

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-546

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
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Office of Pharmacoepidemiology and Statistical Science
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21-546 / N000

Drug Name: REBETOL™ (ribavirin) 15 mg/kg/day
Oral Solution and Capsules

Indication(s): Treatment of pediatric chronic hepatitis C

Applicant: Schering Corporation

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TABLE OF CONTENTS

Page

List of Tables.....	3
List of Figures.....	4
1. Executive Summary.....	5
1.1 Conclusions and Recommendations.....	5
1.2 Brief Overview of Clinical Studies.....	5
1.3 Statistical Issues and Findings.....	6
2. Introduction.....	9
2.1 Overview.....	9
2.2 Data Sources.....	10
3. Statistical Evaluation.....	11
3.1 Evaluation of Efficacy.....	11
3.1.1 Study Designs.....	12
3.1.1.1 Study P00018—Dose-ranging Study.....	12
3.1.1.2 Study P00321—Single-arm, Open-label, Fixed Dose Study.....	14
3.1.2 Patient Disposition.....	17
3.1.3 Demographics and Baseline Characteristics.....	19
3.1.4 Applicant's Results and Statistical Reviewer's Findings.....	25
3.1.4.1 Hepatitis C Virologic Response.....	25
3.1.4.2 ALT.....	33
3.2 Evaluation of Safety.....	34
4. Findings in Special/Subgroup Populations.....	35
4.1 Gender, Race and Age.....	35
4.2 Other Special/Subgroup Populations.....	36
5. Summary and Conclusions.....	38
5.1 Statistical Issues and Collective Evidence.....	38
5.2 Conclusions and Recommendations.....	40

LIST OF TABLES

	Page
Table 1: Studies of INTRON A/REBETOL in Children with Chronic Hepatitis C	11
Table 2: Patient Disposition—Study P00321	17
Table 3: Patient Disposition—Study P00018 and P00321 combined	18
Table 4: Demographics and Baseline Characteristics—Study P00018 (Without Site 10)	20
Table 5: Demographics and Baseline Characteristics—Study P00321	23
Table 6: Sustained Hepatitis C Virologic Response Rates through 48 weeks of treatment plus 24 weeks of follow-up—Studies P00018 and P00321	26
Table 7: Sustained Hepatitis C Virologic Response Rates by Week of Conversion and by Genotype—Studies P00018 and P00321 pooled	27
Table 8: Sustained Virologic Response Rates by Baseline HCV RNA and Genotype — Studies P00018 and P00321	30
Table 9: Sustained Virologic Response Rates by Demographics (Age, Gender, Race) — Studies P00018 and P00321	35
Table 10: Sustained Virologic Response Rates by Age and by REBETOL (ribavirin) Formulation —Studies P00018 and P00321	36

**APPEARS THIS WAY
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LIST OF FIGURES

	Page
Figure 1: Sustained Hepatitis C Virologic Response Rates by Genotype and Week of Conversion to HCV Negativity.....	28
Figure 2: Sustained Hepatitis C Virologic Response Rates by Week of Conversion to HCV Negativity (Rebetol Capsules vs. and Baseline HCV RNA ≤ 2 million copies/mL vs. > 2 million copies/mL)	29
Figure 3: Mean Log ₁₀ HCV RNA copies/mL of Sustained Responders by Study Week	31
Figure 4: Mean Log ₁₀ HCV RNA copies/mL of Non-Responders by Study Week	32
Figure 5: Mean ALT (x ULN) of Sustained Responders with Abnormal Baseline ALT	33
Figure 6: Mean ALT (x ULN) of Non-Responders with Abnormal Baseline ALT	34

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

About 46% (54/118) of pediatric patients (age 3 to 16 years) with compensated chronic hepatitis C and detectable hepatitis C virus (HCV) RNA had a sustained virologic response to treatment with REBETOL (ribavirin) 15 mg/kg/day given in combination with INTRON A (interferon alpha-2b) 3 MIU/m² SC TIW.¹ A 95% confidence interval on the sustained response rate is (37% to 55%). This response rate is comparable to the sustained virologic response rate among previously untreated adults in a U.S. study in which response rate in adults receiving Intron A + Rebetol was 37% (85/228). Response rates in adults receiving Intron A alone was 12% (27/225).²

Majority of the pediatric patients had a sustained virologic response by Week 16 of treatment. HCV RNA among the sustained responders remained undetectable from the time they first responded through 24 weeks of follow-up post-treatment. Patients with genotype 1 HCV were less likely and slower to respond to the treatment than patients with genotypes 2, 3,4,5, or 6). There was no significant difference in response rates whether patients had baseline HCV RNA \leq 2 million copies/mL or $>$ 2 million copies/mL, or whether pediatric patients (ages 5 years and older) received REBETOL capsules or oral solution. Children under 5 years of age only received REBETOL oral solution with INTRON A.

1.2 Brief Overview of Clinical Studies

The focus of this statistical review was on the following two clinical studies conducted in the pediatric population:

- 1) An open-label, dose-ranging, Phase 1 study (P00018) to assess the safety, tolerability, pharmacokinetics, and antiviral activity of plus REBETOL 8, 12, or 15 mg/kg/day PO, in combination with INTRON A 3 MIU/m² SC (subcutaneous) TIW (three times weekly), and
- 2) an open-label, single-arm, multicenter, Phase 3 trial (P00321) that used the selected dose of 15 mg/kg/day REBETOL (in combination with INTRON A) based on the previous study, P00018.

Study P00018 was conducted in two parts in children with documented presence of HCV RNA and histologic evidence of active hepatitis. In first part, Cohort 1 (n=61) was

¹ SC = subcutaneous and TIW=three time weekly

² Clinical data in adults was reviewed previously in a separate NDA.

randomized to receive REBETOL 8, 12 or 15 mg/kg/day in combination with INTRON A 3 MIU/m². The dose of INTRON A in pediatric patients was determined based on safety data in a small pilot study. Based on the mean reduction in HCV RNA and tolerability profile, the dose of REBETOL 15 mg/kg/day was selected and carried forward for the second part of the study. In the second part (Cohort 2, n=35), the objective of Study P00018 was to measure multiple-dose trough pharmacokinetics and the efficacy of the combination of REBETOL 15 mg/kg/day + INTRON A.

Study P00321 was a single-arm, open label study in which all 70 patients received REBETOL 15 mg/kg/day. In Study P00018, all patients received REBETOL capsules (50 mg/capsule) and in Study P00321, patients were given REBETOL capsules or — depending on their weight.

In both studies, HCV RNA was detected using a PCR assay at an in-house laboratory in Schering Plough Research Institute, Union, New Jersey, USA. This assay had a lower limit of detection of 100 HCV RNA copies/mL.

1.3 Statistical Issues and Findings

Dose selection of REBETOL

This submission contained data in pediatric patients from two clinical studies: a two-part Phase 1 dose-ranging study, P00018, and a second larger Phase 3 study, P00321. In part 1 (Cohort 1) of Study P00018 a dose-ranging assessment was made to select one of the following doses of REBETOL: 8 mg/kg/day, 12 mg/kg/day, or 15 mg/kg/day. Based on the following endpoints in Cohort 1 of Study P00018: Week 4 pharmacokinetic assessments, serum HCV-RNA levels at Weeks 4 and 12, and safety through Week 12, the dose of 15 mg/kg/day was selected which also achieved the maximum mean reduction in HCV-RNA levels at Week 12 and had good tolerability. This data on Cohort 1 was previously reviewed in NDA 20-903 submitted on February 28, 2001.

In part 2 (Cohort 2) of Study P00018, all pediatric patients were assigned the REBETOL 15 mg/kg/day dose in combination with INTRON A 3 MIU/m². Multiple dose trough pharmacokinetics and the efficacy of the combination therapy were measured.

No comparators for assessing efficacy

Neither of the two studies had a comparator arm for the INTRON A + REBETOL combination therapy. Therefore efficacy was assessed mainly on a single arm of INTRON A 3 MIU/m² subcutaneous injection three times a week plus REBETOL 15 mg/kg/day (I/R combination therapy) capsules or —.

The FDA Statistical Reviewer pooled data on the REBETOL 15 mg/kg/day dose from Study P00018 (n=48) with data on the same dose in Study P00321 (n=70). The focus of reviewing efficacy data was to assess the antiviral activity of REBETOL 15 mg/kg/day dose in terms of a sustained virologic response through 48 weeks of treatment and 24

weeks of follow-up in 118 patients. Similarity of data between adults and pediatric patients were established through the pharmacokinetics profiles of REBETOL + INTRON A.

Exclusion of data from P00018 Site 10 due to quality auditing issues

In the efficacy analyses presented throughout this review, data from Site 10 in Study 00018 was excluded. This is because the Applicant reported in the NDA submission that there were discrepancies in the management and reporting of data from one investigational site under Protocol No. P00018. Data from Site 10 could not be verified. A total of 7 patients at Site 10 had received at least one dose of ribavirin 15 mg/kg/day. Two additional patients from this site receiving 8 mg/kg/day or 12 mg/kg/day of ribavirin were also excluded. Since the overall efficacy results do not change whether data from Site 10 was included or not, in this review we present the results after excluding data from Site 10.

Virologic Response and ALT changes in Pediatric Patients

Based on the efficacy data in Study P00018 and P00321, we conclude as follows:

1. Among the 118 pediatric patients of age 3 to 16 years with compensated chronic hepatitis C receiving REBETOL 15 mg/kg/day plus INTRON A 3 MIU/m² TIW, the proportion of patients with sustained virologic response was 46% (54/118).

A 95% confidence interval for the proportion of response is (36.8% to 54.8%). This rate is comparable to previously reviewed data on previously untreated adult patients with compensated chronic hepatitis C in a U.S. study. The response rate in adults receiving INTRON A + REBETOL was 37% (85/228) and those receiving INTRON A alone was 12% (27/225). In pediatric patients, no other comparator treatment such as INTRON A alone could be administered in a clinical trial.

2. The majority of pediatric patients who were sustained responders had responded by Week 16. However, there were differences in time to sustained response based on whether patients had genotype 1 HCV or other genotype HCV.
3. Patients with HCV genotype 1 had a significantly lower rate of response of 36% (95% confidence interval: 26% to 46%) as compared with patients with other genotype HCV of 2, 3, 4, 5, or 6 who had a response rate of 81% (95% confidence interval: 62%, 92%). Also, patients with other genotype HCV were more likely to respond as soon as Week 4 of treatment while patients with HCV genotype 1 could take as long as Week 32 to show a sustained response to treatment.
4. The sustained virologic response rates were similar regardless of whether patients had baseline HCV RNA \leq 2 million copies/mL or $>$ 2 copies/mL or whether patients received REBETOL capsules or oral solution.
5. Mean HCV RNA levels of patients who were sustained responders dropped by Week 8 to levels close to lower limit of assay detection (\approx 100 HCV RNA copies/mL) and

remained at low levels through 48 weeks of treatment and 24 weeks of follow-up.

6. Mean HCV RNA levels of patients who were not sustained responders also continued to decline through 48 weeks of treatment without reaching undetectable levels. However, during the off-therapy follow-up period of 24 weeks, the mean HCV RNA levels rose by about 3 log₁₀ HCV RNA copies/mL.
7. Mean ALT levels of patients who were sustained responders and had abnormal ALT levels at baseline normalized after Week 1 and remained normal through the entire 48 week on-treatment period and 24 week follow-up period. One patient who was an exception to this phenomenon was an 8-year old Caucasian male child who was receiving REBETOL — had ALT greater than 18xULN at Week 32.
8. Mean ALT levels of patients who were nonresponders and had abnormal ALT at baseline also reached normal levels during 48 weeks of treatment. However, mean ALT returned to abnormal levels during the off-treatment follow-up period of 24 weeks.
9. Virologic response rates were generally similar across male and female patients as well as across Caucasian and Hispanic patients (who were the majority). Children between 5 to 10 years (both inclusive) generally had a higher response rate (61%=28/46) than children 11 years and older (34%=22/64).

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2. INTRODUCTION

2.1 Overview

This is a priority review of the clinical data in hepatitis C infected pediatric patients as submitted in new drug application, NDA 21-546, serial number 000, for REBETOL™ (ribavirin).

REBETOL™ (ribavirin) capsules were previously approved by the Division of Antiviral Drug Products, FDA, in 1998 for use in combination with INTRON™ A for the treatment of chronic hepatitis C in adult patients (18 years or older) with compensated liver disease who have relapsed following alpha interferon therapy. The combination therapy of INTRON™ A/REBETOL™ (interferon alfa-2b, recombinant/ribavirin), 3 million IU injectable/200 mg capsule, was marketed under the name REBETRON™ Combination Therapy.

The applicant, Schering Corporation, is now seeking FDA approval to market REBETOL™ (ribavirin) capsules and — to be used in combination with INTRON™ A (interferon alfa-2b, recombinant) for the **treatment of chronic hepatitis C** among previously untreated **pediatric patients of age 3 years or older**.

The major change in the proposed indication is as follows:

REBETOL (ribavirin, USP) Capsules and — are indicated in combination with INTRON A (interferon alfa-2b, recombinant) Injection for the treatment of chronic hepatitis C in patients 3 years of age and older with compensated liver disease previously untreated with alpha interferon or in patients 18 years of age and older who have relapsed following alpha interferon therapy. ...

This submission contains the following two clinical studies conducted in the pediatric population, which will be the focus of this review:

- 1) An open-label, dose-ranging, Phase 1 study (P00018) to assess the safety, tolerability, pharmacokinetics, and antiviral activity of plus REBETOL 8, 12, or 15 mg/kg/day PO, in combination with INTRON A 3 MIU/m² SC (subcutaneous) TIW (three times weekly), and
- 2) an open-label, single-arm, multicenter, Phase 3 trial (P00321) that used the selected dose of 15 mg/kg/day REBETOL (in combination with INTRON A) based on the previous study, P00018.

2.2 Data Sources

This statistical review is based on data submitted in Studies P00018 and P00321.

The electronic submission of this NDA can be found on the internal network drive of _____

The clinical study report for Study P00018 is located at _____
and that for Study P000321 is at \ _____

The electronic datasets for Cohort 1 in Study P00018, for Cohort 2 in Study P00018, and for Study P00321 are under _____

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3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Table 1 below shows the design of the two clinical studies, P00018 and P00321 that were submitted in support of the claim.

Table 1:
 Studies of INTRON A/REBETOL in Children with Chronic Hepatitis C

Study	Description	Design	Doses	Treatment Duration and Follow-up	Subjects
P00018	Phase 1	Cohort 1: Open-label, uncontrolled, randomized, parallel-group	REBETOL 8, 12, or 15 mg/kg/day PO plus INTRON A 3 MIU/m ² SC TIW	48 weeks; 24 weeks follow-up	61 ^a
		Cohort 2: Open-label, uncontrolled	REBETOL 15 mg/kg/day PO plus INTRON A 3 MIU/m ² SC TIW	48 weeks; 24 weeks follow-up	35
P00321	Phase 3	Multicenter, open-label, fixed dose, single group	REBETOL 15 mg/kg/day PO plus INTRON A 3 MIU/m ² SC TIW	48 weeks; 24 weeks follow-up	70

a: 20 subjects from Cohort 1 received the 15 mg/kg/day REBETOL dose.
 NOTE: Total number of subjects receiving 15 mg/kg/day REBETOL dose = 20 + 35 + 70 = 125. After excluding data from Site 10, the total sample size is 17 + 31 + 70 = 118.

Source: Integrated Summary of Efficacy of NDA 21-546, SN000

Study P00018 was a two-part, Phase 1, open-label, study to assess the safety, tolerability, pharmacokinetics, and antiviral activity of three doses of REBETOL, namely, 8, 12, or 15 mg/kg/day in combination with INTRON A 3 MIU/m² SC TIW. This study was done in children with documented presence of HCV-RNA and histologic evidence of active hepatitis. The first part of study (Cohort 1) was a dose-ranging assessment to select a REBETOL dose for further evaluation of efficacy.

Further details of Study P00018 and Study P00321 designs are explained in the next section.

In the analyses presented throughout this review, data from Site 10 in Study 00018 was excluded. This is because the Applicant reported in the NDA submission that there were discrepancies in the management and reporting of data from Site 10 under Protocol No. P00018. Data from Site 10 could not be verified. Since the overall efficacy results do not change whether data from Site 10 was included or not, in this review we present the results after excluding data from Site 10.

3.1.1 Study Designs

3.1.1.1 Study P00018—Dose-ranging Study

Title: “Assessment of the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of the Combination of Intron™ A Plus Ribavirin in Pediatric Patients With Chronic Hepatitis C” was a multicenter study to be conducted at 15 sites in the U.S.A and 2 sites outside the U.S.A.

Treatment Duration: 48 weeks treatment and 24 weeks follow-up

Study Period: 12 January 1999 to 20 November 2000.

Study Objectives:

The study was designed to be conducted in 2 parts. The first part of the study (Cohort 1) was a dose-ranging PK/PD study to select a REBETOL dose for further evaluation of safety and efficacy in pediatric subjects. The second part of the study (Cohort 2) was to assess the safety and efficacy of the optimal dose in pediatric subjects.

Cohort 1: To assess the safety and tolerability of the combination of INTRON A plus REBETOL, measure the multiple-dose PK of INTRON A plus REBETOL, and examine the effect of INTRON A plus REBETOL on antiviral PD (HCV-RNA levels, ALT levels) in pediatric subjects with chronic hepatitis C (CHC).

Cohort 2: To assess the safety and tolerability of the combination of INTRON A plus REBETOL at the optimal dose, and examine the effect of INTRON A plus REBETOL at the optimal dose on antiviral PD (HCV-RNA levels, ALT levels) in pediatric subjects with CHC.

Population:

- Age 5-16-yr male or female.
- HCV-RNA positive by PCR.
- Liver biopsy compatible with a diagnosis of chronic hepatitis with no evidence of cirrhosis, obtained within 2 yr. prior to enrollment.
- No previous ribavirin treatment for hepatitis C.
- Could not be a nonresponder to prior interferon therapy.
- No parenteral antiviral or immunomodulatory therapy within the previous 6 months.
- Serum hepatitis B surface antigen negative and HIV negative.

- Chronic active hepatitis C with the required minimum hematologic and biochemical criteria.

Efficacy Endpoints

Safety was the primary endpoint; ribavirin and interferon alfa-2b pharmacokinetics were the secondary endpoints; serum ALT levels and HCV-RNA levels were tertiary endpoints.

Sample size

With a total of 120 subjects in this study, there is a >99% chance of at least one occurrence of any untoward event with a true underlying incidence rate of 5%. The chance is 70% if the underlying incidence rate is 1%. With a total of 80% in the 15-mg/kg dose group, there is a 98% chance of at least one occurrence of any untoward event with a true incidence rate of 5%. In addition the HCV-RNA response rate can be estimated within 11%.

Treatment assignment/Blinding

In Cohort 1, approximately 60 patients were to be centrally randomized to one of the following three treatment groups in a 1:1:1 ratio.

- Group I Intron® A solution 3 MIU/m² S.C. TIW plus ribavirin 8 mg/kg/day p.o.
- Group II Intron® A solution 3 MIU/m² S.C. TIW plus ribavirin 15 mg/kg/day p.o.
- Group III Intron® A solution 3 MIU/m² S.C. TIW plus ribavirin 12 mg/kg/day p.o.

Subjects will be stratified according to patient age at study entry (5-11 years old; ≥12-16 years old) to ensure similar proportions of each age cohort are allocated to each treatment group.

In Cohort 2, approximately 60 children will receive the dose selected from Cohort 1 data.

Data Analysis Methods

Adverse events will be tabulated by body system/organ class. Virologic responses over time will be summarized by treatment group.

Summary statistics (means, standard deviations and coefficients of variations) for the HCV-RNA titers will be provided at each sampling time for each treatment group.

Blood samples for HCV RNA were collected during screening, Weeks 1, 4, 12, 24, 26, 48, 52 (follow-up Week 4), and 72 (follow-up Week 24).

3.1.1.2 Study P00321—Single-arm, Open-label, Fixed Dose Study

Title: "SCH 18908: An Open-Label, Fixed Dose Study to Assess the Efficacy, Safety and Tolerability of the Combination of INTRON® A Plus Ribavirin in Pediatric Subjects With Chronic Hepatitis C."

Treatment Duration: 48 weeks treatment and 24 weeks follow-up

Study Period: 26 January, 2000 to 5 November, 2001.

Study Objectives: To assess the efficacy, safety and tolerability of the combination INTRON A 3 MIU/m² three times weekly plus REBETOL 15 mg/kg/day for 48 weeks in pediatric subjects with chronic hepatitis C.

Population

The patient population in Study P00321 was male and female pediatric subjects of age 3-16 years. These subjects had compensated chronic hepatitis C (HCV-RNA positive) and had previously not been treated with interferon, ribavirin, or combination interferon plus ribavirin.

Inclusion/Exclusion Criteria:

Some of the key eligibility criteria for patients to be enrolled in this study were as below.

- Pediatric male or female 3-16 years of age.
- Serum positive for HCV-RNA by (PCR — PCR) assay.
- A liver biopsy within 12 months prior to enrollment with features compatible with chronic hepatitis (a pathology report confirming the diagnosis of chronic hepatitis C with no evidence of cirrhosis).
- No prior interferon, ribavirin or combination interferon + ribavirin treatment.
- No immunomodulatory or antiviral treatment for chronic HCV infection within the previous 2 years.
- Serum hepatitis B surface antigen (HBsAg) negative and HIV negative.
- Chronic active hepatitis C (compensated liver disease) with the required minimum hematologic and biochemical criteria.

Efficacy Endpoints

The primary efficacy endpoint is the **proportion of subjects who have a sustained response to treatment, i.e., achieve sustained virologic response at the end of follow-up.**

The secondary efficacy variable is the normalization of ALT.

Definitions of responders

- Responder: A subject is classified as a responder at a given time point if HCV-RNA PCR is negative at that time point.
- Sustained Responder: A subject is classified as a sustained responder if the subject responds at 24 weeks of follow-up.
- Non-responder: A subject who does not meet the above criteria, including subjects who discontinue before the required HCV-RNA PCR evaluations are obtained, will be classified as non-responders.

Sample size

Approximately 100 subjects will be screened at approximately 23 study sites in order to enrolled about 60 subjects. With 60 subjects in this study, the response rate can be estimated within +/- 13% (based on an estimated sustained response rate of 50%).

Treatment assignment/Blinding

Since this is a single-arm, open-label study, all subjects who are eligible to participate in the study will be assigned sequentially within a study center and will receive the following treatment:

Intron® A solution 3 MIU/m² S.C. TIW plus ribavirin dose 15 mg/kg/day
p.o. given in two divided daily doses for 48 weeks.

INTRON A 3 MIU/m² injection is administered subcutaneously three times per week. Ribavirin 15 mg/kg/day is administered twice daily (BID) orally, with food. The total dose of ribavirin will be based on the subjects weight at entry and will not exceed 1200 mg/day for subjects weighing ≥75 kg. Ribavirin is available as either 200 mg capsules or 40 mg/mL.

Efficacy and Safety Analysis Methods

Efficacy analyses will be conducted on an intent-to-treat basis. The primary efficacy analysis will be to summarize the primary efficacy endpoint of loss of detectable serum HCV-RNA/PCR (<100 copies/mL) and the secondary endpoint of normalization of ALT levels.

Regarding safety analyses, adverse events and laboratory values will be summarized or tabulated by body system/organ class. Adverse event tabulations will include all adverse events and treatment emergent adverse events, which will be further classified by severity and relationship to treatment.

Treatment Evaluations during Treatment Weeks 1-48 and Follow-Up Weeks 4-24

Subjects will receive 48 weeks of treatment and will be followed for 24 weeks post treatment. Any subjects who are HCV-RNA positive at Treatment Week 24 may be withdrawn from treatment and entered into follow-up.

Subjects will be evaluated by the study staff at entry, Treatment Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, and Follow-Up Weeks 4, 12 and 24. The treatment visit evaluations will include clinical evaluations and serum (i.e., blood sample) collection for laboratory evaluations.

All laboratory assessments and HCV PCR assay will be performed by a central laboratory.

Laboratory evaluations include the following:

- Hematology – hemoglobin (Hgb), hematocrit (HCT), RBC, WBC with differential, platelet count, and reticulocytes
- Blood chemistry (complete 12-hour fasting at Treatment Weeks 12, 24, 40 and 48; abbreviated at other visits)
 - Non-fasting (abbreviated) - ALT, AST, GGT, creatinine, alkaline phosphatase, total bilirubin, urea nitrogen, total protein, albumin and uric acid.
 - 12-hour fasting (complete) – In addition to above, lipase, triglycerides, cholesterol, glucose, sodium, potassium, chloride, phosphorus, calcium, saturated transferrin and ferritin.
- Serum neutralizing antibody (SNA) and HCV RNA at Treatment Weeks 4, 8, 12, 16, 20, 24, 32, 40 and 48, and at Follow-up Weeks 4, 12, and 24.

In addition, the pretreatment liver biopsy must have been performed on the subject within 12 months prior to study entry.

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3.1.2 Patient Disposition

Table 2 below shows the disposition of patients in the Phase 3 pediatric Study P00321, through 48 weeks of treatment and 24 weeks of follow-up thereafter.

Table 2:
 Patient Disposition—Study P00321

	INTRON A 3 MIU/m ² TIW + REBETOL 15 mg/kg/day		
	ALL	REBETOL Capsules	REBETOL
Total number of subjects enrolled	70	15	55
Number treated (ITT) †	70	15	55
Randomized but not treated †	0	0	0
Completed study through Week 12	68 (97%)	15(100%)	53 (96%)
Discontinued during first 12 weeks	2 (3%)	0 (0%)	2 (4%)
Adverse event	2 (3%)	0 (0%)	2 (4%)
Completed study through Week 24	68 (97%)	15(100%)	53 (96%)
Discontinued during Week 13 to 24	0 (0%)	0 (0%)	0 (0%)
Completed study through Week 48	43 (61%)	7 (47%)	36 (66%)
Discontinued during Week 25 to 48	25 (36%)	8 (53%)	17 (31%)
Adverse event	3 (4%)	0 (0%)	3 (6%)
Treatment failure	20 (29%)	7 (47%)	13 (24%)
Lost to follow-up	0 (0%)	0 (0%)	0 (0%)
Personal reasons	1 (1%)	0 (0%)	1 (2%)
Non-compliance	1 (1%)	1 (7%)	0 (0%)
Protocol violation	0 (0%)	0 (0%)	0 (0%)
Other	0 (0%)	0 (0%)	0 (0%)
Completed treatment and 24 weeks follow-up	43 (61%)	7 (47%)	36 (66%)
Discontinued during follow-up period	0 (0%)	0 (0%)	0 (0%)

Source: Tables A-19.0 and A-19.1 in Section 14.1.3 of Clinical Study Report for Study P00321.

Of the 70 children that were enrolled in Study P00321, 15 of them received ribavirin 200 mg capsules and 55 received ribavirin 40 mg/mL which were given as a dose of 15 mg/kg/day. All 70 patients were assigned treatment and were treated.

As shown in the Table above, majority of the pediatric patients completed 24 weeks of treatment. However, after 24 weeks, about half (53%) of the patients receiving ribavirin capsules dropped out and about one-thirds (31%) of the patients receiving ribavirin dropped out. All patients who remained in the study through 48 weeks of treatment also completed 24 weeks of follow-up.

Statistical Reviewer's Comment:

Note that most of the discontinuations after 24 weeks of treatment were due to treatment failure. All of the treatment failures occurred between Weeks 25 through 48. About 61% (n=43) patients completed treatment through Week 48 and all of these patients also

completed 24 weeks of follow-up thereafter.

Table 3 below shows the disposition of all patients randomized to the REBETOL 15 mg/kg/day dose in Study P00018 and P00321 combined, through 48 weeks of treatment and 24 weeks of follow-up thereafter.

Table 3:
 Patient Disposition—Study P00018 and P00321 combined

	INTRON A 3 MIU/m ² TIW + REBETOL 15 mg/kg/day		
	ALL	REBETOL Capsules	REBETOL ~
Total number of subjects enrolled	118	63	55
Number treated (ITT) ‡	118	63	55
Randomized but not treated †	0	0	0
Completed study through Week 12	115 (98%)	62 (98%)	53 (96%)
Discontinued during first 12 weeks	3 (3%)	1 (2%)	2 (4%)
Adverse event	3 (3%)	0 (0%)	2 (4%)
Completed study through Week 24	113 (96%)	60(95%)	53 (96%)
Discontinued during Week 13 to 24	2 (2%)	2 (3%)	0 (0%)
Completed study through Week 48	69 (59%)	33 (52%)	36 (66%)
Discontinued during Week 25 to 48	44 (37%)	27 (43%)	17 (31%)
Adverse event	3 (3%)	0 (0%)	3 (6%)
Treatment failure	38 (32%)	25 (40%)	13 (24%)
Lost to follow-up	0 (0%)	0 (0%)	0 (0%)
Personal reasons	2 (2%)	1 (2%)	1 (2%)
Non-compliance	1 (1%)	1 (2%)	0 (0%)
Protocol violation	1 (<1%)	0 (0%)	0 (0%)
Other	0 (0%)	0 (0%)	0 (0%)
Completed treatment and 24 weeks follow-up	69 (59%)	33 (52%)	36 (66%)
Discontinued during follow-up period	0 (0%)	0 (0%)	0 (0%)

Source: Applicant's Results.

In the pooled data, 59% of the patients completed study on REBETOL 15 mg/kg/day + INTRON A through 48 weeks of treatment and the same proportion also completed 24 weeks of follow-up. Discontinuations between Week 24 and Week 48 were mainly due to treatment failures.

3.1.3 Demographics and Baseline Characteristics

As shown in Table 4, the demographics of the pediatric patients in Study P00018 (without Site 10) were as follows. (See Section 3.1.4.1 for explanation of why data from Site 10 was excluded.)

Patients in Study P00018 in Cohort 1 were randomized to receive INTRON A plus ribavirin doses of 8 mg/kg/day, or 12 mg/kg/day, or 15 mg/kg/day. Cohort 2 received the chosen dose of ribavirin 15 mg/kg/day.

- The median age of patients was about 11 years with age ranging from 5 years to 16 years.
- Majority of patients were male and majority were Caucasian in any group.
- The median body weight in any group varied from 34.1 kg to 45.8 kg.
- All of the children in Study P00018 received ribavirin capsules as — formulation was not available during the conduct of this study.

Some baseline characteristics of these patients were as below.

- In most of the patients the source of HCV exposure was either transfusion associated/parenteral or vertical transmission. The source of parenteral exposure excluded vertical transmission, but included blood products, past IV drug use, surgery, dental surgery or procedure, tattoo, and acupuncture.
- The median time since exposure to HCV was about 10 years.
- Majority of the patients (70% or larger) had HCV-RNA levels >2 million copies/mL and majority had HCV genotype 1.
- ALT levels at baseline ranged from 0.49 x ULN to 3.9 x ULN.

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Table 4: Demographics and Baseline Characteristics—Study P00018 (Without Site 10)

	COHORT 1			COHORT 2
	I+R 8 mg/kg/day (n=20)	I+R 12 mg/kg/day (n=19)	I+R 15 mg/kg/day (n=17)	I+R 15 mg/kg/day (n=31)
Age (years)				
Mean	11.2	10.9	10.8	11.4
Median	10.5	11	11	12
Range (min-max)	6 to 16	6 to 16	5 to 16	5 to 16
Age Range [n (%)]				
5-6 yrs.	2 (10)	2 (11)	1 (6)	3 (10)
7-9 yrs.	5 (25)	5 (26)	6 (35)	8 (26)
10-12 yrs.	5 (25)	7 (37)	4 (24)	6 (19)
13-15 yrs.	6 (30)	4 (21)	4 (24)	12 (39)
>15 yrs.	2 (10)	1 (5)	2 (12)	2 (6)
Gender [n(%)]				
Female	6 (30)	11 (58)	6 (35)	11 (35)
Male	14 (70)	8 (42)	11 (65)	20 (65)
Race [n (%)]				
Caucasian	15 (75)	12 (63)	14 (82)	24 (77)
Black	1 (5)	1 (5)	1 (6)	2 (6)
Asian	0	2 (11)	0	1 (3)
Hispanic	4 (19)	3 (16)	2 (12)	4 (13)
Other	0	1 (5)	0	0
Body Weight (kg)				
Mean	46.9	45.9	43.5	47.7
Median	39.4	38.3	34.1	45.8
Range (min-max)	23 to 91	20 to 99	18 to 80	19 to 95
Body Weight Range [n (%)]				
≤ 46 kg	12 (60)	12 (63)	11 (65)	16 (52)
>46-55 kg	1 (5)	2 (11)	0	4 (13)
>55 kg	7 (35)	5 (26)	6 (35)	11 (35)
Height (cm)				
Median	143.1	143.1	145	151.7
Range (min-max)	119 to 184	117 to 181	106 to 177	115 to 180
Source of HCV Exposure [n (%)]				
Transfusion associated/parenteral	12 (60)	8 (42)	10 (59)	14 (45)
Vertical transmission	7 (35)	9 (47)	7 (41)	14 (45)
Sporadic/Other	1 (5)	2 (11)	0	2 (6)
Missing				1 (3)

	COHORT 1			COHORT 2
	I+R 8 mg/kg/day (n=20)	I+R 12 mg/kg/day (n=19)	I+R 15 mg/kg/day (n=17)	I+R 15 mg/kg/day (n=31)
Years Since Exposure to HCV				
Median	10.2	9.8	9.1	11.6
Range (min-max)	2.1 to 16.7	1.3 to 16.9	3.5 to 17	1.3 to 16
HCV Genotype [n (%)]				
1	13 (65)	18 (95)	13 (77)	27 (87)
2/3	6 (30)	1 (5)	4 (24)	4 (13)
4	1 (5)	0	0	
HCV-RNA/PCR (copies/mL)				
Mean (geometric)	5,269,944	2,680,479	3,253,770	3,158,189
≤2 million (n, %)	5 (25)	6 (32)	5 (29)	10 (32)
>2 million (n, %)	15 (75)	13 (68)	12 (71)	21 (68)
ALT (xULN)				
Mean	1.7	1.3	1.4	1.4
Median	1.7	1.2	1.2	1.2
Range (min-max)				
AST (xULN)				
Mean	1.9	1.2	1.2	1.4
Median	1.6	1.1	1.1	1.3
Range (min-max)				
NOTE: I=INTRON A 3 MIU/m ² TIW, R= REBETOL (ribavirin)				

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The demographics of the pediatric patients in Study P00321 were as follows. (See Table 5 below.)

- The median age was 10.5 years with ages ranging between 3 years and >15 years (but up to 16 years).
- Approximately equal numbers of patients were males and females, and majority (80%) were Caucasian.
- The median body weight was 40.9 kg and ranged from 10 kg to 92 kg.
- Most of the children under 12 years of age took the ribavirin — while the older children took either ribavirin capsules or —

Some baseline characteristics of these patients were as below.

- In 61% of the subjects, the source of HCV exposure was vertical transmission, in 36% the source was transfusion associated, and in the remaining it was sporadic or other source.
- The median time since exposure was 10.4 years.
- The majority of patients were infected with HCV Genotype 1 (74%).
- Slightly more than one-half of subjects had baseline serum HCV-RNA levels \leq 2 million copies/mL (56%).
- ALT level was abnormal at baseline in 70% of subjects.
- Baseline biopsies were available on 69 out of the 70 patients. These were assessed by a central pathologist using the Knodell histologic activity index (HAI) scoring system. At baseline, majority of these subjects had evidence of mild to moderate liver injury (including inflammation, necrosis, and/or fibrosis) consistent with chronic hepatitis.

A few patients had relatively more advanced liver injury. Two patients (Patient IDs 21-002106, 25-002502) had marked bridging necrosis (Knodell score=4) and four patients (Patient IDs 05-000502, 25-002502, 34-003407, 37-003702) had bridging fibrosis (Knodell score=3).

None of the enrolled subjects had findings consistent with cirrhosis (i.e., Knodell fibrosis score=4).

Table 5: Demographics and Baseline Characteristics--Study P00321

	INTRON A 3MIU/m ² TIW + REBETOL 15 mg/kg/day		
	All Subjects (n=70)	REBETOL Capsules (n=15)	REBETOL <u> </u> (n=55)
Age (years)			
Mean	10.2	13.7	9.2
Median	10.5	14.0	10.0
Range (min-max)	3 to 16	9 to 16	3 to 16
Age Range [n (%)]			
3-6 yrs.	17 (24)	0	17 (31)
7-9 yrs.	11 (16)	1 (7)	10 (18)
10-12 yrs.	19 (27)	3 (20)	16 (29)
13-15 yrs.	16 (23)	7 (47)	9 (16)
>15 yrs.	7 (10)	4 (27)	3 (5)
Gender [n(%)]			
Female	34 (49)	5 (33)	29 (53)
Male	36 (51)	10 (67)	26 (47)
Race [n (%)]			
Caucasian	56 (80)	13 (87)	43 (78)
Black	2 (3)	1 (7)	1 (2)
Asian	3 (4)	0	3 (5)
Hispanic	8 (11)	1 (7)	7 (13)
Other	1 (1)	0	1 (2)
Body Weight (kg)			
Mean	40.8	65.6	34.0
Median	40.9	63.0	35.0
Range (min-max)	10 to 92	49 to 92	10 to 87
Body Weight Range [n (%)]			
≤ 46 kg	46 (66)	0	46 (84)
>46-55 kg	9 (13)	2 (13)	7 (13)
>55 kg	15 (21)	13 (87)	2 (4)
Height (cm)			
Mean	140.9	165.3	134.2
Median	146.0	164.0	135.4
Range (min-max)	87 to 179	152 to 179	87 to 167
Source of HCV Exposure [n (%)]			
Transfusion associated	25 (36)	3 (20)	22 (40)
Vertical transmission	43 (61)	11 (73)	32 (58)
Sporadic/Other	2 (3)	1 (7)	1 (2)
Years Since Exposure to HCV			
Mean	9.9	13.1	9.1
Median	10.4	14.3	9.2
Range (min-max)	0.8 to 16.9	1.4 to 16.9	0.8 to 16.4
Missing (n)	2	1	1

	INTRON A 3MIU/m ² TIW + REBETOL 15 mg/kg/day		
	All Subjects (n=70)	REBETOL Capsules (n=15)	REBETOL (n=55)
HCV Genotype [n (%)]			
1	52 (74)	10 (67)	42 (76)
2	9 (13)	3 (20)	6 (11)
3	8 (11)	1 (7)	7 (13)
4	1 (1)	1 (7)	0
HCV-RNA/PCR (copies/mL)			
Mean (geometric)	1,498,037	1,495,498	1,498,730
≤2 million (n, %)	39 (56)	8 (53)	31 (56)
>2 million (n, %)	31 (44)	7 (47)	24 (44)
Baseline ALT Level (n, %)			
Normal	21 (30)	5 (33)	16 (29)
Abnormal	49 (70)	10 (67)	39 (71)
ALT (xULN)			
Mean	1.3	1.1	1.3
Median	1.2	1.0	1.3
Range (min-max)			
AST (xULN)			
Mean	1.6	1.3	1.6
Median	1.5	1.2	1.6
Range (min-max)			
Baseline Knodell HAI score [n (%)]			
Bridging necrosis			
0 = none	10 (15%)	4 (29%)	6 (12%)
1 = mild	33 (51%)	6 (43%)	27 (53%)
3 = moderate	20 (31%)	3 (21%)	17 (33%)
4 = marked	2 (3%)	1 (7%)	1 (2%)
Missing	5	5	5
Parenchymal injury			
0 = none	8 (12%)	5 (36%)	3 (6%)
1 = mild	50 (77%)	8 (57%)	42 (82%)
3 = moderate	7 (11%)	1 (7%)	6 (12%)
Missing	5	—	—
Portal Inflammation			
0 = none	3 (5%)	2 (14%)	1 (2%)
1 = mild	25 (39%)	5 (36%)	20 (40%)
3 = moderate	36 (56%)	7 (50%)	29 (58%)
Missing	6	—	—
Fibrosis			
0 = none	5 (8%)	1 (7%)	4 (8%)
1 = portal	56 (86%)	12 (86%)	44 (86%)
3 = bridging	4 (6%)	1 (7%)	3 (6%)
4 = cirrhosis	none reported	—	—
Missing	5	—	—

3.1.4 Applicant's Results and Statistical Reviewer's Findings

3.1.4.1 Hepatitis C Virologic Response

The primary efficacy endpoint in both Studies P00018 and P00321 was proportion of subjects, who have a sustained response to treatment, i.e., proportion of patient who achieve sustained virologic response at the end of 24 weeks of follow-up.

Statistical Reviewer's Comments:

Definition of Sustained Virologic Response

Since the definition used by the Applicant for the primary efficacy endpoint was not explicitly given anywhere in the NDA submission, the FDA Statistical Reviewer (with concurrence from Medical Reviewers) used the following definition for a sustained responder at a given week.

- A subject is a sustained responder at a given week, if the subject has negative HCV RNA at that week and all the subsequent weeks through Week 24 of follow-up period.
- If a patient has a missing value between visits, then the last non-missing HCV RNA is carried forward to fill in the missing value.
- If a patient has positive HCV RNA ("blip") between two visits with undetectable HCV RNA, then the response is considered sustained provided that the detectable HCV RNA is of the same order of magnitude as limit of detection (i.e., $2 < \log_{10} \text{HCV RNA} < 3$ is allowed).
- If the patient's HCV RNA at last visit of follow-up Week 24 is missing or above limit of detection (≥ 100 copies/mL), then the patient is a non-responder, even if all the previous visits from baseline onwards were undetectable.

Assay used for detection of HCV RNA

When the dose-ranging study, P00018, was initiated the Applicant was using the assay by  for detection of HCV-RNA levels. During the course of this study, the Applicant started using a PCR assay at an in-house laboratory of Schering-Plough Research Institute (SPRI, the Applicant) in Union, New Jersey, USA. Since the Applicant wanted to use this in-house assay in subsequent studies (including P00321), samples from Study P00018 were assayed using both the  and SPRI Union assays.

Note that for the primary efficacy analysis, pooled data from Studies P00018 and P00321 using the SPRI assay is used. The lower limit of detection of SPRI assay is 100 HCV RNA copies/mL. However, results of this assay are used only in a qualitative manner, as the assay is not validated by FDA.

Exclusion of data from P00018 Site 10 due to quality auditing issues

In the efficacy analyses presented throughout this review, data from Site 10 in Study 00018 was excluded. This is because the Applicant reported in the NDA submission that there were discrepancies in the management and reporting of data from one investigational site under Protocol No. P00018 (Site 10, the _____)

Based on an audit of this site, the Applicant had decided that a subset of the data from Site 10 could not be verified. A total of 7 patients at Site 10 has received at least one dose of ribavirin 15 mg/kg/day. Two additional patients from this site were also excluded.

Since the overall efficacy results do not change whether data from Site 10 was included or not, we present the results after excluding data from Site 10.

The remaining part of this review will focus on efficacy data on 118 patients (excluding Site 10) in both Studies P00018 (n=48) and P00321 (n=70) who received the pediatric dose of 15 mg/kg ribavirin with INTRON A.

The FDA analysis of the primary efficacy results for sustained hepatitis C virologic response through end of 24 weeks of follow-up for each of the two studies, P00018 and P00321 are given in Table 6.

Table 6:
 Sustained Hepatitis C Virologic Response Rates
 through 48 weeks of treatment plus 24 weeks of follow-up—Studies P00018 and P00321

INTRON A 3 MIU/m ² and REBETOL 15 mg/kg/day			
	Study P00018 n=48	Study P00321 n=70	Pooled Studies P00018 and P00321 n=118
Sustained Responders	20 (42%)	34 (49%)	54 (46%)
Virologic Failures	28 (58%)	36 (51%)	64 (54%)
95% CI on response rate	(27.7%, 55.6%)†	(36.9%, 60.3%)†	(36.8%, 54.8%)†
NOTE:			
1. In this table, a subject is a sustained responder at a given week, if the subject has negative HCV RNA at that week and all the subsequent weeks through Week 24 of follow-up period.			
2. Percentages calculated are based on the total number of subjects in that group. Never responders are treated as failures.			
† Confidence interval based on normal approximation to binomial.			

Source: FDA Statistical Reviewer's analysis

The proportion of sustained responders among patients who received ribavirin 15 mg/kg/day along with INTRON A in Study P00018 was 42% and that in Study P000321 was 49%. The sustained response rate for the pooled data from the two studies was 46% at the end of 24 weeks of follow-up.

The FDA analysis of the primary efficacy results for sustained hepatitis C virologic response by week of conversion to HCV negativity through end of 24 weeks of follow-up for the pooled data from Studies P00018 and P00321 is given in Table 7.

Table 7:
 Sustained Hepatitis C Virologic Response Rates
 by Week of Conversion and by Genotype—Studies P00018 and P00321 pooled

INTRON A 3 MIU/m ² and REBETOL 15 mg/kg/day			
	All Subjects n=118	Genotype 1 n=92	Genotype Other (2/3 or 4/5/6) n=26
Week converted			
Treatment Week			
Baseline	1 (0.8%)	1 (1%)	0 (0%)
4	20 (17%)	6 (7%)	14 (54%)
8	15 (13%)	10 (11%)	5 (19%)
12	10 (8%)	9 (10%)	1 (4%)
16	4 (3%)	3 (3%)	1 (4%)
20	0 (0%)	0 (0%)	0 (0%)
24	1 (0.8%)	1 (1%)	0 (0%)
32	1 (0.8%)	1 (1%)	0 (0%)
36	0 (0%)	0 (0%)	0 (0%)
40	0 (0%)	0 (0%)	0 (0%)
48	0 (0%)	0 (0%)	0 (0%)
Follow-up Week			
4	1 (0.8%)	1 (1%)	0 (0%)
12	0 (0%)	0 (0%)	0 (0%)
24	1 (0.8%)	1 (1%)	0 (0%)
Sustained Responders	54 (46%)	33 (36%)	21 (81%)
Virologic Failures	64 (54%)	59 (64%)	5 (19%)
95% CI on response rate	(36.8% to 54.8%)†	(26.1%, 45.7%)†	(61.5%, 91.8%)‡
NOTE:			
3. In this table, a subject is a sustained responder at a given week, if the subject has negative HCV RNA at that week and all the subsequent weeks through Week 24 of follow-up period.			
4. Percentages calculated are based on the total number of subjects in that group. Never responders are treated as failures.			
5. Data from patients who received 15/mg/kg/day of ribavirin in Study P00018 is pooled with data from Study P00321 where all patients had received 15/mg/kg/day dose of ribavirin.			
† Confidence interval based on normal approximation to binomial.			
‡ Confidence interval based on Agresti-Coull method (add 2 successes and 2 failures) since binomial distribution is skewed and not well approximated by normal distribution.			

Source: FDA Statistical Reviewer's analysis

At the end of 24 weeks of follow-up post-treatment with ribavirin 15 mg/kg/day plus INTRON A 3 MIU/m², 46% (54/118) patients with hepatitis C had sustained response to treatment and their HCV RNA remained undetectable. The proportion of sustained responders with genotype 1 HCV (36%) was significantly lower than the proportion of sustained responders with other genotype HCV (81%).

Also, as shown in Figure 1, patients with other genotypes (2/3 or 4/5/6) responded to treatment earlier than patients with genotype 1. Majority of patients with genotypes 2, 3, 4, 5, or 6 who were responders had converted to HCV negativity by Week 4 and sustained response thereafter.

In comparison, time to first sustained response in patients with genotype 1 ranged from Week 4 to as late as Week 32. Most of the patients with genotype 1 had a sustained response by Week 16 of treatment. Two patients with genotype 1 had a time to first response as late as Week 52 (i.e., Week 4 of follow-up) and Week 72 (i.e., Week 24 of follow-up), respectively, because they had several relapses during the on-treatment period.

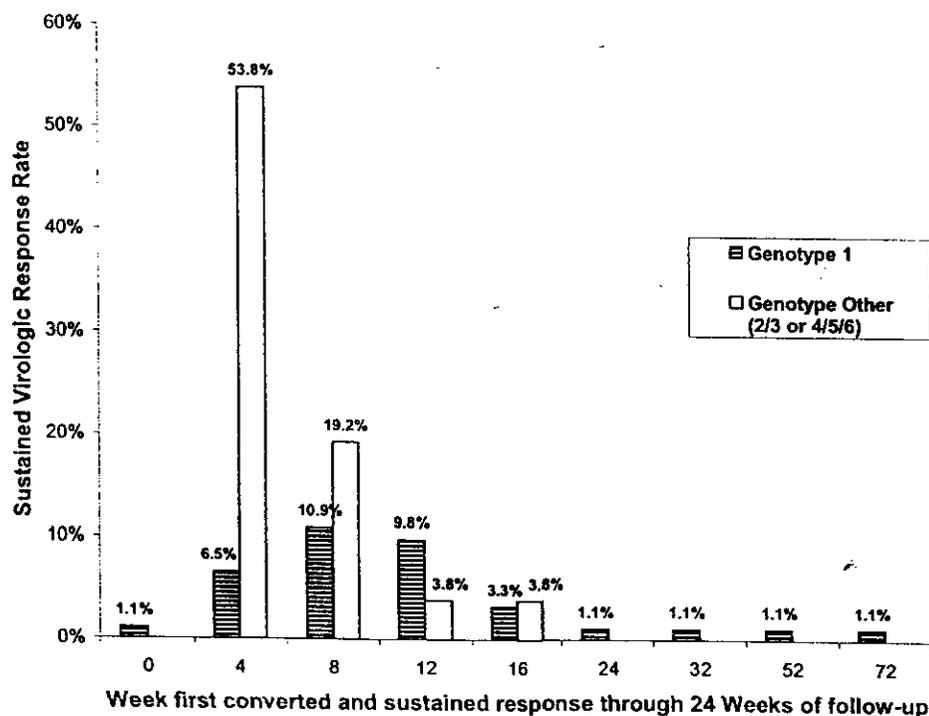


Figure 1: Sustained Hepatitis C Virologic Response Rates by Genotype and Week of Conversion to HCV Negativity

Statistical Reviewer's Comments:

We also compared the time to sustained response for other groups of interest, such as Capsules versus — , or Baseline HCV RNA ≤ 2 million copies/mL vs > 2 million copies/mL. These comparisons did not show any apparent differences in the patterns of time to response. See Figure 2.

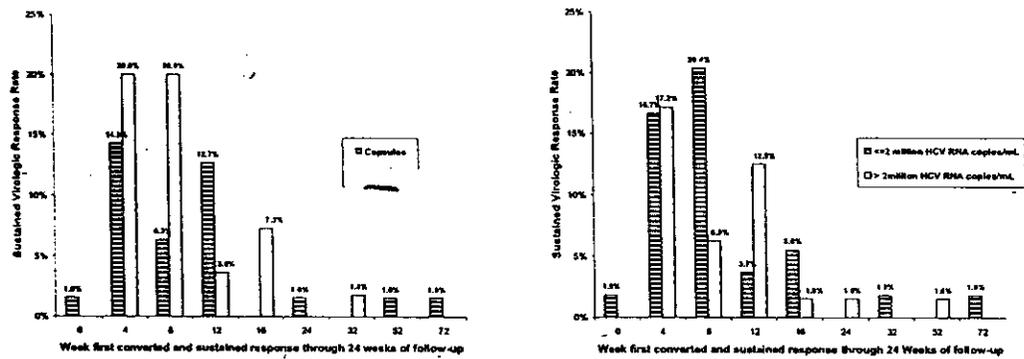


Figure 2: Sustained Hepatitis C Virologic Response Rates by Week of Conversion to HCV Negativity (Rebetol Capsules vs. [Symbol]) and Baseline HCV RNA ≤ 2 million copies/mL vs. > 2 million copies/mL)

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The sustained virologic response rates by the following baseline characteristics are shown in Table 8:

- 1) baseline HCV RNA,
- 2) HCV genotype (1 or other [2, 3, 4, 5, or 6]), and
- 3) baseline HCV RNA by Genotype.

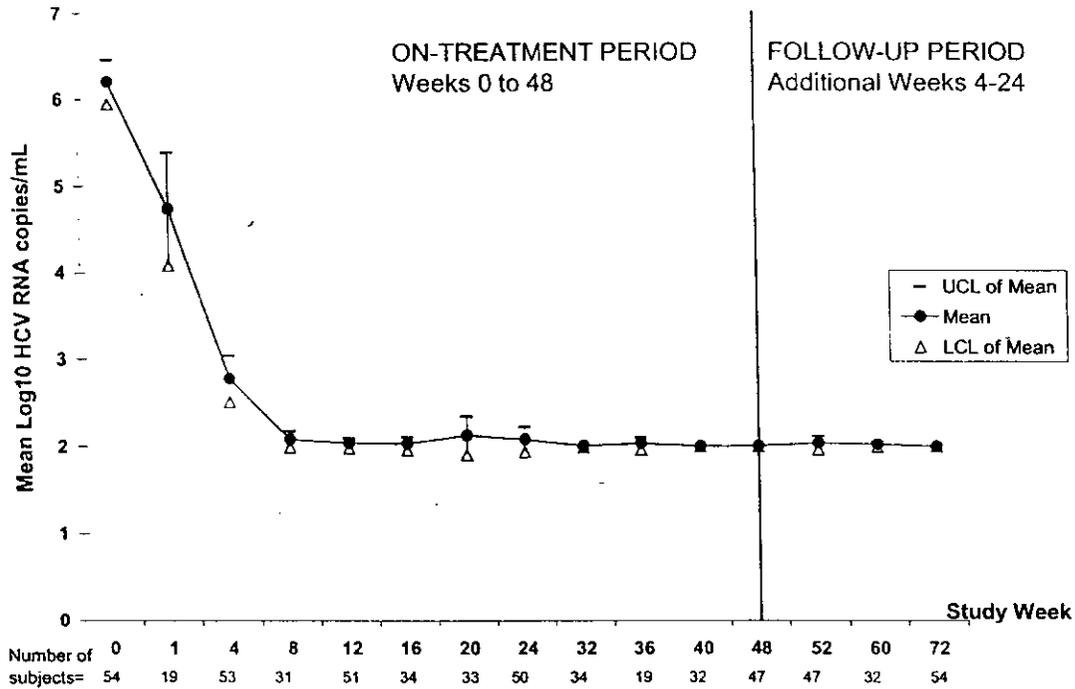
Table 8:
 Sustained Virologic Response Rates by Baseline HCV RNA and Genotype
 —Studies P00018 and P00321

INTRON A 3 MIU/m ² and REBETOL 15 mg/kg/day		
Subgroup	Response Rates n (%)	95% CI for Response Rate
Baseline HCV RNA		
≤ 2 million copies/mL (n=54)	28 (52%)	(39%, 65%)
> 2 million copies/mL (n=64)	26 (41%)	(29%, 53%)
Genotype		
1 (n=92)	33 (36%)	(26%, 46%)
Other (2/3 or 4/5/6) (n=26)	21 (81%)	(62%, 92%)†
Baseline HCV RNA		
≤ 2 million copies/mL		
Genotype 1 (n=42)	20 (48%)	(33%, 63%)
Genotype Other (2/3 or 4/5/6) (n=12)	8 (67%)	(38%, 86%)†
> 2 million copies/mL		
Genotype 1 (n=50)	13 (26%)	(16%, 40%)†
Genotype Other (2/3 or 4/5/6) (n=14)	13 (93%)	(66%, 100%)†
Note: Confidence intervals (CI) are based on normal approximation of the binomial distribution when binomial proportion is approximately symmetric (i.e., proportions close to 50%).		
† Confidence interval calculated using Agresti-Coull method (add 2 successes and 2 failures) when binomial distribution is skewed.		

Source: FDA Statistical Reviewer's analysis

There was no statistically significant difference in the sustained response rates whether patients had baseline HCV RNA ≤2 million copies/mL (52%) or >2 million copies/mL (41%). However, there was a statistically significant difference in the sustained virologic response rate in whether patients had genotype 1 HCV or other genotype (2, 3, 4, 5, or 6). Patients with genotype 1 were less likely to respond than patients with other genotypes (36% with genotype 1 responded vs. 81% with other genotype responded).

Figure 3 shows the mean log₁₀ HCV RNA copies/mL and 95% confidence intervals around the mean for those patients in Study P00018 and P00321 were classified as sustained responders.

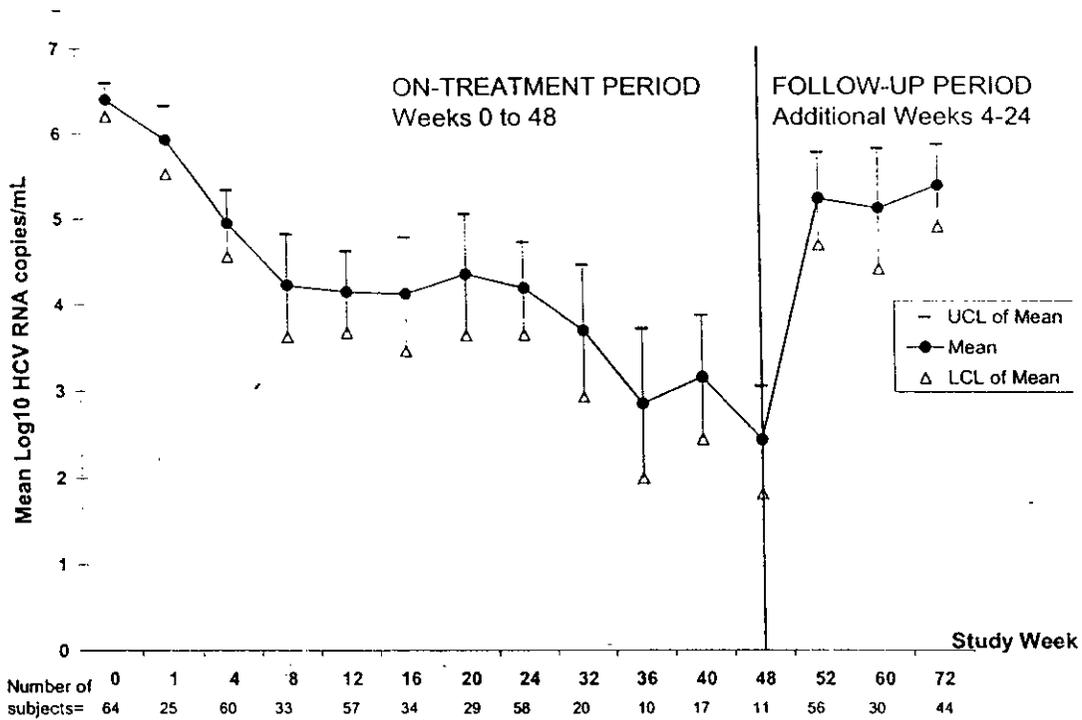


Source: FDA Statistical Reviewer's analysis

Figure 3: Mean Log₁₀ HCV RNA copies/mL of Sustained Responders by Study Week

Statistical Reviewer's Comments:

In Study P00018, HCV RNA was measured at Baseline, Weeks 1, 4, 12, 24, 36, 48, and follow-up Weeks 4 and 24 (i.e., Weeks 52 and 72). In Study P00321, HCV RNA was measured at Baseline, Weeks 4, 8, 12, 16, 20, 24, 32, 40, 48, and follow-up Weeks 4, 12, and 24 (i.e., Weeks 52, 60, and 72). As shown in the figure above, among patients who were classified as sustained responders, the mean HCV RNA dropped by Week 8 and reached the limit of assay detection of approximately 2 log₁₀ HCV RNA copies/mL or 100 HCV RNA copies/mL. Note that this does not imply that the time to sustained response is Week 8 for every patient. Some patients may have still have detectable HCV RNA levels close to limit of assay detection prior to Week 8 and have undetectable HCV RNA after Week 8.



Source: FDA Statistical Reviewer's analysis

Figure 4: Mean Log₁₀ HCV RNA copies/mL of Non-Responders by Study Week

Statistical Reviewer's Comments:

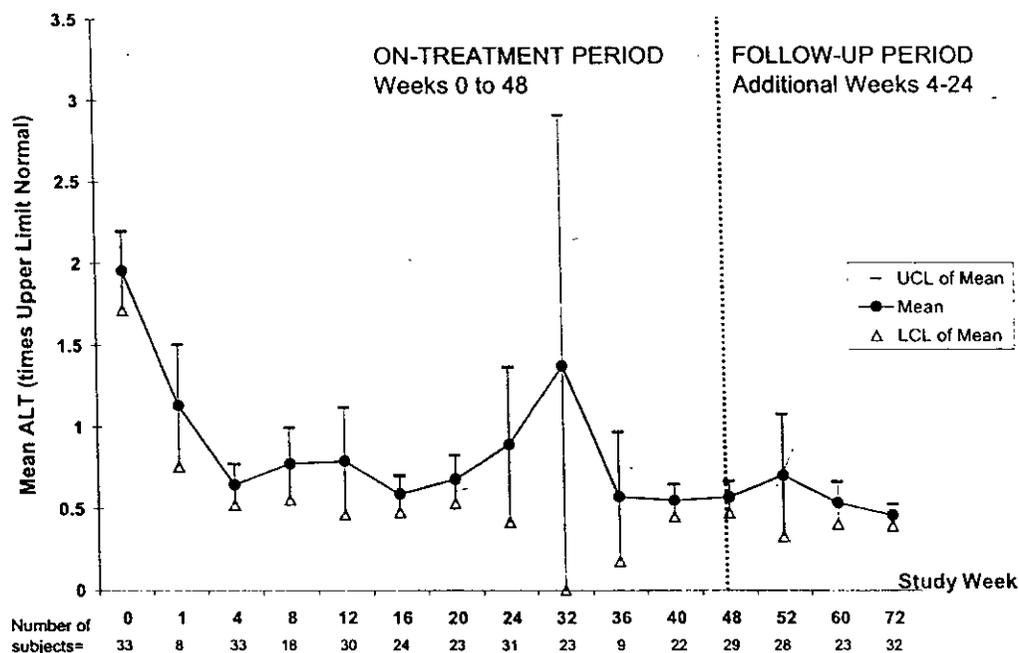
As shown in the figure above, among patients who were classified as non-responders, the mean HCV RNA declined through 48 weeks of treatment and was 2.43 log₁₀ HCV RNA copies/mL at Week 48. However, during the 24 weeks of follow-up period, the mean HCV RNA rose by about 3 log₁₀ and reached 5.4 log₁₀ HCV RNA copies/mL at Follow-up Week 24 (i.e. Week 72).

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3.1.4.2 ALT

In Studies P00018 and P00321 combined, there were a total of 77 patients on the ribavirin 15 mg/kg/day dose who had abnormal ALT at baseline (excluding 1 patient from Site 10 who also had abnormal ALT at baseline). Out of these, 33 patients were sustained responders through 24 weeks of follow-up and 44 patients were non-responders.

Figure 5 shows the mean ALT (times Upper Limit Normal) of patients who were sustained responders and had abnormal ALT at baseline. Similarly, Figure 6 shows the mean ALT (x ULN) of those patients who were non-responders and had abnormal ALT at baseline.



Source: FDA Statistical Reviewer's analysis

Figure 5: Mean ALT (x ULN) of Sustained Responders with Abnormal Baseline ALT

As shown in Figure 5, among the patients who were sustained responders and had abnormal ALT at baseline, the mean ALT was normal (ALT < 1x ULN) from Week 1 through 24 weeks of follow-up with the exception of Week 32. At Week 32, the mean ALT was above normal (ALT > 1 x ULN) because of the result of one patient. In Study P00321, an 8-year old Caucasian male patient (ID 22-002203) with weight 28.1 kg receiving ribavirin — who also was a sustained responder (based on undetectable levels of HCV RNA) had ALT greater than 18 x ULN at Week 32.

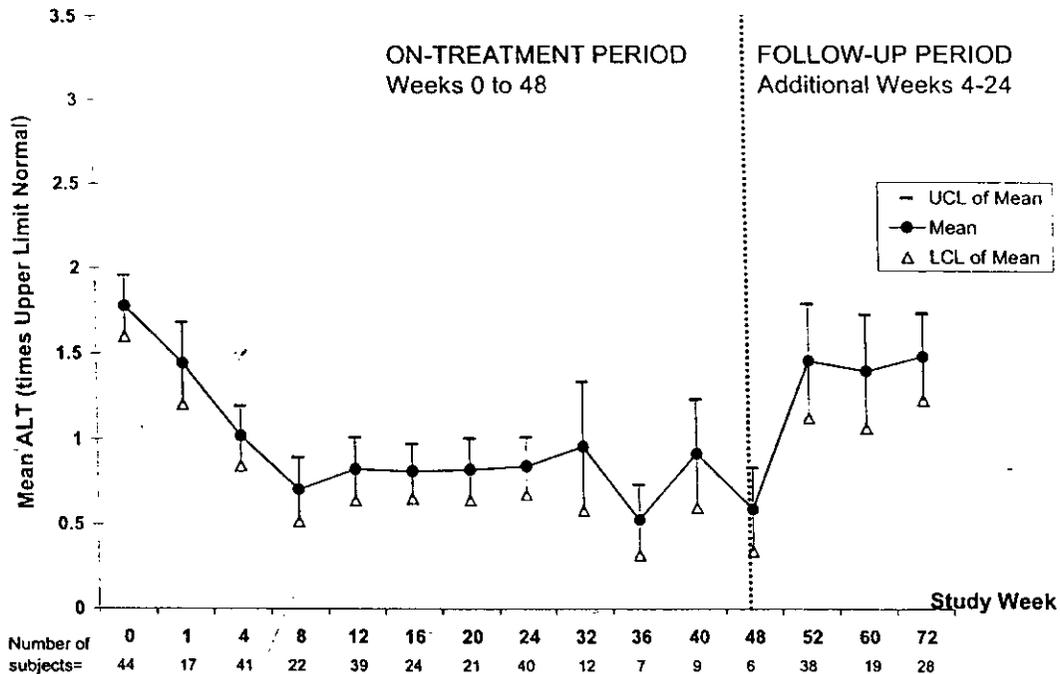


Figure 6: Mean ALT (x ULN) of Non-Responders with Abnormal Baseline ALT

As shown in Figure 6, among the 44 non-responder patients who had abnormal baseline ALT, the mean ALT was normalized by Week 8 and stayed normal through the 48 weeks of treatment period. However, during the post-treatment follow-up period the mean ALT rose to above Upper Limit Normal.

3.2 Evaluation of Safety

The focus of this review was the efficacy data. For review of safety data, please see medical review by Dr. Kassa Ayalew.

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4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Table 9 shows the sustained virologic response rates by baseline demographics including age, gender and race. Confidence intervals for some of the subgroups are also provided.

Table 9:
 Sustained Virologic Response Rates by Demographics (Age, Gender, Race)
 —Studies P00018 and P00321

INTRON A 3 MIU/m ² and REBETOL 15 mg/kg/day			
Subgroup		Response Rates n (%)	95% CI for Response Rate
Age (years)			
0 to 4	(n=8)	4 (50%)	(15%, 85%)
5 to 10	(n=46)	28 (61%)	(47%, 75%)
11 to 16	(n=64)	22 (34%)	(24%, 47%)†
Gender			
Male	(n=67)	29 (43%)	(31%, 55%)
Female	(n=51)	25 (49%)	(35%, 63%)
Race			
Asian	(n=4)	4 (100%)	—
Black	(n=5)	0 (0%)	—
Caucasian	(n=94)	44 (47%)	(37%, 57%)
Hispanic	(n=14)	5 (36%)	(16%, 61%)†
Other	(n=1)	1 (100%)	—
Note: Confidence intervals (CI) are based on normal approximation of the binomial distribution when binomial proportion is approximately symmetric (i.e., proportions close to 50%). † Confidence interval calculated using Agresti-Coull method (add 2 successes and 2 failures) when binomial distribution is skewed.			

Source: FDA Statistical Reviewer's analysis

Since the number of patients in some of the subgroups such as children of Asian, Black or Other race, confidence intervals for those groups are not provided.

Statistical Reviewer's Comments:

Out of the total of 118 patients in Studies P00018 and P00321 receiving the 15 mg/kg dose, only 8 patients were under the age of 5 years. All of these 8 children received the ribavirin and 4 of them responded to treatment (50% response with 95% CI of 15% to 85%). Children between the age of 5 years and 10 years (inclusive) generally had a higher response rate than children >10 years of age.

There was no significant difference in response rates between male and female patients. Majority of the patients (80%=94/118) were of Caucasian origin. Comparisons across patients of different races cannot be made due to small numbers in the non-Caucasian groups.

4.2 Other Special/Subgroup Populations

In Study P00321, children under the age of 5 years (0 to 4 years) received only the formulation of REBETOL (ribavirin). There were no children under the age of 5 years in Study P00018 in which all patients received only the capsule formulation.

Table 10 below shows the sustained virologic responses with the ribavirin capsule formulation versus the formulation for children in the age group 5 to 10 years and 11 to 16 years. Since the median age for the pooled data was 11 years, these categories were selected for this summary.

Table 10:
 Sustained Virologic Response Rates by Age and by REBETOL (ribavirin) Formulation
 —Studies P00018 and P00321

Subgroup	INTRON A 3 MIU/m ² and REBETOL 15 mg/kg/day		
	All subjects	REBETOL Capsules	REBETOL
Age (years)			
0 to 4	4/8 (50%)	0 (0%)	4/8 (50%)
5 to 10	28/46 (61%)	12/20 (60%)	16/26 (62%)
11 to 16	22/64 (34%)	13/43 (30%)	9/21 (43%)
Total	54/118 (46%)	25/63 (40%)	29/55 (53%)
95% CI on response rate	(37%, 55%)	(28%, 52%)	(40%, 66%)

Source: FDA Statistical Reviewer's analysis

As shown above, the response rates were similar whether children in any age group greater than or equal to 5 years were given ribavirin capsules or Children under 5 years of age were given only ribavirin.

The total sustained response rate with ribavirin capsules was 40% with 95% confidence interval of (28%, 52%). The total sustained response rate with ribavirin was 53% with 95% confidence interval of (40%, 66%).

Statistical Reviewer's Comments:

The sustained response rate for ribavirin capsules (25/63=40%) appears to be numerically higher than that for the ribavirin (29/55=53%).

During the review process, the applicant tried to explain this numerical difference. Among

the patients receiving ribavirin capsules, 25 patients were sustained responders at the end of 24-week follow-up, and 8 additional patients who had negative virology at the end of 48-week treatment had missing data during the follow-up period. The applicant argued that 7 of the 8 patients receiving capsules could have been successes had their follow-up data not been missing. Therefore, according to the Applicant, the proportion of sustained responders for capsule could have been $(25+7)/63=51\%$ and is comparable to the success rate of 53% for ribavirin — The Applicant's approach is likely an overestimate of the response rate for capsules.

In comparison, the analysis shown in Table 10 is conservative where the 8 patients with missing data are treated as failures. Using this approach the difference in response rate of capsules versus — (40% vs. 53%) is not statistically significant (p -value=0.214).

Therefore, based on the above sensitivity analyses, we do not have sufficient evidence to conclude that ribavirin capsules have a lower response rate than ribavirin —

Subgroup analyses for the baseline characteristics such as baseline HCV RNA and genotype were discussed previously in Section 3.1.4.1 Hepatitis C Virologic Response.

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5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

NDA 21-546, SN 000 contained safety and efficacy data of a combination therapy of INTRON A and REBETOL (capsules or oral solution) in pediatric patients with compensated chronic hepatitis C. REBETOL capsules have previously been approved for use in combination with INTRON A in adults of age 18 years and older who have relapsed following alpha interferon therapy.

Dose selection of REBETOL

This submission contained data in pediatric patients from two clinical studies: a two-part Phase 1 dose-ranging study, P00018, and a second larger Phase 3 study, P00321. In part 1 (Cohort 1) of Study P00018 a dose-ranging assessment was made to select one of the following doses of REBETOL: 8 mg/kg/day, 12 mg/kg/day, or 15 mg/kg/day. Based on the following endpoints in Cohort 1 of Study P00018: Week 4 pharmacokinetic assessments, serum HCV-RNA levels at Weeks 4 and 12, and safety through Week 12, the dose of 15 mg/kg/day was selected which also achieved the maximum mean reduction in HCV-RNA levels at Week 12 while maintaining good tolerability. This data on Cohort 1 was previously reviewed in NDA 20-903 submitted on February 28, 2001.

In part 2 (Cohort 2) of Study P00018, all pediatric patients were assigned the REBETOL 15 mg/kg/day dose in combination with INTRON A 3 MIU/m². Multiple dose trough pharmacokinetics and the efficacy of the combination therapy were measured.

No comparators for assessing efficacy

Neither of the two studies had a comparator arm for the INTRON A + REBETOL combination therapy. Therefore efficacy was assessed mainly on a single arm of INTRON A 3 MIU/m² subcutaneous injection three times a week plus REBETOL 15 mg/kg/day (I/R combination therapy) capsules or

The FDA Statistical Reviewer pooled data on the REBETOL 15 mg/kg/day dose from Study P00018 (n=48) with data on the same dose in Study P00321 (n=70). The focus of reviewing efficacy data was to assess the antiviral activity of REBETOL 15 mg/kg/day dose in terms of a sustained virologic response through 48 weeks of treatment and 24 weeks of follow-up in 118 patients. Similarity of data between adults and pediatric patients were established through the pharmacokinetics profiles of REBETOL + INTRON A.

Exclusion of data from P00018 Site 10 due to quality auditing issues

In the efficacy analyses presented throughout this review, data from Site 10 in Study 00018 was excluded. This is because the Applicant reported in the NDA submission that there were discrepancies in the management and reporting of data from one investigational site under Protocol No. P00018. Data from Site 10 could not be verified. A total of 7 patients at Site 10 had received at least one dose of ribavirin 15 mg/kg/day. Two additional patients from this site receiving 8 mg/kg/day or 12 mg/kg/day of ribavirin were also excluded. Since the overall efficacy results do not change whether data from Site 10 was included or not, in this review we present the results after excluding data from Site 10.

Time to Sustained Virologic Response and Proportion of Responders in Pediatric Patients

Based on the results presented in Section 3.1 Evaluation of Efficacy and Section 4 Findings in Special/Subgroup Populations, we conclude as follows:

1. Among the 118 pediatric patients of age 3 to 16 years with compensated chronic hepatitis C receiving REBETOL 15 mg/kg/day plus INTRON A 3 MIU/m² TIW, the proportion of patients with sustained virologic response was 46% (54/118).

A 95% confidence interval for the proportion of response is (36.8% to 54.8%). This rate is comparable to previously reviewed data on previously untreated adult patients with compensated chronic hepatitis C in a U.S. study. The response rate in adults receiving INTRON A + REBETOL was 37% (85/228) and those receiving INTRON A alone was 12% (27/225). In pediatric patients, no other comparator treatment such as INTRON A alone could be administered in a clinical trial.

2. The majority of pediatric patients who were sustained responders had responded by Week 16. However, there were differences in time to sustained response based on whether patients had genotype 1 HCV or other genotype HCV.
3. Patients with HCV genotype 1 had a significantly lower rate of response of 36% (95% confidence interval: 26% to 46%) as compared with patients with other genotype HCV of 2, 3, 4, 5, or 6 who had a response rate of 81% (95% confidence interval: 62%, 92%). Also, patients with other genotype HCV were more likely to respond as soon as Week 4 of treatment while patients with HCV genotype 1 could take as long as Week 32 to show a sustained response to treatment.
4. The sustained virologic response rates were similar regardless of whether patients had baseline HCV RNA ≤ 2 million copies/mL or >2 copies/mL or whether patients received REBETOL capsules or oral solution.
5. Mean HCV RNA levels of patients who were sustained responders dropped by Week 8 to levels close to lower limit of assay detection (≈ 100 HCV RNA copies/mL) and remained at low levels through 48 weeks of treatment and 24 weeks of follow-up.

6. Mean HCV RNA levels of patients who not sustained responders also continued to decline through 48 weeks of treatment without reaching undetectable levels. However, during the off-therapy follow-up period of 24 weeks, the mean HCV RNA levels rose by about 3 log₁₀ HCV RNA copies/mL.
7. Mean ALT levels of patients who were sustained responders and had abnormal ALT levels at baseline normalized after Week 1 and remained normal through the entire 48 week on-treatment period and 24 week follow-up period. One patient who was an exception to this phenomenon was an 8-year old Caucasian male child who was receiving REBETOL — had ALT greater than 18xULN at Week 32.
8. Mean ALT levels of patients who were nonresponders and had abnormal ALT at baseline also reached normal levels during 48 weeks of treatment. However, mean ALT returned to abnormal levels during the off-treatment follow-up period of 24 weeks.
9. Virologic response rates were generally similar across male and female patients as well as across Caucasian and Hispanic patients (who were the majority). Children between 5 to 10 years (both inclusive) generally had a higher response rate (61%=28/46) than children 11 years and older (34%=22/64).

5.2 Conclusions and Recommendations

About 46% (54/118) of pediatric patients (age 3 to 16 years) with compensated chronic hepatitis C and detectable hepatitis C virus (HCV) RNA had a sustained virologic response to treatment with REBETOL (ribavirin) 15 mg/kg/day given in combination with INTRON A (interferon alpha-2b) 3 MIU/m² SC TIW.³ A 95% confidence interval on the sustained response rate is (37% to 55%). This response rate is comparable to the sustained virologic response rate among previously untreated adults in a U.S. study in which response rate in adults receiving Intron A + Rebetol was 37% (85/228) and adults receiving Intron A alone was 12% (27/225).⁴

Majority of the pediatric patients had a sustained virologic response by Week 16 of treatment. HCV RNA among the sustained responders remained undetectable from the time they first responded through 24 weeks of follow-up post-treatment. Patients with genotype 1 HCV were less likely and slower to respond to the treatment than patients with genotypes 2, 3,4,5, or 6). There was no significant difference in response rates whether patients had baseline HCV RNA ≤2 million copies/mL or >2 million copies/mL, or whether pediatric patients (ages 5 years and older) received REBETOL capsules or oral solution. Children under 5 years of age only received REBETOL oral solution with INTRON A.

³ SC = subcutaneous and TIW=three time weekly

⁴ Clinical data in adults was reviewed previously in a separate NDA.

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