the lowest exposure regimen (ie, 24 weeks of treatment and the 800 mg daily dose of Copegus). Shorter duration of Pegasys and Copegus combination therapy and administration of a lower daily ribavirin dose offer a safety advantage over 48 weeks of treatment with Pegasys and the higher dose (1000 or 1200 mg) of Copegus.
- Overall safety profile of Pegasys and Copegus combination therapy in patients with compensated cirrhosis was similar to that in the overall patient population. Differences observed were a higher frequency of platelet counts decreasing to between 20 and 50 x 10^9/L and a higher frequency of dose modification of Pegasys for thrombocytopenia.

4.3.2 Study NV15801

4.3.2.1 Comparison of Pegasys Monotherapy with Pegasys and Copegus Combination Therapy

The safety profile of Pegasys and Copegus combination therapy is consistent with the safety profiles of the individual drugs and was additive in nature. No new adverse events were observed with the combination that would not have been expected from combination therapy with interferon and ribavirin. Some clinical adverse events and laboratory abnormalities, mainly anemia, that are known side effects of treatment with ribavirin occurred at a higher incidence with Pegasys combination therapy than with Pegasys monotherapy. Key safety data are summarized in Table 24; more complete information can be found in the other summary tables provided in Section 4.3.2.1 and in the appendixes.

Table 24 Overview of Safety Profile in Study NV15801

Adverse Event	Pegasys (N = 223)	Pegasys + Copegus 1000 or 1200 mg (N = 451)	Intron A + Rebetol 1000 or 1200 mg (N = 443)
Any AE	212 (95%)	446 (99%)	435 (98%)
Severe AEs	63 (28%)	131 (29%)	127 (29%)
Treatment-related AEs[a]	205 (92%)	443 (98%)	435 (98%)
Serious AEs	26 (12%)	53 (12%)	38 (9%)
Treatment-related serious AEs[a]	8 (4%)	16 (4%)	19 (4%)
Deaths	2	0	1
Premature withdrawal for AEs and laboratory abnormalities	15 (7%)	44 (10%)	47 (11%)
Aes	13 (6%)	32 (7%)	43 (10%)
Laboratory abnormalities	2 (<1%)	12 (3%)	4 (<1%)
Dose modification for AEs and laboratory abnormalities			
Pegasys or Intron A	61 (27%)	145 (32%)	81 (18%)
AEs	14 (6%)	48 (11%)	47 (11%)
Neutropenia	38 (17%)	91 (20%)	24 (5%)
Thrombocytopenia	14 (6%)	18 (4%)	1 (<1%)
Copegus or Rebetol		181 (40%)	164 (37%)
AEs		95 (21%)	97 (22%)
Anemia		99 (22%)	83 (19%)
Lowest hemoglobin level			
8.5 to <10 g/dL	7 (3%)	40 (9%)	47 (11%)
<8.5 g/dL	1 (<1%)	9 (2%)	1 (<1%)

[a] Events judged by investigator to be remotely, possibly, or probably related to treatment.

The following clinical adverse events occurred at a higher incidence with Pegasys combination therapy than with Pegasys monotherapy, suggesting that these adverse events are exacerbated by ribavirin: insomnia, decreased appetite, vomiting, weight decrease, dyspnea, cough, and dermatitis (Table 25). These findings are consistent with the known adverse effects of ribavirin.

The incidence of anemia, the main hematological abnormality associated with ribavirin treatment, was higher with Pegasys combination therapy than with Pegasys monotherapy. The addition of ribavirin resulted in a higher percentage of patients experiencing a decrease in hemoglobin concentration to <10 g/dL. However, premature withdrawal from treatment (discontinuation of both Pegasys and ribavirin) for anemia was infrequent with Pegasys combination therapy (two patients) (Appendix 22). In most patients, anemia could be managed by modification of the ribavirin dose and infrequently by discontinuation of ribavirin only.

Serious adverse events, including serious infections and serious depression, neutrophil counts <0.5 x 10^9/L, platelet counts <50 x 10^9/L, premature withdrawal for adverse events, and modification of the Pegasys dose for adverse events or laboratory abnormalities occurred at a similar incidence with Pegasys combination therapy and Pegasys monotherapy. Premature withdrawal for laboratory abnormalities, which occurred at a low frequency in both groups, was slightly more frequent with Pegasys combination therapy than with Pegasys monotherapy. Neutropenia and thrombocytopenia were the most common laboratory abnormalities leading to premature withdrawal from treatment in both groups.

4.3.2.2 Comparison of Combination Therapies: Common Adverse Events

The most common clinical adverse events in patients treated with either Pegasys and Copegus combination therapy or Rebetron were those usually associated with interferon treatment and included fatigue, headache, pyrexia, and myalgia (Table 25). Clinical adverse events occurred at a similar frequency with the two combination therapies. Some differences in the point estimates for certain flu-like symptoms (pyrexia, rigors, and myalgia) and depression were observed between Pegasys and Copegus combination therapy and Rebetron therapy (Table 25).

Table 25 Common Clinical Adverse Events (≥10% of Patients) during Treatment and 24 Weeks Posttreatment in Study NV15801, Safety Population

Adverse Event	Pegasys N = 223 No. (%)	Pegasys + Copegus 1000 or 1200 mg N = 451 No. (%)	Intron A + Rebetol 1000 or 1200 mg N = 443 No. (%)
FATIGUE	98 (44)	242 (54)	244 (55)
HEADACHE NOS	115 (52)	211 (47)	230 (52)
PYREXIA	85 (38)	195 (43)	247 (56)
MYALGIA	94 (42)	189 (42)	220 (50)
INSOMNIA	52 (23)	168 (37)	174 (39)
NAUSEA	58 (26)	130 (29)	145 (33)
ALOPECIA	48 (22)	128 (28)	151 (34)
RIGORS	52 (23)	106 (24)	157 (35)
ARTHRALGIA	64 (29)	121 (27)	112 (25)
IRRITABILITY	56 (25)	109 (24)	123 (28)
DEPRESSION NOS	44 (20)	95 (21)	131 (30)
PRURITUS	41 (18)	101 (22)	88 (20)
APPETITE DECREASED	24 (11)	96 (21)	98 (22)
DERMATITIS NOS	29 (13)	95 (21)	80 (18)
DIARRHOEA NOS	54 (24)	77 (17)	68 (15)
DIZZINESS (EXC VERTIGO)	31 (14)	81 (18)	70 (16)
ASTHENIA	26 (12)	69 (15)	72 (16)
DYSPNOEA	20 (9)	70 (16)	72 (16)
COUGH	23 (10)	73 (16)	51 (12)
DRY SKIN	20 (9)	50 (11)	64 (14)
ANXIETY	18 (8)	51 (11)	60 (14)
BACK PAIN	29 (13)	52 (12)	46 (10)
ABDOMINAL PAIN UPPER	35 (16)	41 (9)	50 (11)
INJECTION SITE INFLAMMATION	26 (12)	56 (12)	44 (10)
CONCENTRATION IMPAIRMENT	28 (13)	41 (9)	53 (12)
VOMITING NOS	17 (8)	52 (12)	51 (12)
WEIGHT DECREASE	18 (8)	52 (12)	49 (11)
ABDOMINAL PAIN NOS	28 (13)	44 (10)	34 (8)

As noted above, a difference was seen in the point estimates for depression between patients treated with Pegasys and Copegus combination therapy and patients treated with Rebetron (21% vs 30%). This observation was further explored. The results of this more detailed analysis of clinical depression are provided in Table 26. In this additional analysis, multiple preferred terms (depression nos, depression aggravated, depression reactive, depression endogenous) have been collapsed into a single term "depression."

A consistent trend was noted in the difference in the point estimates for serious depression, suicide attempts, and suicidal ideation between the Pegasys and Copegus combination therapy and Rebetron therapy, while the point estimates for withdrawal and dose modification for depression-related events were similar in the two combination groups.

Only a small percentage of patients in these two groups had a history of depression within 1 year of the study (1%) or active depression at baseline (3% to 4%). Thus, exacerbation of baseline depression does not account for most of the reported cases of depression in this study.

Table 26 Incidence and Severity of Depression in Study NV15801, Safety Population

	Pegasys (N = 223)	Pegasys + Copegus 1000 or 1200 mg (N = 451)	Intron A + Rebetol 1000 or 1200 mg (N = 443)
Overall incidence of depression[a]	45 (20%)	100 (22%)	134 (30%)
Severe depression	3 (1%)	11 (2%)	14 (3%)
Serious depression	0	2 (<1%)	7 (2%)
Treatment for depression	25 (11%)	64 (14%)	91 (21%)
Dose mod for depression	1 (<1%)	4 (<1%)	6 (1%)
Suicidal ideation	1 (<1%)	3 (<1%)	5 (1%)
Suicide attempt	1 (<1%)	2 (<1%)	4 (<1%)
Premature withdrawals for depression-related events[b]	2 (<1%)	10 (2%)	11 (2%)

[a]Depression includes the following terms: depression nos, depression aggravated, depression reactive, depression endogenous.
[b]Withdrawals for any of above depression-related events (ie, depression and/or suicidal ideation or suicide attempt).

4.3.2.3 Serious Adverse Events

The overall frequency of serious clinical adverse events was comparable with Pegasys and Copegus combination therapy and with Rebetron (12% vs 9%) (Table 27). The point estimates for treatment-related serious adverse events (excluding events assessed as unrelated to treatment) were the same with the two combination therapies (4% vs 4%).

Most types of serious adverse events occurred in only one patient in a group, and thus very few serious adverse events were reported more frequently than others. (Appendix 20). When serious adverse events were examined grouped by body system, some small differences in the point estimates for certain types of serious adverse events were observed between Pegasys and Copegus combination therapy and Rebetron therapy. The reported frequency of serious psychiatric disorders, the most common adverse events being serious depression and suicide attempt, was 1% in patients receiving Pegasys and Copegus combination therapy and 3% in patients receiving Rebetron therapy (Appendix 20). The reported frequency of serious infections was 3% with Pegasys and Copegus combination therapy and 1% with Rebetron.

A difference in the point estimates for all serious and nonserious infections was seen between Pegasys and Copegus combination therapy (46%) and Rebetron (35%). The most common infections in both combination groups were sinusitis, upper respiratory tract infections, tooth abscess, herpes simplex, bronchitis, and influenza. Since serious infections are a potential concern in patients receiving long-acting interferons because of the association of neutropenia with interferon treatment and the possible increased risk of serious infections in the presence of marked neutropenia, a more systematic analysis that explored this observation was performed. A comprehensive review of all serious adverse

Table 27 Incidence of Serious Adverse Events (Including Unrelated) by Body System during Treatment and 24 Weeks Posttreatment in Study NV15801, Safety Population

Body System	Pegasys N = 223 No. (%)	Pegasys + Copegus 1000 or 1200 mg N = 451 No. (%)	Intron A + Rebetol 1000 or 1200 mg N = 443 No. (%)
ALL BODY SYSTEMS	26 (12)	53 (12)	38 (9)
INFECTIONS	6 (3)	13 (3)	4 (1)
PSYCHIATRIC DISORDERS	2 (1)	6 (1)	13 (3)
GASTROINTESTINAL DISORDERS	2 (1)	8 (2)	8 (2)
NEUROLOGICAL DISORDERS	2 (1)	5 (1)	2 (<1)
BENIGN & MALIGNANT NEOPLASMS	3 (1)	2 (<1)	3 (1)
GENERAL DISORDERS	1 (<1)	4 (1)	2 (<1)
CARDIAC DISORDERS	3 (1)	3 (1)	-
INJURY & POISONING	2 (1)	4 (1)	-
RESPIRATORY DISORDERS	-	3 (1)	2 (<1)
MUSCULOSKELETAL DISORDERS	1 (<1)	2 (<1)	1 (<1)
BLOOD DISORDERS	1 (<1)	3 (1)	-
METABOLISM DISORDERS	1 (<1)	-	3 (1)
HEPATOBILIARY DISORDERS	1 (<1)	1 (<1)	2 (<1)
SKIN DISORDERS	2 (1)	1 (<1)	1 (<1)
EAR DISORDERS	-	3 (1)	-
ENDOCRINE DISORDERS	1 (<1)	2 (<1)	-
VASCULAR DISORDERS	-	-	2 (<1)
EYE DISORDERS	-	1 (<1)	1 (<1)
IMMUNE SYSTEM DISORDERS	1 (<1)	-	-
REPRODUCTIVE DISORDERS	1 (<1)	-	-
SURGICAL & MEDICAL PROCEDURES	-	1 (<1)	-

events identified several additional infections that were not grouped under the body system "Infections" (for example, appendicitis, endocarditis, abdominal abscess) but are considered infections because they were either confirmed by a culture or treated with antibiotics. The results of this more in-depth analysis of serious infections are provided in Appendix 21.

The reported frequency of serious infections based on this comprehensive review was 4% with Pegasys and Copegus combination therapy and 2% with Rebetron. In both combination therapy groups as well as in the Pegasys monotherapy group, most of the infections were bacterial infections that were either confirmed by culture or presumed to

be bacterial because they were treated with antibiotics. A variety of different organ systems and organisms were involved. None of these infections were preceded by a neutrophil count <0.5 x 10^9/L.

4.3.2.4 Deaths

Three patients died, two in the Pegasys monotherapy group and one in the Rebetron group (Table 28). No deaths occurred during treatment. Two of the patients died during the study follow-up period; one patient in the Pegasys monotherapy group died of hepatic cancer 1 year after the end of treatment. All three deaths were considered unrelated to treatment.

Table 28 Patient Deaths in Study NV15801

Treatment Group & CRTN/Pt No.	Age y	Sex	Weight kg	Race	Cause of Death	Last Trt Day	Day of Death	Relation to Trial Treatment
Pegasys (n = 223)								
23183/1135	40	F	62	CAUCASIAN	DROWNING	337	485	UNRELATED
23231/1896	57	F	94	CAUCASIAN	MALIGNANT HEPATIC NEOPLASM	316	680	UNRELATED
Intron A + Rebetol 1000 or 1200 mg (n = 443)								
23219/7401	44	M	106	CAUCASIAN	HYPERTENSIVE HEART DISEASE	295	340	UNRELATED

Note: CRTN = clinical research task number (unique number identifying protocol, center, and investigator).

4.3.2.5 Adverse Events and Laboratory Abnormalities Leading to Premature Withdrawal

Premature withdrawal from treatment for safety reasons occurred with a similar frequency in patients receiving Pegasys and Copegus combination therapy and in patients receiving Rebetron (10% vs 11%) (Appendix 22). Most adverse events and laboratory abnormalities were successfully managed with dose modification and did not require withdrawal of patients from treatment.

Clinical adverse events rather than laboratory abnormalities were the most common reason for treatment discontinuation with Pegasys and Copegus combination therapy (7%) and with Rebetron (10%). Psychiatric disorders were the most common clinical adverse event leading to withdrawal from treatment in patients receiving Pegasys and Copegus combination therapy (3%) and in patients receiving Rebetron (4%), with depression and depression-related events being the most frequent reasons (Appendix 22). Hematological abnormalities resulting in premature withdrawal from treatment occurred in 2% of patients receiving Pegasys and Copegus combination therapy and 1% of patients receiving Rebetron.

4.3.2.6 Dose Modification for Adverse Events or Laboratory Abnormalities

Modification of the Pegasys dose for safety reasons was more frequent with Pegasys combination therapy (32%) than modification of the Intron A dose with Rebetron therapy

(18%) (Table 24 and Appendix 23). The percentage of patients who had their dose of Pegasys or Intron A modified for clinical adverse events was the same (11%), but modification of the Pegasys dose for laboratory abnormalities (25%) was higher than modification of the Intron A dose for laboratory abnormalities (8%). Neutropenia accounted for most of these Pegasys dose modifications (20%) as well as for the majority of the Intron A dose modifications (5%) for laboratory abnormalities. However, only 3% of patients receiving Pegasys and Copegus combination therapy withdrew for laboratory abnormalities, suggesting that dose modification successfully managed these events in the majority of patients.

Modification of the ribavirin dose for safety reasons occurred with a similar frequency in patients receiving Pegasys and Copegus combination therapy (40%) and in patients receiving Intron A and Rebetol combination therapy (37%), with about half the dose modifications for anemia and the remainder for clinical adverse events.

4.3.2.7 Neutropenia

Median neutrophil counts decreased from baseline values in both the Pegasys and Copegus combination therapy and Rebetron groups, with the largest decreases occurring during the first 2 weeks of treatment. Neutrophil counts had stabilized by week 4, remaining at around 45% of their baseline value in the Pegasys and Copegus group and around 60% of their baseline value in the Rebetron group during the remainder of the 48-week treatment period. By 4 weeks posttreatment, median neutrophil counts had increased to close to baseline levels.

A summary of the number of patients with neutrophil counts that decreased to less than 1 x 10^9/L during the study is shown in Table 29.

Table 29 Summary of Patients' Lowest Neutrophil Counts during Treatment and Follow-up in Study NV15801, Safety Population

Lowest Neutrophil Count	Pegasys (N = 223)	Pegasys + Copegus 1000 or 1200 mg (N = 451)	Intron A + Rebetol 1000 or 1200 mg (N = 443)
0.75 - 0.99 x 10^9/L	47 (21%)	106 (24%)	62 (14%)
0.50 - 0.749 x 10^9/L	34 (15%)	99 (22%)	32 (7%)
<0.50 x 10^9/L	8 (4%)	21 (5%)	5 (1%)

Neutrophil counts decreased to <0.5 x 10^9/L in a higher percentage of patients receiving Pegasys and Copegus combination therapy (5%) than in patients receiving Rebetron (1%) (Table 30). Most patients with neutrophil counts <0.5 x 10^9/L required at least a temporary reduction in the dose of Pegasys or Intron A, but <1% of patients in the two combination groups were withdrawn from treatment because of neutrophil counts <0.5 x 10^9/L (Table 30). About half the patients with neutrophil counts <0.5 x 10^9/L in the

Pegasys and Copegus group required permanent reduction of the Pegasys dose, while in the Rebetron group the majority of patients with neutrophil counts <0.5 x 10^9/L had only a temporary reduction of the Intron A dose. Reduction of the Copegus or Rebetol dose for neutrophil counts <0.5 x 10^9/L occurred only infrequently. In no case did neutrophil counts <0.5 x 10^9/L precede the onset of a serious infection.

Table 30 Dose Modifications in Patients with Neutrophil Counts <0.5 x 10^9/L in Study NV15801, Safety Population

	Pegasys N = 223	Pegasys + Copegus 1000 or 1200 mg N=451	Intron A + Rebetol 1000 or 1200 mg N=443
No. of pts with neutrophil counts <0.5 x 10^9/L	8 (4%)	21 (5%)	5 (1%)
No. of pts withdrawn	0	3 (0.7%)	1 (<1%)
Dose Modifications	**Pegasys**	**Pegasys**	**Intron A**
No. of pts with permanent dose reduction	6 (3%)	10 (2%)	1 (<1%)
No. of pts with temporary dose reduction	1 (<1%)	5 (1%)	3 (<1%)
No. of pts with no dose modification	1 (<1%)	3 (<1%)	0

4.3.2.8 Thrombocytopenia

Median platelet counts decreased from baseline values progressively during the first 8 weeks of treatment in both the Pegasys and Copegus combination therapy and Rebetron groups, although the decreases from baseline in the Pegasys and Copegus combination group were greater than in the Rebetron group. In both groups of patients, median platelet counts then stabilized and remained at these levels until the end of treatment. By 4 weeks posttreatment, median platelet counts had increased to close to baseline levels. Of note, the decrease in median platelet counts was smaller in the Pegasys combination therapy group than in the Pegasys monotherapy group.

Platelet counts did not fall below 20 x 10^9/L in any patient during the study. Platelet counts decreased to between 20 and <50 x 10^9/L in a higher percentage of patients receiving Pegasys and Copegus combination therapy than in patients receiving Rebetron (5% vs <1%) (Table 31). Most patients in the Pegasys and Copegus combination group with platelet counts <50 x 10^9/L required at least a temporary reduction in the dose of Pegasys, but <1% of patients receiving Pegasys and Copegus were withdrawn from treatment because of platelet counts <50 x 10^9/L (Table 31). About half the patients with platelet counts <50 x 10^9/L in the Pegasys and Copegus group required permanent reduction of the Pegasys dose, while in the Rebetron group the one patient with platelet counts <50 x 10^9/L continued treatment without modification of the Intron A dose. No

serious bleeding events were noted in patients with platelet counts <50 x 10^9/L receiving either combination therapy.

Table 31 Dose Modifications in Patients with Platelet Counts between 20 to <50 x 10^9/L in Study NV15801, Safety Population

	Pegasys N = 223	Pegasys + Copegus 1000 or 1200 mg N=451	Intron A + Rebetol 1000 or 1200 mg N=443
No. of pts with platelet counts between 20 to <50 x 10^9/L	14 (6%)	22 (5%)	1 (<1%)
No. of pts withdrawn	1 (<1%)	4 (<1%)	0
Dose Modifications	**Pegasys**	**Pegasys**	**Intron A**
No. of pts with permanent dose reduction	6 (3%)	12 (3%)	0
No. of pts with temporary dose reduction	5 (2%)	2 (<1%)	0
No. of patients with no dose modification	2 (<1%)	4 (<1%)	1 (<1%)

4.3.2.9 Anemia

A similar progressive decrease in median hemoglobin concentration during the first 8 weeks of treatment, stabilization thereafter during treatment, and a return to baseline levels within 8 to 12 weeks posttreatment was seen in the Pegasys and Copegus combination therapy and the Rebetron groups. As would be expected, the decrease in median hemoglobin levels in the Pegasys monotherapy arm was much smaller than that in the two ribavirin combination arms.

Decreases in hemoglobin concentration to <10 g/dL occurred in a similar proportion of patients in the Pegasys and Copegus combination therapy group and in the Rebetron group (11%) (Table 32). However, more patients receiving Pegasys and Copegus combination therapy experienced decreases in hemoglobin concentration to <8.5 g/dL (2%) than patients receiving Rebetron (<1%).

Most patients in both combination groups whose hemoglobin concentration decreased to <10 g/dL were managed by modification of the ribavirin dose rather than premature withdrawal from treatment (discontinuation of both study drugs) or discontinuation of ribavirin only (Table 32). Very few patients in either combination therapy group were prematurely withdrawn from treatment for anemia (Appendix 22). The majority of the modifications of Copegus and Rebetol were permanent dose reductions. Modification of the Pegasys or Intron A dose for anemia was very infrequent.

Table 32 Dose Modifications in Patients with Hemoglobin < 10 g/dL in Study NV15801, Safety Population

	Pegasys N = 223	Pegasys + Copegus 1000 or 1200 mg N=451	Intron A + Rebetol 1000 or 1200 mg N=443
No. of pts with hemoglobin <10 g/dL	8 (4%)	49 (11%)	48 (11%)
8.5 <10 g/dL	7 (3%)	40 (9%)	47 (11%)
<8.5 g/dL	1 (<1%)	9 (2%)	1 (<1%)
No. of pts withdrawn from treatment (both study drugs)	0	2 (<1%)	1 (<1%)
Dose Modifications	**Placebo**	**Copegus**	**Rebetol**
No. of pts who discontinued ribavirin	1 (<1%)	9 (2%)	1 (<1%)
No. of pts with permanent dose reduction	5 (2%)	34 (8%)	35 (8%)
No. of pts with temporary dose reduction	0	3 (<1%)	4 (<1%)
No. of pts with no dose modification	2 (<1%)	1 (<1%)	7 (2%)

[a]The Roche normal range for hemoglobin level is 13.0 to 18.0 g/dL.

4.3.3 Study NV15942

As mentioned earlier in this document, studies NV15942 and NV15801 had a common treatment arm. In study NV15942, the safety profile in the Pegasys and Copegus common treatment arm (48 weeks of treatment with Pegasys and 1000 or 1200 mg of Copegus) was consistent with that seen in study NV15801.

In study NV15942, treatment-limiting events occurred with the lowest frequency in patients receiving 24 weeks of treatment and the 800 mg dose of Copegus. These treatment-limiting events included serious adverse events and premature withdrawal for adverse events (Table 33). In addition, the group receiving 800 mg of Copegus for 24 weeks had the lowest percentage of patients who experienced a decrease in hemoglobin levels to <10 g/dL or who required modification of the Copegus dose. Hemoglobin levels did not fall to <8.5 g/dL in any patient in this group. Thus, the shorter treatment duration and lower dose of Copegus offer a safety advantage over 48 weeks of treatment with Pegasys and the higher dose (1000 or 1200 mg) of Copegus.

Table 33 Overall Safety Profile of Pegasys and Copegus Combination Therapy in Study NV15942

	24 Weeks of Treatment		48 Weeks of Treatment	
	Pegasys + Copegus 800 mg (N = 207)	Pegasys + Copegus 1000 or 1200 mg (N = 280)	Pegasys + Copegus 800 mg (N = 361)	Pegasys + Copegus 1000 or 1200 mg (N = 436)
Any AE	200 (97%)	275 (98%)	355 (98%)	427 (98%)
Severe AEs	46 (22%)	63 (23%)	116 (32%)	141 (32%)
Treatment-related AEs	198 (96%)	272 (97%)	355 (98%)	425 (97%)
Serious AEs	7 (3%)	19 (7%)	33 (9%)	44 (10%)
Treatment-related serious AEs[a]	3 (1%)	8 (3%)	15 (4%)	14 (3%)
Deaths	0	1	1	2
Premature withdrawal for AEs and laboratory abnormalities	10 (5%)	13 (5%)	59 (16%)	67 (15%)
AEs	8 (4%)	10 (3%)	52 (14%)	55 (12%)
Laboratory abnormalities	2 (1%)	3 (1%)	7 (2%)	12 (3%)
Dose modification for AEs and laboratory abnormalities				
Pegasys	63 (30%)	73 (26%)	120 (33%)	159 (36%)
AEs	15 (7%)	25 (9%)	41 (11%)	60 (14%)
Neutropenia	42 (20%)	46 (16%)	79 (22%)	106 (24%)
Thrombocytopenia	9 (4%)	10 (4%)	14 (4%)	20 (5%)
Ribavirin	39 (19%)	76 (27%)	101 (28%)	166 (38%)
AEs	24 (12%)	50 (18%)	70 (19%)	98 (22%)
Anemia	16 (8%)	31 (11%)	33 (9%)	85 (19%)
Lowest hemoglobin level				
8.5 - <10 g/dL	7 (3%)	24 (9%)	22 (6%)	61 (14%)
<8.5 g/dL	0	4 (1%)	1 (0.3%)	6 (1%)

[a]Events judged by investigator to be remotely, possibly, or probably related to treatment.

4.3.3.1 Common Adverse Events

The most common clinical adverse events in all four treatment groups were those usually associated with interferon treatment and included headache, fatigue, myalgia, and pyrexia (Appendix 24). The incidence of individual adverse events as well as the incidence of adverse events by body system was similar in the four treatment groups. Depression occurred with a similar frequency in all four treatment groups and was not more frequent in the group receiving 48 weeks of treatment than in the group receiving 24 weeks of treatment.

4.3.3.2 *Serious Adverse Events*

The lowest incidence of serious clinical adverse events occurred in patients treated for 24 weeks with the lower dose (800 mg) of Copegus (Table 34 and Appendix 25). The serious adverse events reported most frequently, regardless of treatment group, were serious infections and serious psychiatric disorders. Patients treated for 24 weeks with the lower dose of Copegus experienced the lowest incidence of serious infections (<1%), while serious psychiatric disorders occurred with a similarly low frequency in patients treated for 24 weeks and in patients treated for 48 weeks.

Table 34 Incidence of Serious Adverse Events by Body System during Treatment and 24 Weeks Posttreatment in Study NV15942, Safety Population

Body System	24 Weeks Pegasys + Copegus 800 mg N = 207 No. (%)	24 Weeks Pegasys + Copegus 1000 or 1200 mg N = 280 No. (%)	48 Weeks Pegasys + Copegus 800 mg N = 361 No. (%)	48 Weeks Pegasys + Copegus 1000 or 1200 mg N = 436 No. (%)
ALL BODY SYSTEMS	7 (3)	19 (7)	33 (9)	44 (10)
INFECTIONS	1 (<1)	3 (1)	4 (1)	7 (2)
PSYCHIATRIC DISORDERS	1 (<1)	5 (2)	3 (<1)	4 (<1)
INJURY & POISONING	-	2 (<1)	2 (<1)	7 (2)
GENERAL DISORDERS	1 (<1)	-	4 (1)	4 (<1)
NEUROLOGICAL DISORDERS	-	1 (<1)	5 (1)	3 (<1)
GASTROINTESTINAL DISORDERS	1 (<1)	-	2 (<1)	5 (1)
MUSCULOSKELETAL DISORDERS	1 (<1)	1 (<1)	2 (<1)	4 (<1)
BENIGN & MALIGNANT NEOPLASMS	-	2 (<1)	1 (<1)	2 (<1)
IMMUNE SYSTEM DISORDERS	1 (<1)	1 (<1)	2 (<1)	1 (<1)
VASCULAR DISORDERS	-	-	1 (<1)	3 (<1)
CARDIAC DISORDERS	-	-	1 (<1)	2 (<1)
BLOOD DISORDERS	-	-	1 (<1)	2 (<1)
METABOLISM DISORDERS	1 (<1)	-	2 (<1)	-
HEPATOBILIARY DISORDERS	-	2 (<1)	1 (<1)	-
SKIN DISORDERS	-	2 (<1)	-	1 (<1)
RENAL & URINARY DISORDERS	1 (<1)	-	-	1 (<1)
SURGICAL & MEDICAL PROCEDURES	-	1 (<1)	-	1 (<1)
CONGENITAL DISORDERS	-	-	-	1 (<1)
EAR DISORDERS	-	-	1 (<1)	-
EYE DISORDERS	-	-	1 (<1)	-
REPRODUCTIVE SYSTEM DISORDERS	-	-	-	1 (<1)
RESPIRATORY DISORDERS	-	-	1 (<1)	-

As in study NV15801, an in-depth review of all serious clinical adverse events was performed in order to further examine the relationship between Pegasys and Copegus combination therapy and serious infections. This review identified several additional infections not grouped under the body system "Infections" but considered to be infections

because they were either confirmed by culture or treated with antibiotics. In this additional review, the incidence of serious infections remained low in all four groups; the point estimates were lowest in patients treated for 24 weeks with 800 mg of Copegus (<1%) and highest in patients treated for 48 weeks with the higher dose of Copegus (2%) (Appendix 26).

Most of the infections were bacterial infections that were either confirmed by culture or presumed to be bacterial because they were treated with antibiotics. A variety of different organ systems and organisms were involved. None of these infections were preceded by a neutrophil count <0.5 x 10^9/L.

4.3.3.3 Deaths

Four patients died in this study; three of the four deaths occurred during treatment, and two of these three deaths were considered by investigators to be related to study medication (septic shock and suicide) (Table 35). The other two deaths (overdose of opiates and overdose from amphetamines, opiates, atropines, and alcohol) were assessed by investigators as unrelated to study medication.

Table 35 Patient Deaths in Study NV15942

Treatment Group & CRTN/Pt No.	Age y	Sex	Weight kg	Race	Cause of Death	Last Trt Day	Day of Death	Relation to Trial Treatment
Pegasys + Copegus 1000 or 1200 mg, 24 Weeks								
25769/2335	32	M	101	CAUCASIAN	OVERDOSE NOS	32	33	UNRELATED
Pegasys + Copegus 800 mg, 48 Weeks								
25965/0641	45	M	62	CAUCASIAN	SEPTICAEMIA NOS	63	65	POSSIBLE
Pegasys + Copegus 1000 or 1200 mg, 48 Weeks								
25721/3046	38	F	77	CAUCASIAN	SUICIDE (ACCOMPLISHED)	177	182	PROBABLE
25742/0001	40	M	99	CAUCASIAN	DRUG TOXICITY NOS	172	317	UNRELATED

Note: CRTN = clinical research task number (unique number identifying protocol, center, and investigator).

4.3.3.4 Premature Withdrawal and Dose Modifications for Adverse Events and Laboratory Abnormalities

The percentage of patients discontinuing treatment for a clinical adverse event or laboratory abnormality in the two groups being treated for 24 weeks was approximately one third that in the two groups being treated for 48 weeks (Appendix 27). The 24-week shorter treatment duration was better tolerated than the longer 48-week treatment duration, while Copegus dose did not appear to have an effect on the frequency of discontinuation of treatment for safety reasons.

Psychiatric disorders were the most common reason for discontinuing treatment, the most frequent of these being depression (Appendix 27). The percentage of patients who discontinued treatment for depression was the same in the group treated for 24 weeks with 800 mg of Copegus (2%) and in the group treated for 48 weeks with 1000 or 1200 mg of Copegus (2%). In contrast, general disorders (mainly fatigue and asthenia) and hematological disorders (neutropenia and anemia) more frequently led to discontinuation

of treatment in patients treated for 48 weeks than in patients treated for 24 weeks (Appendix 27).

The majority of clinical adverse events and laboratory abnormalities were successfully managed with modification of the Pegasys or Copegus dose and did not require discontinuation of treatment. Although modification of the Pegasys dose was only slightly less frequent in patients being treated for 24 weeks than in patients being treated for 48 weeks, the percentage of patients requiring modification of the Copegus dose was considerably lower in patients treated for 24 weeks with 800 mg of Copegus (19%) than in patients treated for 48 weeks with 1000 or 1200 mg of Copegus (38%) (Table 33). Anemia was the most frequent laboratory abnormality necessitating modification of the Copegus dose. The proportion of patients requiring modification of the Copegus dose for anemia was lowest in the group being treated for 24 weeks with the lower Copegus dose (8%) and highest in the group being treated for 48 weeks with the higher dose of Copegus (19%).

4.3.3.5 Neutropenia and Thrombocytopenia

The effects of Pegasys and Copegus combination therapy on neutrophil and platelet counts in study NV15942 were similar to the effects seen in study NV15801. Treatment duration and ribavirin dose had little or no effect on the proportion of patients who experienced either a decrease in neutrophil counts to <0.5 x 10^9/L (3% to 5% of patients) or a decrease in platelet counts to between 20 and <50 x 10^9/L (3% to 5% of patients) (Table 36). Platelet counts did not fall below 20 x 10^9/L in any patient during the study

Table 36 Summary of Patients' Lowest Neutrophil and Platelet Counts during Treatment and Follow-up in Study NV15942, Safety Population

Laboratory Abnormality	24 Weeks Pegasys + Copegus 800 mg N = 207	24 Weeks Pegasys + Copegus 1000 or 1200 mg N =280	48 Weeks Pegasys + Copegus 800 mg N = 361	48 Weeks Pegasys + Copegus 1000 or 1200 mg N = 436
Lowest Neutrophil Count				
0.75 - 0.99 x 10^9/L	49 (24%)	70 (25%)	87 (24%)	117 (27%)
0.5 - 0.749 x 10^9/L	38 (18%)	45 (16%)	85 (24%)	115 (26%)
<0.5 x 10^9/L	10 (5%)	8 (3%)	17 (5%)	20 (5%)
Lowest Platelet Count				
20 - <50 x 10^9/L	8 (4%)	9 (3%)	15 (4%)	21 (5%)
<20 x 10^9/L	0	0	0	0

4.3.3.6 Anemia

A decrease in hemoglobin concentration to <10 g/dL appeared to be dependent on the ribavirin dose and to a lesser extent on the duration of treatment. Patients treated for 24 weeks with 800 mg of Copegus had the lowest incidence of hemoglobin concentration decreasing to <10 g/dL, while patients treated for 48 weeks with 1000 or 1200 mg of Copegus had the highest incidence (Table 37). No patient in the group treated for 24 weeks with 800 mg of Copegus experienced a decrease in hemoglobin concentration to <8.5 g/dL.

Most patients whose hemoglobin concentration decreased to <10 g/dL were managed by modification of the ribavirin dose rather than premature withdrawal from treatment (discontinuation of both study drugs) or discontinuation of ribavirin only. Very few patients were prematurely withdrawn from treatment for anemia (Table 37 and Appendix 27). The majority of the modifications of Copegus were permanent dose reductions (Table 37). Modification of the Pegasys or Intron A dose for anemia was very infrequent.

Table 37 Dose Modification in Patients with Hemoglobin < 10 g/dL in Study NV15942, Safety Population

	24 Weeks Pegasys + Copegus 800 mg N = 207	24 Weeks Pegasys + Copegus 1000 or 1200 mg N =280	48 Weeks Pegasys + Copegus 800 mg N = 361	48 Weeks Pegasys + Copegus 1000 or 1200 mg N = 436
No. of pts with hemoglobin <10 g/dL	7 (3%)	28 (10%)	23 (6%)	67 (15%)
8.5 - <10 g/dL	7 (3%)	24 (9%)	22 (6%)	61 (14%)
<8.5 g/dL	0	4 (1%)	1 (<1%)	6 (1%)
No. of pts withdrawn from treatment (both study drugs)	0	0	1 (0.3%)	2 (0.5%)
Dose Modifications	**Copegus**	**Copegus**	**Copegus**	**Copegus**
Permanently discontinued Copegus	0	4 (1%)	2 (0.6%)	1 (0.2%)
Permanent dose reduction	4 (2%)	15 (5%)	13 (4%)	45 (10%)
Temporary dose reduction	0	0	1 (0.3%)	7 (2%)
No dose modification	3 (2%)	9 (3%)	6 (2%)	12 (3%)

[a]The Roche normal range for hemoglobin level is 13.0 to 18.0 g/dL.

4.3.4 Safety Profile in Patients with Cirrhosis

The subpopulation of patients with cirrhosis are perceived to be more likely to experience adverse effects from IFN alfa-based therapies, and safety concerns have been raised about treating patients with cirrhosis with these therapies. In order to address this concern, the safety profile of Pegasys and Copegus combination therapy in the subgroup

of patients with cirrhosis from the two phase III studies, NV15801 and NV15942, was examined.

For this analysis, patients with cirrhosis in the common arm of studies NV15801 and NV15942 (48 week of treatment with 180 µg of Pegasys and 1000 or 1200 mg of Copegus) were pooled in order to increase the number of patients in this arm and thereby increase the ability to detect differences in the incidence of less common events between Pegasys and Copegus combination therapy and other treatments. The treatment regimens in the other groups from these two studies differed, and thus no other groups were pooled.

4.3.4.1 Cirrhotic Study Population

Demographic and baseline characteristics in patients with cirrhosis were similar in those treated for 48 weeks with Pegasys and 1000 or 1200 mg of Copegus and in those treated for 48 weeks with Rebetron. The majority of patients were male (72% and 76%, respectively), and most were Caucasian (91% in each group). The median age was 46 and 47 years. The percentage of cirrhotic patients in the overall population was higher in the Pegasys combination group (19%, 171 of 887 patients) than in the Rebetron group (12%, 54 of 443 patients).

Demographic and baseline characteristics of cirrhotic patients in the Pegasys combination groups were also similar. As in the overall population, the majority of patients were male (63% to 80%), and most were Caucasian (79% to 91%). The median age was 43 to 47 years, which was a few years older than that in the overall population, and body weight ranged from 78 to 84 kg, which was slightly heavier than that in the overall population. In the overall population, the percentage of patients with cirrhosis ranged from 19% to 25% in the four Pegasys combination groups.

4.3.4.2 Comparison of Safety Profiles of Pegasys and Copegus Combination Therapy and Rebetron Therapy in Patients with Cirrhosis

As was seen in the overall population, the most common clinical adverse events in cirrhotic patients treated for 48 weeks with either Pegasys and 1000 or 1200 mg of Copegus combination therapy or Rebetron therapy were those usually associated with interferon treatment and included fatigue, headache, pyrexia, and myalgia (Appendix 28). As in the overall population, a difference was seen in the point estimates for several interferon-related side effects including a number of flu-like symptoms (pyrexia, rigors, and myalgia) and depression between cirrhotic patients receiving Pegasys and Copegus combination therapy and cirrhotic patients receiving Rebetron (Appendix 28). Of note, the incidence of depression in cirrhotic patients was 19% in the Pegasys and Copegus combination group and 41% in the Rebetron group (Table 38 and Appendix 28).

In both the Pegasys and Copegus combination group and the Rebetron group, a similar percentage of patients with cirrhosis experienced serious adverse events (11% vs 13%). The incidence of serious adverse events in cirrhotic patients was very similar to that for

the overall populations in study NV15801 (Table 24). None of the patients receiving combination therapy who died were cirrhotic.

Table 38 Clinical Adverse Event Profile in Cirrhotic Patients from Studies NV15801 and NV15942, Pooled Safety Population

	24 Weeks Pegasys + Copegus 800 mg N = 44	24 Weeks Pegasys + Copegus 1000 or 1200 mg N = 71	48 Weeks Pegasys + Copegus 800 mg N = 91	48 Weeks Pegasys + Copegus 1000 or 1200 mg N = 171	48 Weeks Intron A + Rebetol 1000 or 1200 mg N = 54
Any AE	41 (93%)	69 (97%)	90 (99%)	166 (97%)	54 (100%)
Severe AEs	8 (18%)	16 (23%)	30 (33%)	69 (40%)	18 (33%)
Treatment-related AEs[a]	41 (93%)	67 (94%)	90 (99%)	163 (95%)	54 (100%)
Depression[b]	7 (16%)	11 (15%)	18 (20%)	32 (19%)	22 (41%)
Severe depression	0	1 (1%)	0	3 (2%)	2 (4%)
Serious depression	0	1 (1%)	0	0	1 (2%)
Suicide ideation	0	0	0	0	2 (4%)
Suicide attempt	0	0	0	0	1 (2%)
Premature withdrawal for depression-related events	0	0	0	3 (2%)	3 (6%)
Serious AEs	1 (2%)	7 (10%)	10 (11%)	19 (11%)	7 (13%)
Deaths	0	0	0	0	0

[a]Events judged by investigator to be possibly or probably related to treatment.
[b]Depression includes the following terms: aggravated depression, depression nos, and reactive depression.

The percentage of patients whose neutrophil counts decreased to <0.5 x 10^9/L (5% vs 0%) and the percentage of patients whose platelet counts decreased to between 20 to <50 x 10^9/L (12% vs 2%) were higher in cirrhotic patients receiving Pegasys and 1000 or 1200 mg of Copegus combination therapy for 48 weeks than in cirrhotic patients receiving Rebetron for 48 weeks (Table 39). Modifications of the Pegasys dose for neutropenia or thrombocytopenia were also more frequent in cirrhotic patients receiving Pegasys combination therapy than in cirrhotic patients receiving Rebetron (Table 39).

Except for thrombocytopenia, these results, including the frequencies, were similar to those for the overall population. In patients with cirrhosis in both combination groups, the percentage of patients whose platelet counts decreased to between 20 and <50 x 10^9/L was higher than that in the overall population, 12% vs 5%, respectively, for Pegasys and Copegus combination therapy and 2% vs <1%, respectively, for Rebetron therapy (Table 39 and Table 31). A higher percentage of cirrhotic patients in the Pegasys combination group had their dose of Pegasys modified for thrombocytopenia than in the overall population (11% vs 4%) (Table 39 and Table 24).

The percentage of cirrhotic patients with decreases in hemoglobin concentration to <10 g/dL was similar in the Pegasys and Copegus combination group (15%) and Rebetron group (11%). The frequency of dose modification of ribavirin for anemia in patients with cirrhosis was also similar in the Pegasys and Copegus combination group (25%) and Rebetron group (19%). These results were similar to those in the overall population (Table 39 and Table 24).

A similar percentage of patients with cirrhosis in the Pegasys and Copegus combination therapy group and in the Rebetron group were prematurely withdrawn from treatment for safety reasons (13% vs 11%) (Table 39). As in the overall population, clinical adverse events rather then laboratory abnormalities were the most common reason for treatment discontinuation. The percentage of cirrhotic patients receiving Pegasys and Copegus combination therapy and the percentage of cirrhotic patients receiving Rebetron therapy who were prematurely withdrawn for clinical adverse events were similar (8% vs 11%, respectively). Laboratory abnormalities (thrombocytopenia, neutropenia, and anemia) were clinically managed by dose reduction rather than by administration of growth factors, and in the majority of cases did not require discontinuation of treatment.

Table 39 Hematological Laboratory Abnormalities and Dose Modification and Premature Withdrawal in Patients with Cirrhosis from Studies NV15801 and NV15942, Pooled Safety Population

	24 Weeks Pegasys + Copegus 800 mg N = 44	24 Weeks Pegasys + Copegus 1000 or 1200 mg N = 71	48 Weeks Pegasys + Copegus 800 mg N = 91	48 Weeks Pegasys + Copegus 1000 or 1200 mg N = 171	48 Weeks Intron A + Rebetol 1000 or 1200 mg N = 54
Lowest neutrophil count					
0.75 - 0.99 x 10^9/L	9 (21%)	15 (21%)	21 (23%)	50 (29%)	8 (15%)
0.50 - 0.749 x 10^9/L	11 (25%)	15 (21%)	22 (24%)	46 (27%)	6 (11%)
<0.5 x 10^9/L	1 (2%)	1 (1%)	8 (9%)	8 (5%)	0
Lowest platelet count					
20 - <50 x 10^9/L	5 (11%)	4 (6%)	11 (12%)	20 (12%)	1 (2%)
<20 x 10^9/L	0	0	0	0	0
Lowest hemoglobin level					
8.5 - <10 g/dL	0	6 (8%)	10 (11%)	23 (13%)	5 (9%)
<8.5 g/dL	0	1 (1%)	0	4 (2%)	1 (2%)
Dose modification for AEs and lab abnormalities					
Pegasys or Intron A	14 (32%)	18 (25%)	34 (37%)	64 (37%)	16 (30%)
AEs	2 (5%)	4 (6%)	9 (10%)	18 (11%)	10 (19%)
Neutropenia	9 (20%)	13 (18%)	23 (25%)	40 (23%)	4 (7%)
Thrombocytopenia	4 (9%)	4 (6%)	10 (11%)	18 (11%)	0
Copegus or Rebetol	6 (14%)	20 (28%)	31 (34%)	73 (43%)	26 (48%)
AEs	5 (11%)	12 (17%)	16 (18%)	36 (21%)	18 (33%)
Anemia	2 (5%)	10 (14%)	15 (16%)	42 (25%)	10 (19%)
Premature withdrawal for AEs and laboratory abnormalities	0	4 (6%)	11 (12%)	22 (13%)	6 (11%)
AEs	0	3 (4%)	10 (11%)	14 (8%)	6 (11%)
Laboratory abnormalities	0	1 (1%)	1 (1%)	8 (5%)	0

4.3.4.3 *Effect of Treatment Duration and Copegus Dose on Safety Profile of Pegasys and Copegus Combination Therapy in Patients with Cirrhosis*

The safety profile of Pegasys and Copegus combination therapy in patients with cirrhosis in study NV15942 was consistent with that in study NV15801. As was seen in the overall population in study NV15942, treatment-limiting events occurred with the lowest frequency in cirrhotic patients receiving 24 weeks of treatment and the 800 mg dose of Copegus. These treatment-limiting events included serious adverse events and premature withdrawal for adverse events and laboratory abnormalities (Table 38 and Table 39). In addition, the group of patients with cirrhosis receiving 800 mg of Copegus for 24 weeks had the lowest percentage of patients who required modification of the dose of Copegus for anemia (Table 39). Hemoglobin levels did not fall to <10 g/dL in any patient with cirrhosis in this group. Thus as in the overall population, the shorter treatment duration and lower dose of Copegus also offer patients with cirrhosis a safety advantage over 48 weeks of treatment with Pegasys and the higher dose (1000 or 1200 mg) of Copegus.

5. RECOMMENDED DOSE OF PEGASYS AND COPEGUS IN COMBINATION THERAPY

The recommended dosing regimens for Pegasys and Copegus combination therapy are:

- *For patients with genotype non-1 infection:* 180 µg of Pegasys given once weekly plus 800 mg of Copegus given daily for 24 weeks, which is based on an evaluation of the efficacy, safety, and exposure data and from the two phase III studies NV15801 and NV15942.

- *For patients with genotype 1 infection:* 180 µg of Pegasys given once weekly plus 1000 or 1200 mg of Copegus given daily for 48 weeks, which is based on an evaluation of the efficacy, safety, and exposure data pooled from the two phase III studies NV15801 and NV15492.

The Pegasys 180 µg dose once weekly for 48 weeks, which is the recommended dosing regimen for Pegasys monotherapy, and the 1000 or 1200 mg dose of ribavirin daily for 48 weeks, which is the approved ribavirin dosing regimen in combination with Intron A and considered the maximum tolerated dose in combination with IFN alfa, were selected as the doses and dosing regimens to be evaluated in the Pegasys and Copegus combination program [13]. These regimens were chosen in an effort to maximize efficacy and the benefits of therapy over the risks, that is, to maximize the likelihood of achieving a sustained virological response while simultaneously maintaining an acceptable safety profile. The approved ribavirin regimen in combination with IFN alfa is 1000 mg daily for patients weighing <75 kg and 1200 mg daily for patients weighing ≥75 kg. The potential for a drug-drug interaction between Pegasys and Copegus was also considered.

Results of the two phase III studies, NV15801 and NV15942, demonstrated the following:

- Sustained virological response was statistically significantly higher in patients treated for 48 weeks with 180 μg of Pegasys and 1000 or 1200 mg of Copegus than in patients treated for 48 weeks with Rebetron.
- Treatment of patients infected with genotype non-1 for 24 weeks with 180 μg of Pegasys and 800 mg of Copegus was as effective as treatment for a longer duration or with a higher dose of Copegus.
- In patients infected with genotype 1, the highest sustained virological response was achieved with treatment for 48 weeks with 180 μg of Pegasys and 1000 or 1200 mg of Copegus.
- The safety profile of Pegasys and Copegus combination therapy is consistent with the safety profiles of the individual drugs and was additive in nature. No new adverse events were observed with the combination. Some clinical adverse events and laboratory abnormalities, mainly anemia, that are known side effects of treatment with ribavirin occurred at a higher incidence with Pegasys combination therapy than with Pegasys monotherapy. Also, the frequency and severity of the most commonly reported adverse events were similar in patients treated for 48 weeks with 180 μg of Pegasys and 1000 or 1200 mg of Copegus combination therapy and in patients treated for 48 weeks with Rebetron.
- No evidence was found that the coadministration of Copegus influenced the pharmacokinetic characteristics of Pegasys. Similarly, no evidence was found that the coadministration of Pegasys influenced the pharmacokinetic characteristics of Copegus.

6. BENEFIT-RISK SUMMARY

The data generated from the clinical development program demonstrate that the combination of Pegasys and Copegus represents an advance in the treatment of CHC over Rebetron. In study NV15801, Pegasys and Copegus combination therapy was demonstrated to have superior efficacy to Rebetron. Sustained virological response was statistically significantly higher in patients receiving 180 μg of Pegasys and 1000 or 1200 mg of Copegus than in patients receiving Intron A and 1000 or 1200 mg of Rebetol. This significant improvement in efficacy over Rebetron was seen not only in the overall population but also in the subgroups of patients infected with HCV genotype 1 and genotype non-1, irrespective of the patient's pretreatment viral load. The safety profiles of 48 weeks of treatment with 180 μg of Pegasys and 1000 or 1200 mg of Copegus and 48 weeks of treatment with Intron A and 1000 or 1200 mg of Rebetol were comparable. The majority of the laboratory abnormalities associated with Pegasys combination therapy could be managed clinically by dose modification and did not usually require discontinuation of treatment.

In study NV15942, which examined sustained virological response by treatment duration and Copegus dose in patients prospectively stratified by genotype and viral load, the highest sustained virological response in patients infected with genotype 1, with either a high pretreatment viral load or a low pretreatment viral load, was achieved with 48 weeks of treatment and 1000 or 1200 mg of Copegus. In patients with genotype 1, reducing the treatment duration or the dose of Copegus resulted in a lower sustained virological response. In this same study, treatment of patients infected with genotype non-1 for 24 weeks with Pegasys and 800 mg of ribavirin was as effective as treatment with a higher dose of Copegus or for a longer duration. A similar pattern of response based on genotype was seen in patients with cirrhosis. The sustained virological responses were slightly lower than those in the overall population, which is consistent with the finding that cirrhosis is an independent prognostic factor for sustained virological response. The ability to reduce treatment duration to 24 weeks and the Copegus dose to 800 mg in genotype non-1 infection allows for a substantial decrease in exposure to two drugs and a reduction in the potential for significant toxicities.

The efficacy and safety results from the two pivotal phase III Pegasys combination studies provide further evidence to support a treatment paradigm based on baseline disease characteristics that has been evolving for the treatment of CHC patients, including patients with cirrhosis. In this paradigm, HCV genotype is the determining factor in the selection of the appropriate treatment duration and Copegus dose to achieve a balance of efficacy and safety in the treatment of patients with this serious and life-threatening disease.

For patients infected with genotype 1, the superior efficacy of Pegasys and Copegus compared with Rebetron and the comparable safety profile of Pegasys combination therapy and Rebetron therapy increase the potential benefits of Pegasys combination treatment without a substantial increase in risk. In addition, the high negative predictive value of not achieving an early virological response by week 12 gives physicians the option of stopping treatment early in patients infected with genotype 1, thus providing an improvement in the clinical management of these patients. Patients unlikely to respond receive a limited treatment course and are spared unnecessary exposure to two drugs with the potential for significant toxicities.

For patients infected with genotype non-1, the superior efficacy of Pegasys and Copegus compared with Rebetron and the improved safety profile of 24 weeks of treatment with Pegasys and 800 mg of Copegus result in an improvement of the benefit-risk relationship as compared with available therapies.

7. MANAGING ADVERSE OUTCOMES

7.1 Package Inserts and Medication Guides

The package inserts and medication guides for Pegasys and Copegus include important safety information to help raise awareness and manage the possible serious adverse events associated with the use of Pegasys and Copegus combination therapy. While the

precise labeling of the package inserts and medication guides is under discussion with the FDA, the package inserts and medication guides will contain the following elements based on safety findings from the clinical trials, as well as teratogenicity data on ribavirin from published preclinical studies:

7.1.1 Package Insert

A black-box warning (class labeling) will highlight serious adverse events (ie, neuropsychiatric, autoimmune, ischemic, and infectious disorders) that may be fatal or life-threatening and will indicate that therapy should be withdrawn if patients have persisting or worsening signs or symptoms of these conditions. Furthermore, it will point out that ribavirin is teratogenic, genotoxic, and mutagenic and may cause birth defects and/or death of the unborn child. Therefore, extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. In addition, ribavirin can cause hemolytic anemia and may result in a worsening of cardiac disease.

The label will recommend that physicians closely monitor patients for these and other serious conditions and that periodic clinical and laboratory assessments should be done.

Based on the data from the clinical trials, guidance will be provided in the label regarding dose reduction for both Pegasys and Copegus for the management of clinical adverse events, hematological abnormalities (ie, neutropenia, thrombocytopenia, and anemia in patients with and without underlying cardiovascular disease), renal dysfunction, and hepatic dysfunction.

Labeling also will be provided to ensure that the female patient or partner of a male patient is not pregnant before initiating therapy and that she must not become pregnant during therapy and for 6 months after completing therapy. Patients and their partners will need to use two effective forms of contraception during this time period, and monthly pregnancy testing will be done. Should the patient or female partner become pregnant, the physician will be encouraged to enroll the patient or female partner in the Copegus Pregnancy Registry.

The "Warning" section of the package insert will indicate that therapy should be discontinued in patients developing severe neuropsychiatric disorders, severe hematologic abnormalities, acute hypersensitivity, respiratory insufficiency, hemorrhagic/ischemic colitis, pancreatitis, ophthalmologic disorders, or persistent ALT elevations associated with elevated bilirubin levels.

7.1.2 Medication Guide

The medication guide will raise awareness in patients of the possible serious adverse events associated with the use of Pegasys and Copegus. In layman's terms, the medication guide will highlight serious birth defects and/or fetal death, mental health problems (including irritability, aggression, anxiety, depression, suicidal ideation, suicidal attempt, suicide, and relapse of drug addiction and overdose), cardiac disorders, and hematological abnormalities. Other adverse events discussed will include:

pulmonary disorders, ophthalmologic disorders, autoimmune problems (eg, thyroid disease and psoriasis), severe fatigue, flu-like symptoms, headache, insomnia, dermatitis, injection reactions, and hyperglycemia. The guide will inform patients that they should be aware that these adverse events can occur and that they should inform their health care provider if they develop any new symptoms.

Patients will be informed that they must avoid pregnancy during treatment and for 6 months after completion of treatment and to do so they must use two forms of effective contraception during this time period. Should a patient become pregnant, the patient will be encouraged to inform her physician. In addition, the medication guide will inform the patient of the existence of the Copegus Pregnancy Registry.

Furthermore, the medication guide informs the patient regarding:

- Pegasys and Copegus combination therapy
- Who should not take Pegasys and Copegus
- How to take Pegasys and Copegus
- How to inject Pegasys and how to dispose of injectable materials
- How to store Pegasys and Copegus
- General advice about prescription medications

The package insert and medication guide inform physicians and patients of the known risk factors of therapy so that the physician and patient can make an informed decision regarding the use of medication. Further, the safety information and guidance provided allows physicians and patients to be more cognizant of these serious adverse events and by identifying them early can better modify outcome by dose modifcation or, if necessary, discontinuation of therapy.

7.2 Patient Education Plans

Pegassist, a comprehensive patient education program, has been developed to provide educational support to patients on the safe and appropriate use of Pegasys and Copegus combination therapy. The following is a sample of support materials available for patients on Pegasys and Copegus combination therapy:

- Educational brochures that explain what hepatitis C is, how to live with it, and what to expect from treatment with Pegasys and Copegus combination therapy.
- Monthly newsletters containing information on hepatitis C treatment, nutrition, exercise, and well-being.
- Self-injection video and brochure to supplement the medication guide in educating patients about how to administer therapy.

- Access to information on pregnancy risk management including:
    - Education on the Copegus Pregnancy Risk Management Program and purpose of the pregnancy registry.
    - Patient brochure containing counseling information regarding pregnancy prevention and proper contraceptive use for both female and male patients and the female partners of male patients.
    - Access to a toll-free number for both female and male patients and the female partners of male patients to listen to a pre-recorded message on pregnancy prevention and contraception use and to obtain free urine pregnancy kits.
    - Pregnancy test kits provided in the patient education starter kits and throughout therapy free of charge.

7.3 Copegus (Ribavirin) Pregnancy Risk Management Plans

Data from the literature and Roche preclinical studies indicate that ribavirin is teratogenic and a reproductive toxicant (see Section 2.3). A pregnancy risk management program for Copegus has been developed and includes provider and patient labeling (including a medication guide), pregnancy prevention education, and a pregnancy registry to collect and track information on pregnancies, fetal exposures, and all associated outcomes.

7.3.1 Copegus Pregnancy Risk Management Program

A risk management program is a comprehensive program of identification, assessment, and communication of both proven and potential risks assuring that the essential information about a medication is accurately and properly distributed to providers and patients. The objectives of the Copegus Pregnancy Risk Management Program are

1. Help prevent fetal exposure to ribavirin through comprehensive provider and patient labeling as well as pregnancy prevention education.
2. Collect and track information on pregnancies, fetal exposures, and all associated outcomes in a pregnancy registry.

The ultimate goal of this program is to reduce pregnancies and fetal exposures.

The Copegus US Package Insert will include important safety information regarding pregnancy risk consistent with other ribavirin product labeling in the black-box warning, contraindications, warnings, and precautions sections. The label will include the need to use two effective forms of contraception (one being a condom in male patients), a properly timed pregnancy test that is negative immediately before initiating therapy, and the need for monthly pregnancy testing during and for 6 months after the completion of therapy. If patients do become pregnant, they are encouraged to contact their physician as well as to report the pregnancy to the Copegus Pregnancy Registry.

The Copegus Medication Guide also includes important safety information regarding pregnancy risk consistent with other ribavirin product labeling. The Copegus Medication Guide emphasizes the following with regard to pregnancy risk:

- Potential for serious birth defects and/or death of an unborn child.
- Pregnancy or breast-feeding women should not take ribavirin.
- Recommendation to avoid getting pregnant while taking Copegus treatment. This recommendation includes using two separate effective forms of contraception (one being a condom in male patients), a properly timed pregnancy test that is negative immediately before initiating therapy, and the need for monthly pregnancy testing during and for 6 months after the completion of therapy.
- If patients do become pregnant, they are encouraged to contact their physician as well as to report the pregnancy to the Copegus Pregnancy Registry.

Roche is presently working with the FDA on the development of a pregnancy registry for Copegus. The pregnancy registry, the medication guide for patients, the package insert for providers, and the provider and patient education program are all part of the Copegus Pregnancy Risk Management Program. The educational component of the program includes:

- Education on the Copegus Pregnancy Risk Management Program and purpose of the pregnancy registry.
- Patient brochure containing counseling information regarding pregnancy prevention and proper contraceptive use for both female and male patients and the female partners of male patients.
- Provider brochure containing materials on patient counseling regarding pregnancy prevention and proper contraceptive use.
- Access to a toll-free number for both female and male patients and the female partners of male patients to listen to a pre-recorded message on pregnancy prevention and contraception use and to obtain free urine pregnancy kits.
- Access to toll-free numbers for providers to request patient educational materials, report a pregnancy, and/or listen to a pre-recorded message on pregnancy prevention.
- Pregnancy test kits provided in the patient education starter kits and throughout therapy free of charge.

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Appendix 1 Ongoing Pegasys Studies in HCV-Infected Special Populations

Special Population	Protocol	Planned Enrollment
Pegasys and Copegus Combination Studies		
HCV/HIV coinfected patients	NR15961 A randomized, partially blinded, multicenter, phase III, three-arm study evaluating the efficacy and safety of peginterferonalfa-2a monotherapy versus combination therapy of peginterferon alfa-2a with ribavirin versus combination therapy of interferon alfa-2a with ribavirin for 48 weeks and 24 weeks of follow-up in patients with chronic hepatitis C coinfected with human immunodeficiency virus	860
	NR16155 A randomized, partially blinded, multicenter, phase II study investigating the efficacy and safety of Pegasys and Pegasys with Copegus in treatment-naïve patients with chronic hepatitis C coinfected with human immunodeficiency virus	150
	ACTG 5071 Multicenter, open-label, randomized study of interferon alfa 2b + ribavirin vs Pegasys + ribavirin for HCV in patients with HIV	134
African-American patients	NR16172 A multicenter, open-label study investigating the efficacy of Pegasys in combination with ribavirin as initial treatment of chronic hepatitis C in non-Hispanic African-American genotype 1 patients as compared to non-Hispanic Caucasian genotype 1 patients	108
	PEG110: Virahep-C Study Chronic hepatitis C in African Americans: Study of resistance to antiviral therapy in chronic hepatitis C (NIDDK-sponsored)	400
Patients with cirrhosis	NR15963 Hepatitis C antiviral long-term treatment against cirrhosis (HALT-C, NIDDK-sponsored; combination treatment followed by long-term monotherapy in nonresponders)	900
Patients with persistently normal ALT activity	NR16071 A randomized, open-label, multicenter, phase III study evaluating the efficacy and safety of peginterferon alfa-2a in combination with ribavirin given for 24 weeks versus 48 weeks versus no treatment in patients with chronic hepatitis C and persistently normal ALT	514

(Continued)

Appendix 1 Ongoing Pegasys Studies in HCV-Infected Special Populations (Cont.)

Special Population	Protocol	Planned Enrollment
Pegasys and Copegus Combination Studies (Cont)		
Transplant patients	PEG-096 Prevention of recurrence of hepatitis C following liver transplantation – NIDDK liver transplant database group: A prospective, randomized, multicenter, open-label, comparative safety and efficacy study of prophylactically administered pegylated interferon alfa-2a (Pegasys) plus ribavirin vs no prophylaxis following liver transplantation for hepatitis C	350
Pediatric patients	Pegylated interferon +/- ribavirin for children with HCV (Efficacy trial; sponsors, NIH and Johns Hopkins)	100
Pegasys Monotherapy Studies		
Patients with cirrhosis	NV15495 A phase II/III open-label, randomized, multicenter, parallel-group study evaluating the safety and efficacy of peginterferon alfa-2a versus interferon alfa-2a in the treatment of patients with chronic hepatitis C with cirrhosis. (Completed; monotherapy registration study)	271
Transplant patients	NR15997 A randomized, open-label, multicenter, efficacy and safety study of Pegasys for the treatment of hepatitis C virus infection administered to patients 6 to 60 months post liver transplantation	56
	NR15996 A randomized, open-label, multicenter, efficacy and safety study of Pegasys as a prophylaxis against hepatitis C virus infection recurrence after liver transplantation	50
Pediatric patients	NR16141 The safety, viral kinetics and pharmacokinetics of Pegasys after multiple doses in young children with chronic hepatitis C infection	14

Appendix 2 Ongoing Pegasys and Copegus Drug-Interaction Studies in HCV-Infected Patients

Potential Drug Interactions	Protocol	Planned Enrollment
Pegasys and methadone	NP16048 The pharmacokinetic and pharmacodynamic effects of the concomitant administration of methadone and peginterferon alfa-2a in chronic hepatitis C patients receiving methadone maintenance therapy	24
Ribavirin and nucleoside reverse transcriptase inhibitors	NR16046 Drug interaction companion protocol to NR15961: A randomized, partially blinded, multicenter, phase III, three-arm study evaluating the efficacy and safety of peginterferonalfa-2a monotherapy versus combination therapy of peginterferon alfa-2a with ribavirin versus combination therapy of interferon alfa-2a with ribavirin for 48 weeks and 24 weeks of follow-up in patients with chronic hepatitis C coinfected with human immunodeficiency virus	56

Appendix 3 Inclusion and Exclusion Criteria for Phase III Pegasys and Copegus Combination Studies NV15801 and NV15942

Inclusion criteria

- Outpatients ≥ 18 years old
- Not previously been treated with any form of interferon or ribavirin
- Serological evidence of HCV infection by an anti-HCV antibody test
- Serum HCV RNA quantifiable at ≥2000 copies/mL (by the Amplicor HCV Monitor Test, version 2.0)
- Elevated serum ALT
- Chronic liver disease consistent with CHC shown by liver biopsy
- Compensated liver disease Child-Pugh Grade A
- For women of childbearing potential, a negative urine HCG pregnancy test 24 hours before the first dose of study drug. In addition, all fertile male patients, male patients with female partners of childbearing age, and females had to be using two reliable forms of effective contraception during the study.

Exclusion criteria

- Interferon alfa or ribavirin therapy at any previous time
- Decompensated liver disease or evidence of other chronic liver disease (eg, hemochromatosis, autoimmune hepatitis, alcoholic liver disease, toxin exposures), ceruloplasmin or α_1-antitrypsin levels consistent with an increased risk of metabolic liver disease
- Positive test for anti-hepatitis A virus immunoglobulin M, hepatitis B surface antigen, hepatitis B core immunoglobulin M, or anti-HIV antibodies
- Neutrophil count <1500 cells/mm^3, hemoglobin concentration <12 g/dL in women or <13 g/dL in men, platelet count <90,000 cells/mm^3, or serum creatinine levels >1.5 times the upper limit of normal
- Serum creatinine >1.5 times the upper limit of normal
- History of severe psychiatric disease, especially depression
- History of immunologically mediated disease
- History of thyroid disease poorly controlled on prescribed medication
- History or other evidence of severe retinopathy
- History of severe seizure disorder or current anticonvulsant use
- History of severe cardiac disease
- History of chronic pulmonary disease associated with functional limitation
- Major organ transplantation, with an existing functional graft
- Active or suspected cancer or a history of malignancy in which chance of recurrence is ≥ 20% within 2 years
- Evidence of alcohol and/or drug abuse within 1 year of entry
- Women who are pregnant or breastfeeding. Men whose female partners were pregnant were also excluded.

Appendix 4 Dose Adjustment Guidelines for Adverse Events and Laboratory Abnormalities in Studies NV15801 and NV15942

1. Pegasys Dose

General dose reduction guidelines for Pegasys were provided in the protocols for clinical adverse events and laboratory abnormalities that were considered to be related to Pegasys. In addition, the protocols provided specific dose adjustments for Pegasys for neutropenia, for thrombocytopenia, and for serum ALT activities elevated above pretreatment levels.

If possible, doses of Pegasys were not to be withheld or eliminated. This recommendation stemmed from concerns that extended periods of lowered drug concentrations in the blood might be associated with replication of more resistant clones of the virus, resulting in lack of sustained response at the conclusion of therapy. The lowest dose of Pegasys that was to be administered was 45 µg.

The general dose reduction guidelines for Pegasys and the decremental adjustments in the dose of Pegasys are summarized in the tables below.

General Dose Reduction Guidelines

Intensity of Event	Mild	Moderate Limited	Moderate Persistent	Severe Limited	Severe Persistent	Life-Threatening
Number of Dose Reduction Levels	0	0	0 - 1	0 - 1	1 - 2	Stop drug

Decremental Reductions in Pegasys Dose

Assigned Dose	One-Level Reduction	Two-Level Reduction	Three-Level Reduction
180 µg	135 µg	90 µg	45 µg

Specific dose adjustments of Pegasys for low neutrophil counts or low platelet counts are summarized in the table below.

Dose Adjustments for Neutropenia or Thrombocytopenia

Parameter	Downward Dose Adjustment
Neutrophil Count (cells/mm^3)	
≥1000	None
750 - 999	Weeks 1 - 2: Immediate one-level reduction Weeks 3 - 48: None
500 - 749	Weeks 1 - 2: Delay or hold dose until ≥750, then resume dose with one-level reduction Weeks 3 - 48: Immediate one-level reduction
250 - 499	Weeks 1 - 2: Delay or hold dose until ≥750, then resume dose with two-level reduction Weeks 3 - 48: Delay or hold dose until ≥750, then resume dose with one-level reduction
<250	Stop drug
Platelet Count (cells/mm^3)	
≥50,000	None
35,000 - 49,000	Delay or hold dose until ≥50,000, then resume dose with one-level reduction
25,000 - 34,000	Delay or hold dose until ≥50,000, then resume dose with two-level reduction
<25,000	Stop drug

Note: Weeks 1 - 2 = signifies the abnormality was noted within the first 2 weeks of the initiation of test drug treatment, weeks 3 - 48 = signifies the abnormality was noted more than 2 weeks following the initiation of test drug treatment.

The specific dose adjustments of Pegasys for serum ALT activities elevated above pretreatment levels were dependent on the patient's baseline serum ALT activity and on the percentage the patient's serum ALT activity increased above pretreatment activity during test drug administration. The Pegasys dose was to be adjusted down in 45 μg (one-level reduction) or 90 μg (two-level reduction) decrements. Therapy was to be discontinued if increases in serum ALT were progressive despite dose reduction, or were accompanied by increased bilirubin levels.

2. Ribavirin Dose

The dose of ribavirin was to be reduced to 600 mg per day if

- A patient without significant cardiovascular disease experienced a fall in hemoglobin to <10g/dL and ≥8.5 g/dL
- A patient with stable cardiovascular disease experienced a fall in hemoglobin by ≥2g/dL during any 4 weeks of treatment.

Ribavirin was to be discontinued under the following circumstances

- If a patient without significant cardiovascular disease experienced a fall in hemoglobin to <8.5 g/dL.
- If a patient with stable cardiovascular disease maintained a hemoglobin value of <12 g/dL despite 4 weeks at a reduced dose.

Once a patient's ribavirin dose was held because of a laboratory abnormality or adverse event, the investigator could have attempted to increase the dose of ribavirin to 600 mg daily and further to 800 mg daily. However, it was recommended that the dose not be increased further to 1000 or 1200 mg.

Appendix 5 Revised Randomization Scheme for Allocation of Patients to Different Strata Defined by Genotype, Viral Load, Treatment Duration, and Dose of Ribavirin

	Group	Revised Random Ratio[a]	Revised Stratum Size[a]	Revised Sample Size[a]	Final No. Pts Recruited	Target SVR
Genotype Non-1, Low Viral Load			160			
24 weeks, 800 mg of ribavirin,	A	1		36	41	70%
24 weeks, 1000 or 1200 mg of ribavirin	B	1		44	63	70%
48 weeks, 800 mg of ribavirin,	C	1		36	43	80%
48 weeks, 1000 or 1200 mg of ribavirin	D	1		44	57	80%
Genotype Non-1, High Viral Load			360			
24 weeks, 800 mg of ribavirin	A	1		79	69	70%
24 weeks, 1000 or 1200 mg of ribavirin	B	1		103	101	70%
48 weeks, 800 mg of ribavirin	C	1		79	71	80%
48 weeks, 1000 or 1200 mg of ribavirin	D	1		103	111	80%
Genotype 1, Low Viral Load			240			
24 weeks, 800 mg of ribavirin	A	1		53	52	40%
24 weeks, 1000 or 1200 mg of ribavirin	B	1		65	75	40%
48 weeks, 800 mg of ribavirin	C	1		53	60	52%
48 weeks, 1000 or 1200 mg of ribavirin	D	1		65	86	52%
Genotype 1, High Viral Load			520			
24 weeks, 800 mg of ribavirin	A	1		54	52	10%
24 weeks, 1000 or 1200 mg of ribavirin	B	1		54	49	10%
48 weeks, 800 mg of ribavirin	C	5		208	191	30%
48 weeks, 1000 or 1200 mg of ribavirin	D	5		208	190	30%
Total No. of Patients			1280	1284	1311	

[a] After protocol was amended and randomization scheme was revised.

Appendix 6 Summary of Demographic and Baseline Disease Characteristics in Study NV15801, All Treated Patients

	Pegasys N = 224	Pegasys + Copegus 1000 or 1200 mg N = 453	Intron A + Rebetol 1000 or 1200 mg N = 444
Sex			
n	224	453	444
MALE	151 (67%)	324 (72%)	325 (73%)
FEMALE	73 (33%)	129 (28%)	119 (27%)
Race			
n	224	453	444
CAUCASIAN	186 (83%)	372 (82%)	385 (87%)
BLACK	13 (6%)	27 (6%)	13 (3%)
ORIENTAL	12 (5%)	28 (6%)	24 (5%)
OTHER	13 (6%)	26 (6%)	22 (5%)
Age (y)			
n	224	453	444
Mean	42.4	42.8	42.3
Median	42.0	43.0	42.0
Min-Max	19 - 64	19 - 76	20 - 71
Weight (kg)			
n	224	453	444
Mean	79.1	79.8	78.4
Median	76.0	78.0	76.2
Min-Max	47.0 - 156	42.0 - 156	44.0 - 155
Body Mass Index (kg/sqm)			
n	224	452	444
Mean	26.5	26.8	26.4
Median	25.5	25.9	25.4
Min-Max	17.9 - 46.6	16.4 - 52.3	16.5 - 65.4
Qualifying ALT[a] (U/L)			
n	224	453	444
Mean	87	90	91
Median	68	71	71
Min-Max	3 - 353	31 - 641	31 - 460
Pretreatment HCV RNA Titers (10^3 copies/mL)			
n	224	452	442
Mean	5878	6003	6011
Median	3830	3700	3585
Min-Max	27 - 70600	2 - 61400	1 - 53600
Histological Diagnosis[b]			
Noncirrhotic	190 (85%)	397 (88%)	390 (88%)
Cirrhotic	34 (15%)	56 (12%)	54 (12%)
Genotype			
Type 1	145 (65%)	298 (66%)	285 (64%)
1a	70 (31%)	141 (31%)	154 (35%)
1b	68 (30%)	155 (34%)	122 (27%)
Other	7 (3%)	2 (<1%)	9 (2%)
Non-1	79 (35%)	155 (34%)	159 (36%)
2	37 (17%)	54 (12%)	61 (14%)
3	32 (14%)	86 (19%)	84 (19%)
4	9 (4%)	13 (3%)	11 (2%)
5	1 (<1%)	0 (0%)	2 (<1%)
6	0 (0%)	2 (<1%)	1 (<1%)
Mode of Infection			
Injection drug use	80 (36%)	190 (42%)	180 (41%)
Noninjection drug use	1 (<1%)	2 (<1%)	1 (<1%)
Occupational	3 (1%)	2 (<1%)	1 (<1%)
Other	4 (2%)	6 (1%)	6 (1%)
Other percutaneous	12 (5%)	32 (7%)	27 (6%)
Sexual	6 (3%)	4 (<1%)	10 (2%)
Transfusion	47 (21%)	85 (19%)	97 (22%)
Unknown	71 (32%)	132 (29%)	122 (27%)

[a]Average of the two ALT measurements that qualified patient to be included in the trial, standardized according to Roche's normal range of 0 to 30 U/L.
[b]As judged by the investigator or local pathologist based on pretreatment liver biopsy.

Appendix 7 Disposition of Patients in Study NV15801

	Pegasys	Pegasys + Copegus 1000 or 1200 mg	Intron A + Rebetol 1000 or 1200 mg
Patients randomized	227	465	457
Patients who received study drug	224 (99%)	453 (97%)	444 (97%)
Patients who completed 12 weeks of treatment	217 (96%)	435 (94%)	426 (93%)
Patients who completed 24 weeks of treatment	197 (87%)	414 (89%)	402 (88%)
Patients who completed 48 weeks of treatment	152 (67%)	353 (76%)	304 (67%)
Patients who completed 24 weeks of follow-up[a]	146 (64%)	334 (72%)	290 (63%)

[a]Patients who had an assessment at week 72.

Appendix 8 Summary of Reasons for Premature Withdrawal from Treatment in Study NV15801, All Treated Patients

Reason for Premature Withdrawal	Pegasys (N = 224)	Pegasys + Copegus 1000 or 1200 mg (N = 453)	Intron A + Rebetol 1000 or 1200 mg (N = 444)
Safety			
Clinical adverse event	13 (6%)	32 (7%)	43 (10%)
Laboratory abnormality	2 (<1%)	12 (3%)	4 (<1%)
Total	15 (7%)	44 (10%)	47 (11%)
Nonsafety			
Insufficient therapeutic response	49 (22%)	34 (8%)	59 (13%)
Refused treatment	5 (2%	15 (3%)	22 (5%)
Failure to return	3 (1%)	5 (1%)	7 (<1%)
Protocol violation[a]	0	2 (<1%)	2 (<1%)
Violation of entry criteria	0	0	2 (<1%)
Administrative or other	0	0	1 (<1%)
Total	57 (25%)	56 (12%)	93 (21%)
Total prematurely withdrawn	**72 (32%)**	**100 (22%)**	**140 (32%)**

[a]Other than violation of entry criteria.

Appendix 9 Sustained Virological Response in Genotype Non-1 Patients as a Function of Genotype and Baseline Viral Titer in Study NV15801, All Patients Treated

	Pegasys (N = 224)		Pegasys + Copegus 1000 or 1200 mg (N = 453)		Intron A + Rebetol 1000 or 1200 mg (N = 444)	
	N	SVR	N	SVR	N	SVR
Genotype non-1	79	35 (44%)	155	105 (68%)	159	90 (57%)
Low viral load	25	15 (60%)	44	31 (70%)	56	36 (64%)
High viral load	54	20 (37%)	111	74 (67%)	103	54 (52%)
Genotypes 2 and 3	69	30 (43%)	140	94 (67%)	145	85 (59%)
Low viral load	19	11 (58%)	37	26 (70%)	52	33 (63%)
High viral load	50	19 (38%)	103	68 (66%)	93	52 (56%)
Genotype 4	9	4 (44%)	13	10 (77%)	11	3 (27%)
Low viral load	6	4 (67%)	5	4 (80%)	3	2 (67%)
High viral load	3	0	8	6 (75%)	8	1 (13%)
Genotype 5	1	1 (100%)	0		2	2 (100%)
Low viral load	0		0		1	1 (100%)
High viral load	1	1 (100%)	0		1	1 (100%)
Genotype 6	0		2	1 (50%)	1	0 (0%)
Low viral load	0		2	1 (50%)	0	
High viral load	0		0		1	0 (0%)

Note: High viral load = $>2 \times 10^6$ copies/mL, low viral load = $\leq 2 \times 10^6$ copies/mL, SVR = sustained virological response. SVR is determined based on two HCV RNA measurements <100 copies/mL measured ≥ 21 days apart using a lower time window of week 60.

Appendix 10 Sustained Virological Response in Genotype Non-1 Patients as a Function of Genotype and Baseline Viral Titer in Study NV15801, All Patients Treated

One HCV RNA Measurement 24 Weeks Posttreatment

	Pegasys (N = 224)		Pegasys + Copegus 1000 or 1200 mg (N = 453)		Intron A + Rebetol 1000 or 1200 mg (N = 444)	
	N	SVR	N	SVR	N	SVR
Genotype non-1	79	36 (46%)	155	109 (70%)	159	94 (59%)
Low viral load	25	15 (60%)	44	31 (70%)	56	38 (68%)
High viral load	54	21 (39%)	111	78 (70%)	103	56 (54%)
Genotypes 2 and 3	69	31 (45%)	140	98 (70%)	145	88 (61%)
Low viral load	19	11 (58%)	37	26 (70%)	52	34 (65%)
High viral load	50	20 (40%)	103	72 (70%)	93	54 (58%)
Genotype 4	9	4 (44%)	13	10 (77%)	11	4 (36%)
Low viral load	6	4 (67%)	5	4 (80%)	3	3 (100%)
High viral load	3	0	8	6 (75%)	8	1 (13%)
Genotype 5	1	1 (100%)	0		2	2 (100%)
Low viral load	0		0		1	1 (100%)
High viral load	1	1 (100%)	0		1	1 (100%)
Genotype 6	0		2	1 (50%)	1	0 (0%)
Low viral load	0		2	1 (50%)	0	
High viral load	0		0		1	0 (0%)

Note: High viral load = >2 x 10^6 copies/mL, low viral load = ≤2 x 10^6 copies/mL, SVR = sustained virological response. SVR is determined based on one HCV RNA measurement <100 copies/mL measured on or after week 68.

Appendix 11 Summary of Demographic Characteristics in Study NV15942, All Treated Patients

	24 Weeks Pegasys + Copegus 800 mg N = 207	24 Weeks Pegasys + Copegus 1000 or 1200 mg N = 280	48 Weeks Pegasys + Copegus 800 mg N = 361	48 Weeks Pegasys + Copegus 1000 or 1200 mg N = 436
Sex				
MALE	140 (68%)	185 (66%)	226 (63%)	287 (66%)
FEMALE	67 (32%)	95 (34%)	135 (37%)	149 (34%)
n	207	280	361	436
Race				
n	207	280	361	436
CAUCASIAN	183 (88%)	254 (91%)	315 (87%)	394 (90%)
BLACK	7 (3%)	9 (3%)	11 (3%)	11 (3%)
ORIENTAL	14 (7%)	16 (6%)	31 (9%)	26 (6%)
OTHER	3 (1%)	1 (0%)	4 (1%)	5 (1%)
Age (y)				
n	207	280	361	436
Mean	41.2	42.0	42.6	43.0
Median	41.0	42.0	42.0	42.0
Min-Max	18 - 66	19 - 76	19 - 74	20 - 73
Weight (kg)				
n	207	280	361	435
Mean	78.27	77.07	76.97	77.32
Median	76.00	75.25	75.00	77.60
Min-Max	48.3 - 150.0	41.0 - 129.1	41.0 - 148.2	45.0 - 136.8
Body Surface Area (sqm)				
n	207	280	361	435
Mean	1.909	1.883	1.886	1.892
Median	1.890	1.875	1.890	1.910
Min-Max	1.44 - 2.89	1.16 - 2.46	1.33 - 2.70	1.35 - 2.51
Qualifying ALT[a] (U/L)				
n	207	280	361	436
Mean	88.3	91.1	81.3	87.0
Median	68.3	70.3	64.9	68.2
Min-Max	31 - 546	31 - 626	30 - 365	23 - 539
Pretreatment RNA Titers (10^3 copies/mL)				
n	207	280	361	436
Mean	5047	5513	7156	6059
Median	3240	2732	5340	4332
Min-Max	3 - 26500	0 - 47100	12 - 63700	5 - 51500
Histological Diagnosis[b]				
Noncirrhotic	163 79%	209 75%	270 75%	321 74%
Cirrhotic	10 5%	20 7%	25 7%	35 8%
Bridging Fibrosis	34 16%	51 18%	66 18%	80 18%
Genotype				
Type 1	101 49%	118 42%	250 69%	271 62%
1a	46 22%	54 19%	117 32%	124 28%
1b	55 27%	64 23%	132 37%	147 34%
Other	0 0%	0 0%	1 <1%	0 0%
Non-1	106 51%	162 58%	111 31%	165 38%
2	39 19%	53 19%	46 13%	66 15%
3	57 28%	91 33%	53 15%	87 20%
4	5 2%	12 4%	8 2%	11 3%
5	2 <1%	4 1%	0 0%	1 <1%
6	3 1%	2 <1%	4 1%	0 0%
Mode of Infection				
Injection drug use	74 36%	96 34%	124 34%	163 37%
Other percutaneous	20 10%	35 13%	36 10%	53 12%
Sexual exposure	2 <1%	5 2%	6 2%	7 2%
Surgery	0 0%	2 <1%	1 <1%	0 0%
Transfusion	39 19%	45 16%	67 19%	80 18%
Unknown	72 35%	97 35%	127 35%	131 30%
Vertical transmission	0 0%	0 0%	0 0%	2 <1%

[a] Average of the two ALT measurements that qualified patient to be included in the trial, standardized according to Roche's normal range of 0 to 30 U/L.
[b] As judged by the investigator or local pathologist based on pretreatment liver biopsy.

Appendix 12 Disposition of Patients in Study NV15942

	24 Weeks Treatment		48 Weeks Treatment	
	Pegasys + Copegus 800 mg	Pegasys + Copegus 1000 or 1200 mg	Pegasys + Copegus 800 mg	Pegasys + Copegus 1000 or 1200 mg
Patients randomized	214	288	365	444
Patients who received study drug	207 (97%)	280 (97%)	361 (99%)	436 (98%)
Patients who completed 12 weeks of treatment	198 (93%)	269 (93%)	353 (97%)	421 (95%)
Patients who completed 24 weeks of treatment	193 (90%)	258 (90%)	326 (89%)	399 (90%)
Patients who completed 48 weeks of treatment			244 (67%)	319 (72%)
Patients who completed 24 weeks of follow-up[a]	191 (89%)	251 (87%)	255 (70%)	325 (73%)

[a]Patients assigned to 24 weeks of treatment who had an assessment at week 48 and patients assigned to 48 week of treatment who had an assessment at week 72..

Appendix 13 Summary of Reasons for Premature Withdrawal from Treatment in Study NV15942, All Treated Patients

Reason for Premature Withdrawal	24 Weeks Treatment		48 Weeks Treatment	
	Pegasys + Copegus 800 mg (N = 207)	Pegasys + Copegus 1000 or 1200 mg (N = 280)	Pegasys + Copegus 800 mg (N = 361)	Pegasys + Copegus 1000 or 1200 mg (N = 436)
Safety				
Clinical adverse event	8 (4%)	9 (3%)	51 (14%)	54 (12%)
Lab abnormality	2 (<1%)	3 (1%)	7 (2%)	12 (3%)
Death	0	1 (<1%)	1 (<1%)	1 (<1%)
Total	10 (5%)	13 (5%)	59 (16%)	67 (15%)
Nonsafety				
Insufficient therapeutic response	0	o	31 (9%)	24 (6%)
Refused treatment	1 (<1%)	3 (1%)	18 (5%)	20 (5%)
Failure to return	2 (<1%)	4 (1%)	7 (2%)	5 (1%)
Protocol violation[a]	0	1 (<1%)	1 (<1%)	0
Violation of entry criteria	1 (<1%)	0	0	1 (<1%)
Administrative or other	0	1 (<1%)	1 (<1%)	0
Total	4 (2%)	9 (3%)	58 (16%)	50 (11%)
Total prematurely withdrawn	**14 (7%)**	**22 (8%)**	**117 (32%)**	**117 (27%)**

[a]Patients assigned to 24 weeks of treatment who had an assessment at week 48 and patients assigned to 48 week of treatment who had an assessment at week 72..

Appendix 14 Statistical Pooled Analysis of Sustained Virological Response in Study NV15942, All Treated Patients

	Treatment Duration		Copegus Dose	
	24 Weeks (N=487)	48 Weeks (N=797)	800 mg (N=568)	1000/1200 mg (N=716)
Pooled Sustained Virological Response				
Odds ratio	1.32[a] (1.01, 1.73)		1.35[b] (1.05, 1.73)	
P-value	0.0393[c]		0.0177[d]	

Note: Patients received PEG-IFN alfa-2a (180 µg) and ribavirin (800 mg or 1000 or 1200 mg) for 24 weeks or 48 weeks. Data from patients receiving either 800 mg or 1000 or 1200 mg of ribavirin are pooled for the analysis of treatment duration. Data from patients being treated for either 24 or 48 weeks are pooled for the analysis of ribavirin dose.
[a] Ratio of the odds of a response in the group receiving 48 weeks of treatment to the odds of a response in the group receiving 24 weeks of treatment.
[b] Ratio of the odds of a response when treated with 1000 or 1200 mg of ribavirin to the odds of a response when treated with 800 mg of ribavirin.
[c] Assessed by Cochran-Mantel-Haenszel test stratified by a combination of region, HCV genotype, viral load, and ribavirin dose.
[d] Assessed by Cochran-Mantel-Haenszel test stratified by a combination of region, HCV genotype, viral load, and treatment duration.

Appendix 15 Statistical Pooled Analysis of Sustained Virological Response in Study NV15942, All Treated Patients
One HCV RNA Measurement 24 Weeks Posttreatment

	Treatment Duration		Copegus Dose	
	24 Weeks (N=487)	48 Weeks (N=797)	800 mg (N=568)	1000/1200 mg (N=716)
Pooled Sustained Virological Response				
Odds ratio	1.39[a] (1.07, 1.81)		1.38[b] (1.08, 1.77)	
P-value	0.0151[c]		0.0100[d]	

Note: Patients received PEG-IFN alfa-2a (180 µg) and ribavirin (800 mg or 1000 or 1200 mg) for 24 weeks or 48 weeks. Data from patients receiving either 800 mg or 1000 or 1200 mg of ribavirin are pooled for the analysis of treatment duration. Data from patients being treated for either 24 or 48 weeks are pooled for the analysis of ribavirin dose.
[a] Ratio of the odds of a response in the group receiving 48 weeks of treatment to the odds of a response in the group receiving 24 weeks of treatment.
[b] Ratio of the odds of a response when treated with 1000 or 1200 mg of ribavirin to the odds of a response when treated with 800 mg of ribavirin.
[c] Assessed by Cochran-Mantel-Haenszel test stratified by a combination of region, HCV genotype, viral load, and ribavirin dose.
[d] Assessed by Cochran-Mantel-Haenszel test stratified by a combination of region, HCV genotype, viral load, and treatment duration.

Appendix 16 Sustained Virological Response in Genotype Non-1 Patients with Cirrhosis in Study NV15801, All Treated Patients

	Pegasys		Pegasys + Copegus 1000 or 1200 mg		Intron A + Rebetol 1000 or 1200 mg	
	N	SVR	N	SVR	N	SVR
Genotypes 2 and 3	10	3 (30%)	16	10 (63%)	21	10 (48%)
Genotype 4	0		1	1 (100%)	1	0 (0%)
Genotype 6	0		1	1 (100%)	0	

Note: SVR = sustained virological response. SVR is determined based on two HCV RNA measurements <100 copies/mL measured ≥ 21 days apart using a lower time window of week 60.

Appendix 17 Sustained Virological Response in Genotype Non-1 Patients with Cirrhosis in Study NV15942, All Treated Patients

	24 Weeks Treatment				48 Weeks Treatment			
	Pegasys + Copegus 800 mg		Pegasys + Copegus 1000 or 1200 mg		Pegasys + Copegus 800 mg		Pegasys + Copegus 1000 or 1200 mg	
	N	SVR	N	SVR	N	SVR	N	SVR
Genotype 2	7	5 (71%)	18	15 (83%)	5	3 (60%)	18	14 (78%)
Low viral load	2	2 (100%)	3	3 (100%)	1	1 (100%)	3	2 (67%)
High viral load	5	3 (60%)	15	12 (80%)	4	2 (50%)	15	12 (80%)
Genotype 3	13	9 (69%)	21	14 (67%)	15	11 (73%)	15	10 (67%)
Low viral load	1	0 (0%)	5	4 (80%)	7	6 (86%)	3	2 (67%)
High viral load	12	9 (75%)	16	10 (63%)	8	5 (63%)	12	8 (67%)
Genotypes 2 & 3	20	14 (70%)	39	29 (74%)	20	14 (70%)	33	24 (73%)
Genotype 4	1	0 (0%)	4	3 (75%)	2	1 (50%)	4	4 (100%)
Low viral load	1	0 (0%)	4	3 (75%)	1	1 (100%)	4	4 (100%)
High viral load	0		0		1	0 (0%)	0	
Genotype 6	0		1	1 (100%)	2	0 (0%)	0	
Low viral load	0		1	1 (100%)	1	0 (0%)	0	
High viral load	0		0		1	0 (0%)	0	

Note: Low viral load = $\leq 2 \times 10^6$ copies/mL, high viral load = $>2 \times 10^6$ copies/mL, SVR = sustained virological response. SVR is determined based on two HCV RNA measurements <100 copies/mL measured ≥21 days apart using a lower time window of week 60.

Appendix 18 Sustained Virological Response in Genotype Non-1 Patients with Cirrhosis in Study NV15801, All Treated Patients

One HCV RNA Measurement 24 Weeks Posttreatment

	Pegasys		Pegasys + Copegus 1000 or 1200 mg		Intron A + Rebetol 1000 or 1200 mg	
	N	SVR	N	SVR	N	SVR
Genotypes 2 and 3	10	4 (40%)	16	10 (63%)	21	10 (48%)
Genotype 4	0		1	1 (100%)	1	0 (0%)
Genotype 6	0		1	1 (100%)	0	

Note: SVR = sustained virological response. SVR is determined based on one HCV RNA measurement <100 copies/mL measured on or after week 68.

Appendix 19 Sustained Virological Response in Genotype Non-1 Patients with Cirrhosis in Study NV15942, All Treated Patients

One HCV RNA Measurement 24 Weeks Posttreatment

	24 Weeks Treatment				48 Weeks Treatment			
	Pegasys + Copegus 800 mg		Pegasys + Copegus 1000 or 1200 mg		Pegasys + Copegus 800 mg		Pegasys + Copegus 1000 or 1200 mg	
	N	SVR	N	SVR	N	SVR	N	SVR
Genotype 2	7	5 (71%)	18	15 (83%)	5	3 (60%)	18	14 (78%)
Low viral load	2	2 (100%)	3	3 (100%)	1	1 (100%)	3	2 (67%)
High viral load	5	3 (60%)	15	12 (80%)	4	2 (50%)	15	12 (80%)
Genotype 3	13	9 (69%)	21	14 (67%)	15	9 (60%)	15	8 (53%)
Low viral load	1	0 (0%)	5	4 (80%)	7	5 (71%)	3	2 (67%)
High viral load	12	9 (75%)	16	10 (63%)	8	4 (50%)	12	6 (50%)
Genotypes 2 & 3	20	14 (70%)	39	29 (74%)	20	12 (60%)	33	22 (67%)
Genotype 4	1	0 (0%)	4	3 (75%)	2	1 (50%)	4	4 (100%)
Low viral load	1	0 (0%)	4	3 (75%)	1	1 (100%)	4	4 (100%)
High viral load	0		0		1	0 (0%)	0	
Genotype 6	0		1	1 (100%)	2	0 (0%)	0	
Low viral load	0		1	1 (100%)	1	0 (0%)	0	
High viral load	0		0		1	0 (0%)	0	

Note: Low viral load = $\leq 2 \times 10^6$ copies/mL, high viral load = $>2 \times 10^6$ copies/mL, SVR = sustained virological response. SVR is determined based on one HCV RNA measurement <100 copies/mL measured on or after week 44 for patients treated for 24 weeks and on or after week 68 for patients treated for 48 weeks.

Appendix 20 Incidence of Serious Adverse Events during Treatment and 24 Weeks Posttreatment in Study NV15801, Safety Population

Body System/ Adverse Event	Pegasys N = 223 No. (%)	Pegasys + Copegus 1000 or 1200 mg N = 451 No. (%)	Intron A + Rebetol 1000 or 1200 mg N = 443 No. (%)
ALL BODY SYSTEMS			
Total Pts with at Least one AE	26 (12)	53 (12)	38 (9)
Total Number of AEs	31	64	50
INFECTIONS & INFESTATIONS			
Total Pts With at Least one AE	6 (3)	13 (3)	4 (1)
CELLULITIS	2 (1)	1 (<1)	-
PNEUMONIA NOS	-	2 (<1)	1 (<1)
GASTROENTERITIS NOS	-	1 (<1)	1 (<1)
OTITIS EXTERNA (EXC BOIL OF MEATUS) NOS	-	2 (<1)	-
AMOEBIASIS NOS	1 (<1)	-	-
ARTHRITIS INFECTIVE NOS	-	1 (<1)	-
BRONCHIECTASIS NOS	-	1 (<1)	-
CERVICITIS	1 (<1)	-	-
LOWER RESPIRATORY TRACT INFECTION NOS	-	-	1 (<1)
NEUROSYPHILIS	-	1 (<1)	-
PNEUMONIA VIRAL NOS	1 (<1)	-	-
PYELONEPHRITIS NOS	-	-	1 (<1)
SINUSITIS NOS	-	1 (<1)	-
SKIN & SUBCUTANEOUS TISSUE ABSCESS	-	1 (<1)	-
STAPHYLOCOCCAL INFECTION NOS	-	1 (<1)	-
URINARY TRACT INFECTION NOS	-	1 (<1)	-
VIRAL INFECTION NOS	1 (<1)	-	-
Total Number of AEs	6	13	4
PSYCHIATRIC DISORDERS			
Total Pts With at Least one AE	2 (1)	6 (1)	13 (3)
DEPRESSION NOS	-	2 (<1)	6 (1)
SUICIDE ATTEMPT	1 (<1)	2 (<1)	4 (1)
SUICIDAL IDEATION	1 (<1)	-	2 (<1)
DRUG ABUSE	-	1 (<1)	1 (<1)
ALCOHOLISM	-	1 (<1)	-
BIPOLAR AFFECTIVE DISORDER	-	1 (<1)	-
DEPRESSION ENDOGENOUS	-	-	1 (<1)
DRUG DEPENDENCE	-	-	1 (<1)
DRUG WITHDRAWAL SYNDROME	-	-	1 (<1)
PARANOIA	-	-	1 (<1)
Total Number of AEs	2	7	17
GASTROINTESTINAL DISORDERS			
Total Pts With at Least one AE	2 (1)	8 (2)	8 (2)
ABDOMINAL PAIN NOS	-	3 (1)	2 (<1)
APPENDICITIS	-	1 (<1)	2 (<1)
DIARRHOEA NOS	1 (<1)	-	1 (<1)
ABDOMINAL ABSCESS NOS	-	1 (<1)	-
ABDOMINAL PAIN LOWER	-	-	1 (<1)
HAEMATEMESIS	-	-	1 (<1)
HAEMORRHOIDS	-	1 (<1)	-
INTESTINAL FISTULA	-	-	1 (<1)
NAUSEA	-	1 (<1)	-
OESOPHAGEAL REFLUX	1 (<1)	-	-
PERITONITIS BILIARY	-	-	1 (<1)
RECTAL BLEEDING	-	1 (<1)	-
Total Number of AEs	2	8	9

(Continued)

Appendix 20 Incidence of Serious Adverse Events during Treatment and 24 Weeks Posttreatment in Study NV15801, Safety Population (Cont.)

Body System/ Adverse Event	Pegasys N = 223 No. (%)	Pegasys + Copegus 1000 or 1200 mg N = 451 No. (%)	Intron A + Rebetol 1000 or 1200 mg N = 443 No. (%)
NEUROLOGICAL DISORDERS			
Total Pts With at Least one AE	2 (1)	5 (1)	2 (<1)
CLUSTER HEADACHES	1 (<1)	-	-
FACIAL PALSY	-	1 (<1)	-
HEADACHE NOS	-	1 (<1)	-
MIGRAINE	-	-	1 (<1)
PERIPHERAL NEUROPATHY NOS	-	-	1 (<1)
POLYNEUROPATHY NOS	1 (<1)	-	-
SYNCOPE	-	1 (<1)	-
TRIGEMINAL NEURALGIA	-	1 (<1)	-
VASOVAGAL ATTACK	-	1 (<1)	-
Total Number of AEs	2	5	2
BENIGN & MALIGNANT NEOPLASMS (INCLUDING CYSTS AND POLYPS)			
Total Pts With at Least one AE	3 (1)	2 (<1)	3 (1)
MALIGNANT HEPATIC NEOPLASM	1 (<1)	2 (<1)	-
COLONIC CANCER	-	-	1 (<1)
OESOPHAGEAL CANCER	-	-	1 (<1)
OVARIAN NEOPLASM NOS	-	-	1 (<1)
PARATHYROID TUMOUR	1 (<1)	-	-
PITUITARY TUMOUR BENIGN	1 (<1)	-	-
Total Number of AEs	3	2	3
GENERAL DISORDERS			
Total Pts With at Least one AE	1 (<1)	4 (1)	2 (<1)
PYREXIA	1 (<1)	2 (<1)	-
CHEST PAIN NOS	-	-	1 (<1)
FATIGUE	-	1 (<1)	-
HAEMORRHAGE NOS	-		1 (<1)
PAIN NOS	-	1 (<1)	-
Total Number of AEs	1	4	2
CARDIAC DISORDERS			
Total Pts With at Least one AE	3 (1)	3 (1)	-
ATRIAL FIBRILLATION	1 (<1)	1 (<1)	-
PERICARDITIS NOS	2 (1)	-	-
ARRHYTHMIA NOS	-	1 (<1)	-
MYOCARDIAL ISCHAEMIA	-	1 (<1)	-
Total Number of AEs	3	3	-
INJURY & POISONING			
Total Pts With at Least one AE	2 (1)	4 (1)	-
CARTILAGE INJURY	1 (<1)	-	-
DROWNING	1 (<1)	-	-
HEAD INJURY	-	1 (<1)	-
INJURY NOS	-	1 (<1)	-
RETINAL DETACHMENT	-	1 (<1)	-
ROAD TRAFFIC ACCIDENT	-	1 (<1)	-
Total Number of AEs	2	4	-
RESPIRATORY, THORACIC & MEDIASTINAL DISORDERS			
Total Pts With at Least one AE	-	3 (1)	2 (<1)
DYSPNOEA	-	1 (<1)	1 (<1)
ASTHMA	-	1 (<1)	-
HAEMOPTYSIS	-	-	1 (<1)
PNEUMOTHORAX NOS	-	1 (<1)	-
Total Number of AEs	-	3	2

(Continued)

Appendix 20 Incidence of Serious Adverse Events during Treatment and 24 Weeks Posttreatment in Study NV15801, Safety Population (Cont.)

Body System/ Adverse Event	Pegasys N = 223 No. (%)	Pegasys + Copegus 1000 or 1200 mg N = 451 No. (%)	Intron A + Rebetol 1000 or 1200 mg N = 443 No. (%)
MUSCULOSKELETAL, CONNECTIVE TISSUE & BONE DISORDERS			
Total Pts With at Least one AE	1 (<1)	2 (<1)	1 (<1)
ARTHRALGIA	1 (<1)	1 (<1)	-
INTERVERTEBRAL DISC LESION NOS	-	1 (<1)	-
MYALGIA	1 (<1)	-	-
POLYARTHRITIS	-	-	1 (<1)
Total Number of AEs	2	2	1
DISORDERS OF BLOOD & THE LYMPHATIC SYSTEM			
Total Pts With at Least one AE	1 (<1)	3 (1)	-
ANAEMIA NOS	-	2 (<1)	-
PANCYTOPENIA	-	1 (<1)	-
THROMBOCYTOPENIA	1 (<1)	-	-
Total Number of AEs	1	3	-
DISORDERS OF METABOLISM & NUTRITION			
Total Pts With at Least one AE	1 (<1)	-	3 (1)
DEHYDRATION	-	-	2 (<1)
DIABETES MELLITUS AGGRAVATED	1 (<1)	-	-
DIABETIC KETOACIDOSIS	-	-	1 (<1)
Total Number of AEs	1	-	3
HEPATO-BILIARY DISORDERS			
Total Pts With at Least one AE	1 (<1)	1 (<1)	2 (<1)
CHOLELITHIASIS	-	-	1 (<1)
HEPATIC DISORDER NOS	-	1 (<1)	-
HEPATOPULMONARY SYNDROME	-	-	1 (<1)
TRANSAMINASE NOS INCREASED	1 (<1)	-	-
Total Number of AEs	1	1	2
SKIN & SUBCUTANEOUS TISSUE DISORDERS			
Total Pts With at Least one AE	2 (1)	1 (<1)	1 (<1)
HAEMANGIOMA NOS	1 (<1)	-	
LICHEN PLANUS	1 (<1)	-	-
PSORIASIS	-	1 (<1)	-
SEBACEOUS CYST	-	-	1 (<1)
Total Number of AEs	2	1	1
DISORDERS OF THE EAR & LABYRINTH			
Total Pts With at Least one AE	-	3 (1)	-
DEAFNESS NOS	-	1 (<1)	-
TINNITUS	-	1 (<1)	-
VERTIGINOUS DISORDER	-	1 (<1)	-
VERTIGO NOS	-	1 (<1)	-
Total Number of AEs	-	4	-
ENDOCRINE DISORDERS			
Total Pts With at Least one AE	1 (<1)	2 (<1)	-
HYPOTHYROIDISM	1 (<1)	1 (<1)	-
HASHIMOTO'S DISEASE	-	1 (<1)	-
Total Number of AEs	1	2	-
VASCULAR DISORDERS			
Total Pts With at Least one AE	-	-	2 (<1)
HYPERTENSIVE HEART DISEASE NOS	-	-	1 (<1)
PULMONARY EMBOLISM	-	-	1 (<1)
VENOUS THROMBOSIS DEEP (LIMBS)	-	-	1 (<1)
Total Number of AEs	-	-	3

(Continued)

Appendix 20 Incidence of Serious Adverse Events during Treatment and 24 Weeks Posttreatment in Study NV15801, Safety Population (Cont.)

Body System/ Adverse Event	Pegasys N = 223 No. (%)	Pegasys + Copegus 1000 or 1200 mg N = 451 No. (%)	Intron A + Rebetol 1000 or 1200 mg N = 443 No. (%)
DISORDERS OF THE EYE			
Total Pts With at Least one AE	-	1 (<1)	1 (<1)
DIPLOPIA	-	-	1 (<1)
RETINAL HAEMORRHAGE	-	1 (<1)	-
Total Number of AEs	-	1	1
DISORDERS OF THE IMMUNE SYSTEM			
Total Pts With at Least one AE	1 (<1)	-	-
ANAPHYLACTIC SHOCK	1 (<1)	-	-
Total Number of AEs	1	-	-
DISORDERS OF THE REPRODUCTIVE SYSTEM AND BREAST			
Total Pts With at Least one AE	1 (<1)	-	-
UTERINE HAEMORRHAGE	1 (<1)	-	-
Total Number of AEs	1	-	-
SURGICAL & MEDICAL PROCEDURES			
Total Pts With at Least one AE	-	1 (<1)	-
CARDIAC PACEMAKER MALFUNCTION	-	1 (<1)	-
Total Number of AEs	-	1	-

Appendix 21 Number of Patients with Serious Infections in Study NV15801, Safety Population

Infection	Pegasys (N = 223)	Pegasys + Copegus 1000 or 1200 mg (N = 451)	Intron A + Rebetol 1000 or 1200 mg (N = 443)
Pneumonia	1	2	2
Bronchiectasis	0	1	0
Sinusitis	0	1	0
Cellulitis	2	1	0
Infected sebacious cyst	0	0	1
Skin abscess	0	1	0
Otitis externa	0	2	0
Appendicitis	0	1	2
Gastroenteritis	0	1	1
Abdominal abscess	0	1	0
Biliary peritonitis	0	0	1
Diarrhea	1	0	0
Epiglottitis	0	1	0
Cervicitis	1	0	0
Infectious arthritis	0	1	0
Neurosyphilis	0	1	0
Pyelonephritis	0	0	1
Urinary tract infection	0	1	0
Fever	0	1	0
Viral infection	1	0	0
Amoebiasis	1	0	0
Total No. of Infections	7	16	8
Total No. of Patients with Infections	7 (3.1%)	16 (3.5%)	8 (1.8%)

Appendix 22 Number and Percentage of Patients Who Withdrew from Treatment for Adverse Events or Laboratory Abnormalities in Study NV15801, Safety Population

Body System & Adverse Event	Pegasys N = 223 No. (%)	Pegasys + Copegus 1000 or 1200 mg N = 451 No. (%)	Intron A + Rebetol 1000 or 1200 mg N = 443 No. (%)
ALL BODY SYSTEMS			
Total Pts with at Least one AE	15 (7)	44 (10)	47 (11)
Total Number of AEs	15	45	48
PSYCHIATRIC DISORDERS			
Total Pts With at Least one AE	3 (1)	12 (3)	18 (4)
DEPRESSION NOS	1 (<1)	9 (2)	5 (1)
SUICIDE ATTEMPT	1 (<1)	2 (<1)	4 (1)
ANXIETY	1 (<1)	-	3 (1)
IRRITABILITY	-	-	2 (<1)
BIPOLAR AFFECTIVE DISORDER	-	1 (<1)	-
DEPRESSION AGGRAVATED	-	-	1 (<1)
DEPRESSION ENDOGENOUS	-	-	1 (<1)
EMOTIONAL INSTABILITY	-	1 (<1)	-
PANIC REACTION	-	-	1 (<1)
PARANOIA	-	-	1 (<1)
SUICIDAL IDEATION	-	-	1 (<1)
Total Number of AEs	3	13	19
DISORDERS OF BLOOD & THE LYMPHATIC SYSTEM			
Total Pts With at Least one AE	2 (1)	7 (2)	3 (1)
NEUTROPENIA	1 (<1)	2 (<1)	2 (<1)
THROMBOCYTOPENIA	1 (<1)	2 (<1)	-
ANAEMIA NOS	-	1 (<1)	1 (<1)
PANCYTOPENIA	-	1 (<1)	-
PLATELET COUNT DECREASED	-	1 (<1)	-
Total Number of AEs	2	7	3
GENERAL DISORDERS			
Total Pts With at Least one AE	2 (1)	3 (1)	5 (1)
FATIGUE	1 (<1)	2 (<1)	4 (1)
ASTHENIA	-	1 (<1)	-
INJECTION SITE INFLAMMATION	1 (<1)	-	
LETHARGY	-	-	1 (<1)
Total Number of AEs	2	3	5
SKIN & SUBCUTANEOUS TISSUE DISORDERS			
Total Pts With at Least one AE	2 (1)	3 (1)	5 (1)
DERMATITIS NOS	1 (<1)	2 (<1)	3 (1)
ECZEMA ASTEATOTIC	-	-	1 (<1)
LICHEN PLANUS	1 (<1)	-	-
PRURITUS	-	-	1 (<1)
RASH MACULO-PAPULAR	-	1 (<1)	-
Total Number of AEs	2	3	5
ENDOCRINE DISORDERS			
Total Pts With at Least one AE	-	1 (<1)	5 (1)
HYPOTHYROIDISM	-	1 (<1)	4 (1)
HYPERTHYROIDISM	-	-	1 (<1)
Total Number of AEs	-	1	5

(Continued)

Appendix 22 Number and Percentage of Patients Who Withdrew from Treatment for Adverse Events or Laboratory Abnormalities in Study NV15801, Safety Population (Cont.)

Body System & Adverse Event	Pegasys N = 223 No. (%)	Pegasys + Copegus 1000 or 1200 mg N = 451 No. (%)	Intron A + Rebetol 1000 or 1200 mg N = 443 No. (%)
MUSCULOSKELETAL, CONNECTIVE TISSUE & BONE DISORDERS			
Total Pts With at Least one AE	1 (<1)	3 (1)	1 (<1)
ARTHRALGIA	1 (<1)	1 (<1)	-
NECK PAIN	-	1 (<1)	-
POLYARTHRITIS	-	-	1 (<1)
RHEUMATOID ARTHRITIS	-	1 (<1)	-
Total Number of AEs	1	3	1
BENIGN & MALIGNANT NEOPLASMS (INCLUDING CYSTS AND POLYPS)			
Total Pts With at Least one AE	1 (<1)	1 (<1)	2 (<1)
MALIGNANT HEPATIC NEOPLASM	1 (<1)	1 (<1)	-
COLONIC CANCER	-	-	1 (<1)
OESOPHAGEAL CANCER	-	-	1 (<1)
Total Number of AEs	1	1	2
DISORDERS OF METABOLISM & NUTRITION			
Total Pts With at Least one AE	-	2 (<1)	2 (<1)
DIABETIC KETOACIDOSIS	-	-	1 (<1)
HYPERTRIGLYCERIDAEMIA	-	1 (<1)	-
RETINOPATHY DIABETIC	-	1 (<1)	-
WEIGHT DECREASE	-	-	1 (<1)
Total Number of AEs	-	2	2
NEUROLOGICAL DISORDERS			
Total Pts With at Least one AE	1 (<1)	2 (<1)	1 (<1)
NEURALGIC AMYOTROPHY	-	1 (<1)	-
PERIPHERAL NEUROPATHY NOS	-	-	1 (<1)
POLYNEUROPATHY NOS	1 (<1)	-	-
WEAKNESS	-	1 (<1)	-
Total Number of AEs	1	2	1
DISORDERS OF THE EYE			
Total Pts With at Least one AE	1 (<1)	1 (<1)	1 (<1)
DIPLOPIA	-	-	1 (<1)
RETINAL HAEMORRHAGE	-	1 (<1)	-
VISUAL ACUITY REDUCED	1 (<1)	-	-
Total Number of AEs	1	1	1
GASTROINTESTINAL DISORDERS			
Total Pts With at Least one AE	2 (1)	1 (<1)	-
APPENDICITIS	-	1 (<1)	-
COLITIS ULCERATIVE	1 (<1)	-	-
DIARRHOEA NOS	1 (<1)	-	-
Total Number of AEs	2	1	-
INVESTIGATIONS			
Total Pts With at Least one AE	-	2 (<1)	1 (<1)
BLOOD THYROID STIMULATING HORMONE DECREASED	-	1 (<1)	-
BLOOD THYROID STIMULATING HORMONE INCREASED	-	1 (<1)	-
HAEMOGLOBIN DECREASED	-	-	1 (<1)
Total Number of AEs	-	2	1
RESPIRATORY, THORACIC & MEDIASTINAL DISORDERS			
Total Pts With at Least one AE	-	1 (<1)	2 (<1)
DYSPNOEA	-	1 (<1)	2 (<1)
Total Number of AEs	-	1	2

(Continued)

Appendix 22 Number and Percentage of Patients Who Withdrew from Treatment for Adverse Events or Laboratory Abnormalities in Study NV15801, Safety Population (Cont.)

Body System & Adverse Event	Pegasys N = 223 No. (%)	Pegasys + Copegus 1000 or 1200 mg N = 451 No. (%)	Intron A + Rebetol 1000 or 1200 mg N = 443 No. (%)
HEPATOBILIARY DISORDERS			
Total Pts With at Least one AE	-	2 (<1)	-
GLUTAMIC-PYRUVATE TRANSAMINASE INCREASED	-	2 (<1)	-
Total Number of AEs	-	2	-
INFECTIONS & INFESTATIONS			
Total Pts With at Least one AE	-	1 (<1)	1 (<1)
GASTROENTERITIS NOS	-	-	1 (<1)
PNEUMONIA NOS	-	1 (<1)	-
Total Number of AEs	-	1	1
DISORDERS OF THE EAR & LABYRINTH			
Total Pts With at Least one AE	-	1 (<1)	-
TINNITUS	-	1 (<1)	-
Total Number of AEs	-	1	-
DISORDERS OF THE REPRODUCTIVE SYSTEM AND BREAST			
Total Pts With at Least one AE	-	1 (<1)	-
PENILE DISORDER NOS	-	1 (<1)	-
Total Number of AEs	-	1	-

Appendix 23 Number and Percentage of Patients Who Had Dose Modified for Adverse Events or Laboratory Abnormalities in Study NV15801, Safety Population

	Pegasys (N = 223)		Pegasys Copegus 1000 or 1200 mg (N = 451)		Intron A Rebetol 1000 or 1200 mg (N = 443)	
	Pegasys	Copegus Placebo	Pegasys	Copegus Active	Intron A	Rebetol
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Dose Modified						
AE or LAB Abnormalities	61 (27%)	46 (21%)	145 (32%)	181 (40%)	81 (18%)	164 (37%)
AE	14 (6%)	39 (17%)	48 (11%)	95 (21%)	47 (11%)	97 (22%)
LAB Abnormalities	54 (24%)	9 (4%)	111 (25%)	108 (24%)	36 (8%)	84 (19%)
ALT Disorder	1 (0%)		2 (0%)	1 (0%)	1 (0%)	
Anemia		8 (4%)	4 (1%)	99 (22%)	13 (3%)	83 (19%)
Neutropenia	38 (17%)		91 (20%)	6 (1%)	24 (5%)	1 (0%)
Thrombocytopenia	14 (6%)	1 (0%)	18 (4%)	2 (0%)	1 (0%)	
Other LAB Abnormalities	1 (0%)		4 (1%)	2 (0%)	2 (0%)	1 (0%)

Note: Patients who had dose withheld or reduced for administrative reasons are not included in this table.

Appendix 24 Common Adverse Events (≥10% of Patients) during Treatment and 24 Weeks Posttreatment in Study NV15942, Safety Population

Adverse Event	24 Weeks Pegasys + Copegus 800 mg N = 207 No. (%)	24 Weeks Pegasys + Copegus 1000 or 1200 mg N = 280 No. (%)	48 Weeks Pegasys + Copegus 800 mg N = 361 No. (%)	48 Weeks Pegasys + Copegus 1000 or 1200 mg N = 436 No. (%)
HEADACHE NOS	102 (49)	136 (49)	187 (52)	239 (55)
FATIGUE	98 (47)	135 (48)	182 (50)	211 (48)
MYALGIA	91 (44)	120 (43)	154 (43)	163 (37)
PYREXIA	81 (39)	114 (41)	156 (43)	173 (40)
INSOMNIA	69 (33)	99 (35)	146 (40)	146 (33)
NAUSEA	64 (31)	91 (33)	107 (30)	151 (35)
RIGORS	64 (31)	87 (31)	87 (24)	119 (27)
IRRITABILITY	59 (29)	76 (27)	96 (27)	112 (26)
ARTHRALGIA	50 (24)	70 (25)	106 (29)	105 (24)
ALOPECIA	53 (26)	74 (26)	106 (29)	92 (21)
PRURITUS	56 (27)	60 (21)	81 (22)	111 (25)
DEPRESSION NOS	43 (21)	42 (15)	79 (22)	104 (24)
DIARRHOEA NOS	44 (21)	46 (16)	65 (18)	96 (22)
DERMATITIS NOS	34 (16)	49 (18)	69 (19)	86 (20)
APPETITE DECREASED	30 (14)	41 (15)	66 (18)	91 (21)
COUGH	26 (13)	39 (14)	65 (18)	84 (19)
ASTHENIA	39 (19)	37 (13)	56 (16)	73 (17)
DIZZINESS (EXC VERTIGO)	34 (16)	40 (14)	53 (15)	72 (17)
DRY SKIN	26 (13)	35 (13)	49 (14)	75 (17)
INJECTION SITE INFLAMMATION	22 (11)	39 (14)	57 (16)	58 (13)
DYSPNOEA	28 (14)	32 (11)	42 (12)	66 (15)
BACK PAIN	19 (9)	38 (14)	50 (14)	44 (10)
ABDOMINAL PAIN UPPER	14 (7)	25 (9)	36 (10)	55 (13)
VOMITING NOS	18 (9)	23 (8)	44 (12)	43 (10)
CONCENTRATION IMPAIRMENT	16 (8)	31 (11)	35 (10)	44 (10)
ANXIETY	21 (10)	23 (8)	28 (8)	40 (9)
ANOREXIA	13 (6)	20 (7)	29 (8)	46 (11)
INJECTION SITE REACTION NOS	20 (10)	11 (4)	24 (7)	18 (4)

Appendix 25 Incidence of Serious Adverse Events during Treatment and 24 Weeks Posttreatment in Study NV15942, Safety Population

Body System & Adverse Event	24 Weeks Pegasys + Copegus 800 mg N = 207 No. (%)	24 Weeks Pegasys + Copegus 1000 or 1200 mg N = 280 No. (%)	48 Weeks Pegasys + Copegus 800 mg N = 361 No. (%)	48 Weeks Pegasys + Copegus 1000 or 1200 mg N = 436 No. (%)
ALL BODY SYSTEMS				
Total Pts with at Least one AE	7 (3)	19 (7)	33 (9)	44 (10)
Total Number of AEs	8	20	35	52
INFECTIONS & INFESTATIONS				
Total Pts With at Least one AE	1 (<1)	3 (1)	4 (1)	7 (2)
PYELONEPHRITIS NOS	-	1 (<1)	-	2 (<1)
CYSTITIS NOS	1 (<1)	-	-	-
GASTROINTESTINAL INFECTION NOS	-	-	-	1 (<1)
INFECTED SKIN ULCER	-	-	1 (<1)	-
LOWER RESPIRATORY TRACT INFECTION NOS	-	1 (<1)	-	-
OSTEOMYELITIS NOS	-	-	-	1 (<1)
PERIANAL ABSCESS	-	-	-	1 (<1)
PERITONSILLAR ABSCESS NOS	-	-	-	1 (<1)
PNEUMONIA NOS	-	-	1 (<1)	-
PNEUMONIA STREPTOCOCCAL	-	-	1 (<1)	-
PYELONEPHRITIS ACUTE NOS	-	-	-	1 (<1)
SEPTICAEMIA NOS	-	-	1 (<1)	-
UPPER RESPIRATORY TRACT INFECTION NOS	-	1 (<1)	-	-
URINARY TRACT INFECTION NOS	-	-	-	1 (<1)
Total Number of AEs	1	3	4	8
PSYCHIATRIC DISORDERS				
Total Pts With at Least one AE	1 (<1)	5 (2)	3 (<1)	4 (<1)
DEPRESSION NOS	-	2 (<1)	1 (<1)	1 (<1)
ALCOHOLISM	-	-	1 (<1)	-
ANXIETY	-	-	1 (<1)	-
DRUG ABUSE	-	1 (<1)	-	-
HYPOMANIA	-	-	1 (<1)	-
PARANOIA	-	1 (<1)	-	-
PARANOID PSYCHOSIS	-	-	-	1 (<1)
PERSONALITY DISORDER NOS	-	-	-	1 (<1)
PSYCHIATRIC DISORDER NOS	-	1 (<1)	-	-
PSYCHOSIS NOS	1 (<1)	-	-	-
SUICIDE (ACCOMPLISHED)	-	-	-	1 (<1)
Total Number of AEs	1	5	4	4
INJURY & POISONING				
Total Pts With at Least one AE		2 (<1)	2 (<1)	7 (2)
BURNS NOS	-	-	1 (<1)	1 (<1)
OVERDOSE NOS	-	1 (<1)	-	1 (<1)
BRAIN DAMAGE (TRAUMATIC)	-	-	-	1 (<1)
FOOT FRACTURE	-	-	-	1 (<1)
HEAD INJURY	-	-	-	1 (<1)
HIP FRACTURE	-	-	-	1 (<1)
INJURY NOS	-	-	-	1 (<1)
NON-ACCIDENTAL INJURY	-	1 (<1)	-	-
RETINAL DETACHMENT	-	-	-	1 (<1)
RIB FRACTURE	-	-	1 (<1)	-
Total Number of AEs	-	2	2	8
GENERAL DISORDERS				
Total Pts With at Least one AE	1 (<1)	-	4 (1)	4 (<1)
CHEST PAIN NOS	-	-	1 (<1)	2 (<1)
PYREXIA	1 (<1)	-	-	1 (<1)
ASTHENIA	-	-	1 (<1)	-
CHEST PAIN (NON-CARDIAC)	-	-	1 (<1)	-
DRUG TOXICITY NOS	-	-	-	1 (<1)
MUCOUS MEMBRANE DISORDER NOS	-	-	1 (<1)	-
PAIN IN LIMB	-	-	-	1 (<1)
Total Number of AEs	1	-	4	5
NEUROLOGICAL DISORDERS				
Total Pts With at Least one AE	-	1 (<1)	5 (1)	3 (<1)
SYNCOPE	-	-	2 (<1)	1 (<1)
HEADACHE NOS	-	1 (<1)	-	1 (<1)
BENIGN INTRACRANIAL HYPERTENSION	-	-	1 (<1)	-
ENTRAPMENT NEUROPATHY	-	-	1 (<1)	-
HEPATIC ENCEPHALOPATHY	-	-	1 (<1)	-
POLYRADICULOPATHY	-	-	-	1 (<1)
Total Number of AEs	-	1	5	3

(Continued)

Appendix 25 Incidence of Serious Adverse Events during Treatment and 24 Weeks Posttreatment in Study NV15942, Safety Population (Cont.)

Body System & Adverse Event	24 Weeks Pegasys + Copegus 800 mg N = 207 No. (%)	24 Weeks Pegasys + Copegus 1000 or 1200 mg N = 280 No. (%)	48 Weeks Pegasys + Copegus 800 mg N = 361 No. (%)	48 Weeks Pegasys + Copegus 1000 or 1200 mg N = 436 No. (%)
GASTROINTESTINAL DISORDERS				
Total Pts With at Least one AE	1 (<1)	-	2 (<1)	5 (1)
ABDOMINAL PAIN NOS	1 (<1)	-	1 (<1)	-
COLONIC PERFORATION	-	-	-	1 (<1)
ILEUS	-	-	1 (<1)	-
INGUINAL HERNIA	-	-	-	1 (<1)
PERITONITIS	-	-	-	1 (<1)
RECTAL BLEEDING	-	-	-	1 (<1)
UMBILICAL HERNIA	-	-	-	1 (<1)
Total Number of AEs	1	-	2	5
MUSCULOSKELETAL, CONNECTIVE TISSUE & BONE DISORDERS				
Total Pts With at Least one AE	1 (<1)	1 (<1)	2 (<1)	4 (<1)
ARTHRALGIA	-	1 (<1)	-	-
ARTHRALGIA AGGRAVATED	1 (<1)	-	-	-
CERVICAL DISC LESION	-	-	-	1 (<1)
INTERVERTEBRAL DISC LESION NOS	-	-	-	1 (<1)
JOINT SPRAIN	-	-	1 (<1)	-
RHEUMATOID ARTHRITIS	-	-	1 (<1)	-
ROTATOR CUFF SYNDROME	-	-	-	1 (<1)
SYSTEMIC LUPUS ERYTHEMATOSUS	-	-	-	1 (<1)
Total Number of AEs	1	1	2	4
BENIGN & MALIGNANT NEOPLASMS (INCLUDING CYSTS AND POLYPS)				
Total Pts With at Least one AE	-	2 (<1)	1 (<1)	2 (<1)
CARCINOID TUMOUR	-	-	-	1 (<1)
CARCINOMA NOS	-	1 (<1)	-	-
MALIGNANT BREAST NEOPLASM	-	-	1 (<1)	-
OVARIAN CANCER	-	1 (<1)	-	-
UTERINE FIBROIDS	-	-	-	1 (<1)
Total Number of AEs	-	2	1	2
DISORDERS OF THE IMMUNE SYSTEM				
Total Pts With at Least one AE	1 (<1)	1 (<1)	2 (<1)	1 (<1)
SARCOIDOSIS NOS	1 (<1)	1 (<1)	2 (<1)	1 (<1)
Total Number of AEs	1	1	2	1
VASCULAR DISORDERS				
Total Pts With at Least one AE	-	-	1 (<1)	3 (<1)
ACUTE CIRCULATORY FAILURE	-	-	-	1 (<1)
SUBARACHNOID HAEMORRHAGE	-	-	-	1 (<1)
TRANSIENT ISCHAEMIC ATTACK	-	-	-	1 (<1)
VENOUS THROMBOSIS DEEP (LIMBS)	-		1 (<1)	-
Total Number of AEs	-	-	1	3
CARDIAC DISORDERS				
Total Pts With at Least one AE	-	-	1 (<1)	2 (<1)
ANGINA PECTORIS	-	-	-	1 (<1)
ATRIAL FIBRILLATION	-	-	-	1 (<1)
ENDOCARDITIS NOS	-	-	1 (<1)	-
Total Number of AEs	-	-	1	2
DISORDERS OF BLOOD & THE LYMPHATIC SYSTEM				
Total Pts With at Least one AE	-	-	1 (<1)	2 (<1)
APLASTIC ANAEMIA	-	-	-	1 (<1)
HAEMOLYTIC ANAEMIA NOS	-	-	-	1 (<1)
NEUTROPENIA	-	-	1 (<1)	-
Total Number of AEs	-	-	1	2
DISORDERS OF METABOLISM & NUTRITION				
Total Pts With at Least one AE	1 (<1)	-	2 (<1)	-
DEHYDRATION	-	-	1 (<1)	-
DIABETES MELLITUS NOS	1 (<1)	-	-	-
WEIGHT DECREASE	-	-	1 (<1)	-
Total Number of AEs	1	-	2	-

(Continued)

Appendix 25 Incidence of Serious Adverse Events during Treatment and 24 Weeks Posttreatment in Study NV15942, Safety Population (Cont.)

Body System & Adverse Event	24 Weeks Pegasys + Copegus 800 mg N = 207 No. (%)	24 Weeks Pegasys + Copegus 1000 or 1200 mg N = 280 No. (%)	48 Weeks Pegasys + Copegus 800 mg N = 361 No. (%)	48 Weeks Pegasys + Copegus 1000 or 1200 mg N = 436 No. (%)
HEPATO-BILIARY DISORDERS				
Total Pts With at Least one AE	-	2 (<1)	1 (<1)	-
BILIARY COLIC	-	2 (<1)	-	-
HEPATITIS NOS	-	-	1 (<1)	-
Total Number of AEs	-	2	1	-
SKIN & SUBCUTANEOUS TISSUE DISORDERS				
Total Pts With at Least one AE	-	2 (<1)	-	1 (<1)
ECZEMA NOS	-	1 (<1)	-	-
LEG ULCER (EXC VARICOSE)	-	-	-	1 (<1)
PRURITUS	-	1 (<1)	-	-
Total Number of AEs	-	2	-	1
RENAL & URINARY DISORDERS				
Total Pts With at Least one AE	1 (<1)	-	-	1 (<1)
LOIN PAIN	-	-	-	1 (<1)
RENAL IMPAIRMENT NOS	1 (<1)	-	-	-
Total Number of AEs	1	-	-	1
SURGICAL & MEDICAL PROCEDURES				
Total Pts With at Least one AE	-	1 (<1)	-	1 (<1)
POST-OPERATIVE HAEMORRHAGE	-	1 (<1)	-	-
POST-OPERATIVE WOUND INFECTION	-	-	-	1 (<1)
Total Number of AEs	-	1	-	1
CONGENITAL AND FAMILIAL/GENETIC DISORDERS				
Total Pts With at Least one AE	-	-	-	1 (<1)
CEREBRAL PALSY	-	-	-	1 (<1)
Total Number of AEs	-	-	-	1
DISORDERS OF THE EAR & LABYRINTH				
Total Pts With at Least one AE	-	-	1 (<1)	-
VERTIGO POSITIONAL	-	-	1 (<1)	-
Total Number of AEs	-	-	1	-
DISORDERS OF THE EYE				
Total Pts With at Least one AE	-	-	1 (<1)	-
OPTIC NERVE OEDEMA	-		1 (<1)	-
Total Number of AEs	-	-	1	-
DISORDERS OF THE REPRODUCTIVE SYSTEM AND BREAST				
Total Pts With at Least one AE	-	-	-	1 (<1)
OVARIAN CYST RUPTURED	-	-	-	1 (<1)
Total Number of AEs	-	-	-	1
RESPIRATORY, THORACIC & MEDIASTINAL DISORDERS				
Total Pts With at Least one AE	-	-	1 (<1)	-
DYSPNOEA	-	-	1 (<1)	-
Total Number of AEs	-	-	1	-

Appendix 26 Number of Patients with Serious Infections in Study NV15942, Safety Population

	24 Weeks Treatment		48 Weeks Treatment	
Infection	Pegasys + Copegus 800 mg (N = 207)	Pegasys + Copegus 1000 or 1200 mg (N = 280)	Pegasys + Copegus 800 mg (N = 361)	Pegasys + Ribavirin 1000 or 1200 mg (N = 436)
Pyelonephritis	0	1	0	3
Cystitis	1	0	0	0
Urinary tract infection	0	0	0	1
Pneumonia	0	0	2	0
Lower respiratory tract infection	0	1	0	0
Upper respiratory tract infection	0	1	0	0
Gastrointestinal infection	0	0	0	1
Peritonitis	0	0	0	1
Infected anal skin ulcer	0	0	1	0
Perianal abscess	0	0	0	1
Peritonsillar abscess	0	0	0	1
Leg ulcer	0	0	0	1
Postoperative wound infection	0	0	0	1
Osteomyelitis	0	0	0	1
Endocarditis	0	0	1	0
Septicemia	0	0	1	0
Total No. of Infections	1	3	5	11
Total No. of Patients with Infections	1 (0.5%)	3 (1.1%)	5 (1.4%)	10 (2.3%)

Appendix 27 Number and Percentage of Patients Who Withdrew from Treatment for Adverse Events or Laboratory Abnormalities in Study NV15942, Safety Population

Body System & Adverse Event	24 Weeks Pegasys + Copegus 800 mg N = 207 No. (%)	24 Weeks Pegasys + Copegus 1000 or 1200 mg N = 280 No. (%)	48 Weeks Pegasys + Copegus 800 mg N = 361 No. (%)	48 Weeks Pegasys + Copegus 1000 or 1200 mg N = 436 No. (%)
ALL BODY SYSTEMS				
Total Pts with at Least one AE	10 (5)	13 (5)	59 (16)	67 (15)
Total Number of AEs	12	13	65	73
PSYCHIATRIC DISORDERS				
Total Pts With at Least one AE	6 (3)	2 (<1)	13 (4)	19 (4)
DEPRESSION NOS	5 (2)	2 (<1)	3 (<1)	8 (2)
AGGRESSION	-	-	1 (<1)	2 (<1)
IRRITABILITY	-	-	1 (<1)	2 (<1)
MOOD SWINGS	-	-	3 (<1)	-
ALCOHOLISM	-	-	2 (<1)	-
ANXIETY	-	-	-	2 (<1)
HYPOMANIA	-	-	1 (<1)	1 (<1)
LIBIDO DECREASED	-	-	2 (<1)	-
DEPRESSED MOOD	-	-	-	1 (<1)
EMOTIONAL INSTABILITY	-	-	-	1 (<1)
PSYCHIATRIC DISORDER NOS	-	-	-	1 (<1)
PSYCHOSIS NOS	1 (<1)	-	-	-
SUICIDE (ACCOMPLISHED)	-	-	-	1 (<1)
Total Number of AEs	6	2	13	19
GENERAL DISORDERS				
Total Pts With at Least one AE	1 (<1)	1 (<1)	7 (2)	10 (2)
FATIGUE	-	1 (<1)	5 (1)	4 (<1)
ASTHENIA	1 (<1)	-	2 (<1)	3 (<1)
PYREXIA	-	-	-	2 (<1)
CHEST PAIN NOS	-	-	-	1 (<1)
Total Number of AEs	1	1	7	10
DISORDERS OF BLOOD & THE LYMPHATIC SYSTEM				
Total Pts With at Least one AE	2 (<1)	1 (<1)	6 (2)	8 (2)
NEUTROPENIA	1 (<1)	1 (<1)	3 (<1)	4 (<1)
THROMBOCYTOPENIA	1 (<1)	-	1 (<1)	1 (<1)
ANAEMIA NOS	-	-	1 (<1)	1 (<1)
BLOOD NEUTROPHIL COUNT DECREASED	-	-	2 (<1)	-
APLASTIC ANAEMIA	-	-	-	1 (<1)
HAEMOLYTIC ANAEMIA NOS	-	-	-	1 (<1)
Total Number of AEs	2	1	7	8
SKIN & SUBCUTANEOUS TISSUE DISORDERS				
Total Pts With at Least one AE	1 (<1)	4 (1)	7 (2)	5 (1)
DERMATITIS NOS	-	1 (<1)	1 (<1)	2 (<1)
PRURITUS	-	1 (<1)	2 (<1)	1 (<1)
ALOPECIA	1 (<1)	-	2 (<1)	-
DERMATITIS ATOPIC	-	-	1 (<1)	-
ECZEMA NOS	-	1 (<1)	-	-
NIGHT SWEATS	1 (<1)	-	-	-
PSORIASIS	-	-	1 (<1)	-
RASH GENERALISED	-	1 (<1)	-	-
TONGUE OEDEMA	-	-	-	1 (<1)
TOXICODERMA	-	-	-	1 (<1)
Total Number of AEs	2	4	7	5
MUSCULOSKELETAL, CONNECTIVE TISSUE & BONE DISORDERS				
Total Pts With at Least one AE	-	-	5 (1)	4 (<1)
MYALGIA	-	-	2 (<1)	1 (<1)
ARTHRALGIA	-	-	1 (<1)	1 (<1)
ARTHRITIS NOS	-	-	1 (<1)	-
BACK PAIN	-	-	1 (<1)	-
BONE PAIN	-	-	1 (<1)	-
MUSCULOSKELETAL PAIN	-	-	-	1 (<1)
RHEUMATOID ARTHRITIS	-	-	1 (<1)	-
SYSTEMIC LUPUS ERYTHEMATOSUS	-	-	-	1 (<1)
Total Number of AEs	-	-	7	4

(Continued)

Appendix 27 Number and Percentage of Patients Who Withdrew from Treatment for Adverse Events or Laboratory Abnormalities in Study NV15942, Safety Population (Cont.)

Body System & Adverse Event	24 Weeks Pegasys + Copegus 800 mg N = 207 No. (%)	24 Weeks Pegasys + Copegus 1000 or 1200 mg N = 280 No. (%)	48 Weeks Pegasys + Copegus 800 mg N = 361 No. (%)	48 Weeks Pegasys + Copegus 1000 or 1200 mg N = 436 No. (%)
ENDOCRINE DISORDERS				
Total Pts With at Least one AE	-	-	3 (<1)	6 (1)
HYPERTHYROIDISM	-	-	1 (<1)	5 (1)
HYPOTHYROIDISM	-	-	2 (<1)	1 (<1)
Total Number of AEs	-	-	3	6
GASTROINTESTINAL DISORDERS				
Total Pts With at Least one AE	-	1 (<1)	5 (1)	3 (<1)
NAUSEA	-	-	2 (<1)	1 (<1)
ABDOMINAL PAIN NOS	-	1 (<1)	-	-
COLONIC PERFORATION	-	-	-	1 (<1)
DIARRHOEA NOS	-	-	-	1 (<1)
DRY MOUTH	-	-	1 (<1)	-
ILEUS	-	-	1 (<1)	-
TOOTH DISORDER NOS	-	-	1 (<1)	-
Total Number of AEs	-	1	5	3
HEPATOBILIARY DISORDERS				
Total Pts With at Least one AE	-	2 (<1)	1 (<1)	5 (1)
GLUTAMIC-PYRUVATE TRANSAMINASE INCREASED	-	1 (<1)	-	4 (<1)
HEPATIC FUNCTION ABNORMAL NOS	-	-	-	1 (<1)
HEPATITIS NOS	-	-	1 (<1)	-
HYPERBILIRUBINAEMIA	-	1 (<1)	-	-
Total Number of AEs	-	2	1	5
NEUROLOGICAL DISORDERS				
Total Pts With at Least one AE	1 (<1)	-	4 (1)	3 (<1)
BENIGN INTRACRANIAL HYPERTENSION	-	-	1 (<1)	-
DIZZINESS (EXC VERTIGO)	-	-	-	1 (<1)
HEADACHE NOS	-	-	-	1 (<1)
INSOMNIA	1 (<1)	-	-	-
LOSS OF CONSCIOUSNESS NOS	-	-	1 (<1)	-
PARAESTHESIA	-	-	1 (<1)	-
SYNCOPE	-	-	-	1 (<1)
WEAKNESS	-	-	1 (<1)	-
Total Number of AEs	1	-	4	3
DISORDERS OF METABOLISM & NUTRITION				
Total Pts With at Least one AE	-	-	2 (<1)	3 (<1)
WEIGHT DECREASE	-	-	1 (<1)	2 (<1)
DIABETES MELLITUS AGGRAVATED	-	-	1 (<1)	-
DIABETES MELLITUS NOS	-	-	-	1 (<1)
Total Number of AEs	-	-	2	3
INFECTIONS & INFESTATIONS				
Total Pts With at Least one AE	-	1 (<1)	3 (<1)	-
LOWER RESPIRATORY TRACT INFECTION NOS	-	1 (<1)	-	-
PNEUMONIA NOS	-	-	1 (<1)	-
SEPTICAEMIA NOS	-	-	1 (<1)	-
UPPER RESPIRATORY TRACT INFECTION NOS	-	-	1 (<1)	-
Total Number of AEs	-	1	3	-
CARDIAC DISORDERS				
Total Pts With at Least one AE	-	-	1 (<1)	2 (<1)
ATRIAL FIBRILLATION	-	-	-	1 (<1)
ENDOCARDITIS NOS	-	-	1 (<1)	-
TACHYCARDIA NOS	-	-	-	1 (<1)
Total Number of AEs	-	-	1	2
RESPIRATORY, THORACIC & MEDIASTINAL DISORDERS				
Total Pts With at Least one AE	-	-	1 (<1)	2 (<1)
COUGH	-	-	-	1 (<1)
DYSPNOEA EXERTIONAL	-	-	1 (<1)	-
NASOPHARYNGITIS	-	-	-	1 (<1)
Total Number of AEs	-	-	1	2

(Continued)

Appendix 27 Number and Percentage of Patients Who Withdrew from Treatment for Adverse Events or Laboratory Abnormalities in Study NV15942, Safety Population (Cont.)

Body System & Adverse Event	24 Weeks Pegasys + Copegus 800 mg N = 207 No. (%)	24 Weeks Pegasys + Copegus 1000 or 1200 mg N = 280 No. (%)	48 Weeks Pegasys + Copegus 800 mg N = 361 No. (%)	48 Weeks Pegasys + Copegus 1000 or 1200 mg N = 436 No. (%)
INJURY & POISONING				
Total Pts With at Least one AE	-	1 (<1)	-	1 (<1)
BRAIN DAMAGE (TRAUMATIC)	-	-	-	1 (<1)
HEAD INJURY	-	-	-	1 (<1)
OVERDOSE NOS	-	1 (<1)	-	-
Total Number of Aes	-	1	-	2
VASCULAR DISORDERS				
Total Pts With at Least one AE	-	-	1 (<1)	1 (<1)
SUBARACHNOID HAEMORRHAGE	-	-	-	1 (<1)
VENOUS THROMBOSIS DEEP (LIMBS)	-	-	1 (<1)	-
Total Number of AEs	-	-	1	1
BENIGN & MALIGNANT NEOPLASMS (INCLUDING CYSTS AND POLYPS)				
Total Pts With at Least one AE	-	-	1 (<1)	-
MALIGNANT BREAST NEOPLASM	-	-	1 (<1)	-
Total Number of AEs	-	-	1	-
DISORDERS OF THE EYE				
Total Pts With at Least one AE	-	-	1 (<1)	-
VISION BLURRED	-	-	1 (<1)	-
Total Number of AEs	-	-	1	-
DISORDERS OF THE IMMUNE SYSTEM				
Total Pts With at Least one AE	-	-	1 (<1)	-
SARCOIDOSIS NOS	-	-	1 (<1)	-
Total Number of AEs	-	-	1	-

Appendix 28 Common Adverse Events (≥ 10% of Patients) in Patients with Cirrhosis in Studies NV15801 and NV15942, Pooled Safety Population

Adverse Event	24 Weeks Pegasys + Copegus 800 mg N = 44	24 Weeks Pegasys + Copegus 1000 or 1200 mg N = 71	48 Weeks Pegasys + Copegus 800 mg N = 91	48 Weeks Pegasys + Copegus 1000 or 1200 mg N = 171	48 Weeks Intron A + Rebetol 1000 or 1200 mg N = 54
Fatigue	17 (39%)	41 (58%)	49 (54%)	89 (52%)	29 (54%)
Headache	20 (45%)	34 (48%)	45 (49%)	86 (50%)	32 (59%)
Pyrexia	17 (39%)	31 (44%)	39 (43%)	69 (40%)	28 (52%)
Myalgia	20 (45%)	31 (44%)	33 (36%)	66 (39%)	31 (57%)
Insomnia	16 (36%)	26 (37%)	39 (43%)	63 (37%)	23 (43%)
Nausea	14 (32%)	21 (30%)	27 (30%)	60 (35%)	22 (41%)
Rigors	14 (32%)	28 (39%)	28 (31%)	50 (29%)	24 (44%)
Irritability	13 (30%)	22 (31%)	31 (34%)	52 (30%)	15 (28%)
Arthralgia	17 (39%)	17 (24%)	28 (31%)	50 (29%)	9 (17%)
Alopecia	10 (23%)	19 (27%)	24 (26%)	38 (22%)	21 (39%)
Pruritus	15 (34%)	14 (20%)	25 (27%)	46 (27%)	12 (22%)
Injection site reaction	14 (32%)	16 (23%)	26 (29%)	44 (26%)	8 (15%)
Anorexia	9 (20%)	16 (23%)	21 (23%)	46 (27%)	11 (20%)
Diarrhea	10 (23%)	16 (23%)	22 (24%)	38 (22%)	10 (19%)
Dermatitis	7 (16%)	19 (27%)	19 (21%)	41 (24%)	5 (9%)
Depression	7 (16%)	11 (15%)	18 (20%)	32 (19%)	22 (41%)
Abdominal pain	5 (11%)	11 (15%)	22 (24%)	31 (18%)	12 (22%)
Cough	6 (14%)	13 (18%)	24 (26%)	29 (17%)	7 (13%)
Dyspnea	5 (11%)	11 (15%)	12 (13%)	29 (17%)	12 (22%)
Dizziness (except vertigo)	6 (14%)	7 (10%)	18 (20%)	25 (15%)	10 (19%)
Back pain	4 (9%)	12 (17%)	17 (19%)	22 (13%)	7 (13%)
Dry skin	4 (9%)	12 (17%)	9 (10%)	23 (13%)	7 (13%)
Asthenia	8 (18%)	7 (10%)	13 (14)	20 (12%)	6 (11%)
Nausea and vomiting	0	5 (7%)	10 (11%)	25 (15%)	14 (26%)
Anxiety	4 (9%)	6 (8%)	10 (11%)	24 (14%)	8 (15%)
Pain	3 (7%)	7 (10%)	13 (14%)	19 (11%)	8 (15%)
Rash	2 (5%)	6 (8%)	7 (8%)	19 (11%)	5 (9%)
Epistaxis	1 (2%)	8 (11%)	7 (8%)	18 (11%)	3 (6%)
Concentration impairment	2 (5%)	5 (7%)	5 (5%)	16 (9%)	7 (13%)
Dyspepsia	2 (5%)	7 (10%)	7 (8%)	15 (9%)	3 (6%)
Dry mouth	2 (5%)	4 (6%)	2 (2%)	19 (11%)	6 (11%)
Sinusitis	2 (5%)	7 (10%)	10 (11%)	13 (8%)	1 (2%)
Emotional disorders	2 (5%)	2 (3%)	10 (11%)	12 (7%)	4 (7%)
Muscle cramps	1 (2%)	7 (10%)	5 (5%)	10 (6%)	6 (11%)
Taste disturbance	1 (2%)	7 (10%)	8 (9%)	9 (5%)	1 (2%)
Memory impairment	3 (7%)	7 (10%)	4 (4%)	7 (4%)	3 (6%)
Weakness	1 (2%)	7 (10%)	3 (3%)	9 (5%)	4 (7%)
Libido decreased	1 (2%)	0	3 (3%)	5 (3%)	6 (11%)

Note: Percentages are based on N. Multiple occurrences of the same adverse event in one individual counted only once.