U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial Number:	BLA103949/5171
Drug Name:	PEG-Intron® Plus REBETOL®
Indication(s):	Treatment of Chronic Hepatitis C infection
Applicant:	Schering-Plough Research Institute
Date(s):	Stamp Date: June 10, 2008 PDUFA Goal Date: Dec 9, 2008
Review Priority:	Priority Review
Biometrics Division:	DB IV
Statistical Reviewer:	Lei Nie, Ph.D.
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Keywords: Chronic hepatitis C (CHC) infection; HCV RNA; reassay of HCV PCR viral load; sustained virologic response (SVR) at Follow-up Week 24; hepatic fibrosis, pediatric; double blind; bootstrap; clinical studies; confidence interval;

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Schering submitted a pediatric study, P2538, to support registration of a pediatric indication for Peglntron™ in combination with Rebetol®, which is a FDA-approved treatment for chronic hepatitis C (CHC).

This single-arm study demonstrated the efficacy of the study treatment in children with CHC. The overall treatment efficacy, represented by sustained viral response (SVR) in all 107 children enrolled in the study, is consistent with its efficacy reported in adults. The study also demonstrated the treatment efficacy across countries, gender, age, and alanine aminotransferase (ALT) levels. Although the study demonstrated the treatment efficacy in Caucasians, it has too small a sample size to evaluate its efficacy in other races.

We conclude this study fulfills its efficacy requirement in children with CHC.

1.2 Brief Overview of Clinical Studies

Study P2538 is a Phase Ib/III, single-arm, open label, global, multicenter study of Peglntron™ in combination with Rebetol® in previously untreated pediatric subjects, ages 3 through 17 years, with chronic hepatitis C (CHC).

Schering enrolled 107 subjects in the United States, Argentina, Austria, Chile, France, Germany, Italy, Puerto Rico, and Spain. All subjects were expected to receive treatments for 24 or 48 weeks.

The Primary objective of this study is to assess the safety, efficacy, and tolerability of the treatment regimen in pediatric subjects with CHC. The primary efficacy endpoint is defined as the proportion of subjects that exhibit sustained virus response (SVR) at Follow-up Week (FW) 24. A patient who had plasma HCV RNA level below limit of quantification at FW 24 is considered to have achieved SVR.

2. INTRODUCTION

2.1 Overview

Study P2538 is a Phase Ib/III, single-arm, open label, global, multicenter study of Peglntron™ in combination with Rebetol® in previously untreated pediatric subjects, ages 3 through 17 years, with chronic hepatitis C (CHC). Treatment consists of Peglntron™ 60 mg/m^2 once weekly in combination with Rebetol® 15 mg/kg/day (in two divided doses).

According to the study plan, subjects were expected to receive treatments for 24 or 48 weeks. Subjects with genotype 2 receive treatment for 24 weeks. Subjects with genotype 3 receive treatment for 24 weeks if their baseline viral loads are less than 600,000IU/ml. All other subjects receive treatment for 48 weeks.

All subjects need to enter a follow-up period of 24 weeks after the end of treatment. Subjects in the 24-week treatment regimen need to be evaluated at screening 1 and 2; day 1; treatment weeks (TW) 2, 4, 6, 8, 12, 18, 24; and follow-up weeks (FW) 4, 12, and 24. Subjects in the 48-week treatment regimen need to be evaluated at screening 1 and 2; day 1; TW 2, 4, 6, 8, 12, 18, 24, 30, 36, 40, 44, 48; and FW 4, 12, and 24.

Schering enrolled 107 subjects in the United States, Argentina, Austria, Chile, France, Germany, Italy, Puerto Rico, and Spain.

Some subjects discontinued the study for a variety of reasons. Subjects in the 48-week treatment regimen discontinued treatment at TW 18 if their TW 12 HCV RNA levels dropped less than 2 log10 compared to baseline levels and remained above the limit of quantitation (LLQ). Subjects in the 48-week treatment regimen who had TW12 and TW 24 HCV RNA levels above LLQ discontinued at TW 30 and proceed into the FW. Subject discontinuation during the study could also be due to any of the following reasons: serious or life-threatening AE; failure to comply with the visit schedule, dosing, evaluations, or other requirements of the study; request of the subject and/or legal guardian; pregnancy; subject is found to violate the protocol exclusion criteria; or the investigator's decision.

The primary objective of this study is to assess the safety, efficacy, and tolerability of the treatment regimen in pediatric subjects with CHC. The primary efficacy endpoint is defined as the proportion of subjects who had plasma HCV RNA level below LLQ at FW 24.

Below we list all major concerns in this study: inaccurate HCV RNA measurements and reassay, non-uniform standard of the SVR definition, inconsistent definition of SVR, and appropriateness of the primary endpoint. We now describe the concerns.

1. The HCV RNA assay conducted in Schering's laboratories to quantitatively assess HCV RNA from some samples reported inaccurate levels of HCV RNA. Schering identified that 23% of the 985 previously assayed samples were potentially impacted. Of these, 95% had back-up samples available for retesting. All HCV RNA results were reviewed by the project physician.

2. There was no uniform standard of limit of detection (LLD) or limit of quantitation (LLQ). The LLD in the revalidation is 125 IU/mL. This level was defined based on the ability to consistently (95%) detect a viral load at this level.

3. The sponsor's determination of the primary endpoint is done 24 weeks after the last dose of study drug. A more suitable determination of the primary endpoint should be done at Week 72 for a 48-week regimen and Week 48 for a 24-week regimen, regardless of when the study agents are discontinued for a given subject.

4. It is important to investigate whether patients had SVR by Schering's definition actually achieved sustained viral response. Specifically, we were concerned whether non-detectable SVR status is stable during a relatively longer period.

We examine and alleviated all these concerns in our assessment.

2.2 Data Sources

Clinical overview: 1 pdf file
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Study report: 2 pdf files
\\cbsap58\m\eCTD_Submissions\STN103949\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\chronic-hepatitis-c\5352-stud-rep-uncontr\study-report-p02538\
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3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

Study P2538 is a Phase Ib/III, single-arm, open label, global, multicenter study of Peglntron™ in combination with Rebetol® in previously untreated pediatric subjects, ages 3 through 17 years, with chronic hepatitis C (CHC). Treatment consists of Peglntron™ 60 mg/m^2 once weekly in combination with Rebetol® 15 mg/kg/day (in two divided doses). The study plans to enroll 100 subjects into two groups at approximately 25 sites: Group 1 includes 50 subjects, ages 3 through 11 years; Group 2 includes the other 50 subjects, ages 12 through 17 years.

The primary efficacy endpoint is the proportion of subjects who have undetectable serum HCV RNA at the Week 24 follow-up visit. Schering considers the treatment efficacious if the lower bound of a 95% confidence interval of the proportion is greater than 10%.

Reviewers' comments on designs and endpoints
1. The primary endpoint itself is appropriate for interferon based regimens. However, determination of the SVR status was not uniformly performed because there were no uniform standards of the limit of quantification.
2. The sponsor's determination of the primary endpoint is done 24 weeks after the last dose of study drug. A more suitable determination of the primary endpoint should be done at Week 72 for a 48-week regimen and Week 48 for a 24-week regimen, regardless of when the study agents are discontinued for a given subject because there is only one study in the application package.

3. Schering considers the treatment efficacious if the lower bound of a 95% confidence interval of the proportion is greater than 10%. This 95% level might not stringent enough to support efficacy of this treatment. Furthermore, the 10% rate needs some justification.

3.1.2 Patient Disposition, Demographic and Baseline Characteristics

Schering actually enrolled 107 subjects. All of the 27 subjects assigned to the 24-week treatment regimen completed the treatment and follow-up phases. Of the 80 subjects assigned to the 48-week treatment regimen, 51 subjects completed the treatment phase and 79 subjects completed the follow-up phase. The primary reason of discontinuation during the treatment phase is treatment failure, which is responsible for 26 among 29 discontinued subjects. See Table 1 for details.

Schering presented demographic and baseline characteristic data in Table 2 and Table 2.a. The results are given below:

- Subjects in the group 3 to 11 years of age had a median age of the 7.0 years; 67% (45/67) of the subjects in this group were between 6 and 11 years old. The median age of the subjects in the group 12 to 17 years of age was 14.0 years; 55% (22/40) were 14 to 17 years old.
- 95 (89%) subjects were white.
- 75 (70%) subjects had vertical transmission.
- 72 subjects (67%) were infected with HCV Genotype 1 and 58 (54%) subjects had low viral load (serum HCV RNA <600,000 IU/mL).
- 82% (88/107) of subjects had minimal fibrosis (F1), and no subject had cirrhosis.
- 44% of subjects had mild and 30% had moderate liver inflammation; 18% had severe inflammatory activity.
- 71% of subjects had no steatosis and 22% had mild steatosis (less than 5%). Four subjects had steatosis between 5% to 32%.
- Biopsy results were similar for the groups aged 3 to 11 and 12 to 17 years.

82% (88/107) of subjects had minimal fibrosis (F1), and no subject had cirrhosis. 44% of subjects had mild and 30% had moderate liver inflammation. 18% had severe inflammatory activity. 71% of subjects had no steatosis and 22% had mild steatosis (less than 5%). Four subjects had steatosis between 5% to 32%. Biopsy results were similar for the groups aged 3 to 11 and 12 to 17 years. Pretherapy biopsies were available for 99% (106/107) of subjects. The biopsy slides for two subjects were considered inadequate for assessment by the central pathologist. Histological results were scored using the METAVIR fibrosis and activity scores, and steatosis was also assessed.

Table 1: Patient Disposition and Status

	Number (%) of Subjects								
	Subjects Assigned 24-week Treatment			Subjects Assigned 48-week Treatment			All Subjects		
	Subject Age (years)			Subject Age (years)			Subject Age (years)		
	3-11	12-17	All	3-11	12-17	All	3-11	12-17	All
Treatment Phase									
Enrolled	13 (100)	14 (100)	27 (100)	54 (100)	26 (100)	80 (100)	67 (100)	40 (100)	107 (100)
Discontinued Treatment Phase	0	0	0	19 (35)	10 (38)	29 (36)	19 (28)	10 (25)	29 (27)
Adverse Event	-	-	-	0	1 (4)	1 (1)	0	1 (3)	1 (1)
Treatment Failure	-	-	-	17 (31)	9 (35)	26 (33)	17 (25)	9 (23)	26 (24)
Subject did not wish to continue, reasons unrelated	-	-	-	2 (4)	0	2 (3)	2 (3)	0	2 (2)
Completed Treatment Phase	13 (100)	14 (100)	27 (100)	35 (65)	16 (62)	51 (64)	48 (72)	30 (75)	78 (73)
Follow-up Phase									
Entered Follow-up	13 (100)	14 (100)	27 (100)	53 (98)	26 (100)	79 (99)	66 (99)	40 (100)	106 (99)
Completed Follow-up	13 (100)	14 (100)	27 (100)	53 (98)	26 (100)	79 (99)	66 (99)	40 (100)	106 (99)
Never Entered Follow-up	-	-	-	1	0	1	1	0	1

Source: Table 4, Page 48 in the Clinical Study Report.

Table 2: Demographic data

	Subjects Assigned 24-week Treatment			Subjects Assigned 48-week Treatment			All Subjects		
	Subject Age (years)			Subject Age (years)			Subject Age (years)		
	3-11 n=13	12-17 n=14	All n=27	3-11 n=54	12-17 n=26	All n=80	3-11 n=67	12-17 n=40	All n=107
Age (yr)[a]									
Mean (SD)	7.1 (1.8)	13.7 (1.3)	10.5 (3.7)	7.0 (2.6)	14.2 (1.6)	9.4 (4.1)	7.0 (2.4)	14.0 (1.5)	9.7 (4.0)
Median	7.0	14.0	12.0	7.0	14.5	9.0	7.0	14.0	9.0
Range (min-max)	4-9	12-16	4-16	3-11	12-17	3-17	3-11	12-17	3-17
Age Range (n, %)									
3 - <6 yr	2 (15)	0	2 (7)	20 (37)	0	20 (25)	22 (33)	0	22 (21)
6 - <12 yr	11 (85)	0	11 (41)	34 (63)	0	34 (43)	45 (67)	0	45 (42)
12 - <14 yr	0	6 (43)	6 (22)	0	12 (46)	12 (15)	0	18 (45)	18 (17)
14 - 17 yr	0	8 (57)	8 (30)	0	14 (54)	14 (18)	0	22 (55)	22 (21)
Sex (n, %)									
Female	6 (46)	6 (43)	12 (44)	34 (63)	10 (38)	44 (55)	40 (60)	16 (40)	56 (52)
Male	7 (54)	8 (57)	15 (56)	20 (37)	16 (62)	36 (45)	27 (40)	24 (60)	51 (48)
Race (n, %)									
White	12 (92)	11 (79)	23 (85)	48 (89)	24 (92)	72 (90)	60 (90)	35 (88)	95 (89)
Non-White	1 (8)	3 (21)	4 (15)	6 (11)	2 (8)	8 (10)	7 (10)	5 (13)	12 (11)
Asian	1 (8)	2 (14)	3 (11)	3 (6)	1 (4)	4 (5)	4 (6)	3 (8)	7 (7)
Black	0	0	0	1 (2)	0	1 (1)	1 (1)	0	1 (1)
Multiracial	0	1 (7)	1 (4)	2 (4)	1 (4)	3 (4)	2 (3)	2 (5)	4 (4)
Ethnicity (n, %)									
Hispanic or Latino	2 (15)	1 (7)	3 (11)	13 (24)	5 (19)	18 (23)	15 (22)	6 (15)	21 (20)
Not Hispanic or Latino	11 (85)	13 (93)	24 (89)	41 (76)	21 (81)	62 (78)	52 (78)	34 (85)	86 (80)
Body Weight (kg)[b]									
Mean (SD)	25.29 (5.20)	56.77 (10.12)	41.61 (17.90)	28.73 (11.76)	57.69 (11.99)	38.14 (18.02)	28.06 (10.85)	57.37 (11.24)	39.02 (17.97)
Median	25.00	56.80	34.00	29.50	56.10	34.85	27.00	56.35	34.70
Range (min-max)	15.0-34.0	34.0-73.4	15.0-73.4	13.5-58.0	37.4-87.0	13.5-87.0	13.5-58.0	34.0-87.0	13.5-87.0
Height (cm)[b]									
Mean (SD)	125.78 (8.98)	165.98 (10.19)	146.63 (22.54)	124.74 (16.77)	162.59 (8.40)	137.04 (23.01)	124.94 (15.52)	163.78 (9.09)	139.46 (23.17)
Median	126.50	162.25	144.00	127.25	163.75	139.35	127.00	164.00	139.50
Range (min-max)	102.5-137.4	144.0-178.5	102.5-178.5	95.3-163.5	144.5-179.8	95.3-179.8	95.3-163.5	144.0-179.8	95.3-179.8

Source: Table 6, Page 53 in the Clinical Study Report.

Table 2.a: Demographic data. Source: Table 7 in the clinical report.

	Subject Age (yr)		
	3-11 n=67	12-17 n=40	All Subjects n=107
Source of HCV Exposure (n, %)			
Transfusion associated	2 (3)	5 (13)	7 (7)
Parenteral	2 (3)	3 (8)	5 (5)
Sporadic[a]	5 (7)	7 (18)	12 (11)
Vertical transmission	52 (78)	23 (58)	75 (70)
Other	6 (9)	2 (5)	8 (7)
Years Since Exposure			
Mean (SD)	6.5 (2.5)	12.3 (4.1)	8.5 (4.2)
Median	7.0	13.0	8.0
Range (min-max)	0.4-11.0	1.5-16.0	0.4-16.0
Missing (n)[a]	5	7	12
HCV-RNA/PCR (IU/mL)[b]			
Mean (geometric)	398,107	531,018	442,748
<600,000 (n, %)	38 (57)	20 (50)	58 (54)
≥600,000 (n, %)	27 (40)	18 (45)	45 (42)
Missing	2 (3)	2 (5)	4 (4)
HCV Genotype by Viral Load, n[b]			
1 HCV-RNA <600,000 IU/mL	26 (39)	13 (33)	39 (36)
HCV-RNA ≥600,000 IU/mL	20 (30)	11 (28)	31 (29)
Missing	1 (1)	1 (3)	2 (2)
2 HCV-RNA <600,000 IU/mL	6 (9)	5 (13)	11 (10)
HCV-RNA ≥600,000 IU/mL	0	4 (10)	4 (4)
3 HCV-RNA <600,000 IU/mL	3 (4)	2 (5)	5 (5)
HCV-RNA ≥600,000 IU/mL	6 (9)	3 (8)	9 (8)
Missing	1 (1)	0	1 (1)
4 HCV-RNA <600,000 IU/mL	3 (4)	0	3 (3)
HCV-RNA ≥600,000 IU/mL	1 (1)	0	1 (1)
Missing	0	1 (3)	1 (1)
Subjects enrolled in 24-wk treatment (n, %)[c]	13 (100)	14 (100)	27 (100)
Genotype 2	6 (46)	9 (64)	15 (56)
Genotype 3 (Total)	7 (54)	5 (36)	12 (44)
HCV-RNA <600,000[b]	3 (23)	2 (14)	5 (19)
HCV-RNA ≥600,000[b]	4 (31)	3 (21)	7 (26)
Subjects enrolled in 48-wk treatment (n, %)[c]	54 (100)	26 (100)	80 (100)
Genotype 1	47 (87)	25 (96)	72 (90)
Genotype 3 (HCV-RNA ≥600,000 IU/mL)[b]	3 (6)	0	3 (4)
Genotype 4	4 (7)	1 (4)	5 (6)
Baseline ALT (× ULN)			
Mean	1.2	0.9	1.09
Median	0.96	0.69	0.87
Range (min-max)	0.3-3.9	0.2-3.7	0.2-3.9

3.1.3 Statistical Methodologies

Sponsor's analysis methodology

The sponsor planned to report the proportion and 95% confidence intervals (CIs) of SVR. They used the following methods to handle the missing data:

- Subjects with undetectable HCV RNA at Follow-up Week 12 (FW 12), but who are missing at FW 24, will be considered to have achieved an SVR.
- Any subject missing an HCV RNA evaluation will be considered a nonresponder at that visit.

Reviewer's alternative analysis methodology

1. We examine concordance and discordance between original impacted measurements and reassayed measurements, and we further evaluate the potential impact to the results.

2. We examine whether the results are sensitive to different definitions of limit of quantification.

3. We compare results based on SVR determined at Week 72 for a 48-week regimen and Week 48 for a 24-week regimen with results based on the sponsor's SVR determined at the last dose of study drug.

4. We examine whether the non-detectable SVR status is stable during the follow-up period.

3.1.4 Sponsor' Results

Sponsor's Analysis of the primary endpoint

Overall, 64.5% (69/107) of the subjects achieved SVR. The SVR rate in the carry-forward analysis was similar (65.4% [70/107]), because only one additional subject with genotype 1 who had undetectable SVR at FW 12 has missing data at FW 24. The SVR rates were 72.5% (29/40) in older subjects (12 to 17 years) and 61.2% (41/67) in younger subjects (3 to 11 years). Response rate was consistently associated with HCV genotype, regardless of subjects' age group. See Table 3 for details.

Subjects who had undetectable HCV RNA at the last treatment visit and detectable HCV RNA at the last follow-up visit were considered relapsers. The overall relapse rate in the study was 6.7%. A total of 75 subjects had undetectable HCV RNA at the end of study treatment; of these, five female subjects with Genotype 1 relapsed within four weeks of treatment discontinuation. According to results presented in Table 4, the sponsor concluded there is no apparent relationship between relapse rate and baseline viral load.

Table 3: Carry-forward Sustained Virologic Response Rates by Genotype, Age Group, and Assigned Treatment Duration

	Subjects Aged 3 to 11 yr n=67				Subjects Aged 12 to 17 yr n=40				All Subjects n=107			
	24 Weeks		48 Weeks		24 Weeks		48 Weeks		24 Weeks		48 Weeks	
	Virologic Response		Virologic Response		Virologic Response		Virologic Response		Virologic Response		Virologic Response	
	n[a]	(%)	n[a]	(%)	n[a]	(%)	n[a]	(%)	n[a]	(%)	n[a]	(%)
Genotype												
All	12/13	(92.3)	29/54	(53.7)	14/14	(100)	15/26	(57.7)[b]	26/27	(96.3)	44/80	(55.0)[d]
1	-	-	24/47	(51.1)	-	-	14/25	(56.0)[c]	-	-	38/72	(52.8)[e]
2	5/6	(83.3)	-	-	9/9	(100)	-	-	14/15	(93.3)	-	-
3	7/7	(100)	2/3	(66.7)	5/5	(100)	-	-	12/12	(100)	2/3	(66.7)
4	-	-	3/4	(75.0)	-	-	1/1	(100)	-	-	4/5	(80.0)

yr = years; "-" = not applicable.

a: % = Percent response; n = number of responders/number of subjects with given genotype, age group, and assigned treatment duration.

b: SVR rate at Follow-up Week 24, n = 14/26 (53.8%).

c: SVR rate at Follow-up Week 24, n = 13/25 (52.0%).

d: SVR rate at Follow-up Week 24, n = 43/80 (53.8%).

e: SVR rate at Follow-up Week 24, n = 37/72 (51.4%).

Source: Table 8, Page 59 in the Clinical Study Report.

Table 4: Relapse Rate by Subgroup

	HCV Genotype 1 n=72		HCV Genotype 2 n=15		HCV Genotype 3 n=15		HCV Genotype 4 n=5	
	Virologic Response		Virologic Response		Virologic Response		Virologic Response	
	n[a]	(%)	n[a]	(%)	n[a]	(%)	n[a]	(%)
Overall relapse	5/43	(11.6%)	0/14	(0)	0/14	(0)	0/4	(0)
Gender								
Female	5/27	(18.5)	0/9	(0)	0/3	(0)	0/3	(0)
Male	0/16	(0)	0/5	(0)	0/11	(0)	0/1	(0)
Age								
12-17 Years	3/17	(17.6)	0/9	(0)	0/5	(0)	0/1	(0)
3-11 Years	2/26	(7.7)	0/5	(0)	0/9	(0)	0/3	(0)
BMI (kg/m^2)								
≤15	1/7	(14.3)	0/1	(0)	0/3	(0)	0/1	(0)
>15-20	1/15	(6.7)	0/8	(0)	0/9	(0)	0/1	(0)
>20-25	0/14	(0)	0/4	(0)	0/2	(0)	0/2	(0)
>25	3/7	(42.9)	0/1	(0)	-	-	-	-
Baseline Viral Load								
<600,000 IU/mL	2/30	(6.7)	0/10	(0)	0/5	(0)	0/3	(0)
≥600,000 IU/mL	2/11	(18.2)	0/4	(0)	0/9	(0)	-	-
Missing	1/2	(50.0)	-	-	-	-	0/1	(0)
Duration Adherence								
<80%	1/1	(100)	-	-	0/1	(0)	-	-
≥80%	4/42	(9.5)	0/14	(0)	0/13	(0)	0/4	(0)
PEG2b Dosing Adherence								
<80%	1/3	(33.3)	-	-	0/1	(0)	-	-
≥80%	4/40	(10.0)	0/14	(0)	0/13	(0)	0/4	(0)
Ribavirin Dosing adherence								
<80%	1/3	(33.3)	0/1	(0)	0/1	(0)	-	-
≥80%	4/40	(10.0)	0/13	(0)	0/13	(0)	0/4	(0)

Source: Table 9, Page 60 in the Clinical Study Report.

3.1.5 Reviewer's Results

1. We evaluated the potential impact of reassay on the results. No more than 12% of the original and reassay measurement pairs are discordant. Less than 8% of these pairs have non-detectable reassay measurements but have detectable original measurements. There is no discordance at FW 24.

There are a total of 12 impacted samples that cannot be retested because of lack of back-up samples. Because one of these 12 samples was from FW 24, which was imputed using

the FW 12 measurement, the primary analysis is not greatly effected. Other samples were treated as missing.

Seven subjects with Genotype 3 and with high viral load (≥600,000 IU/mL) received 24 weeks of therapy, as their treatment assignment was based on initial HCV RNA test results provided by the SPRI laboratory. The reassay results indicated that these subjects had high viral loads and should have been treated for 48 weeks as specified in the protocol. However, all seven subjects attained SVR.

We therefore conclude the impact of reassay is limited.

2. We examine whether the results are sensitive to different definitions of limit of quantification.

If results are sensitive to the limit of quantification definition, we expect to see the results change along with the change of the limit of quantification. We purposefully increase the thereshold of "limit of quantification" from 125 to 400, 1000, 2000, 3000, 5000, 10000. The results remain unchanged when the limit of quantification was defined as 125-2000. When it reaches 3000, there is one more SVR. This number does not increase when the threshold reaches 5000 and 10000.

Ideally, we also expect to inspect the sensitivity for cases when the limit of quantification is defined below 125. This is not possible since no actual viral loads were reported when they were not detectable. However, we believe most limits of quantification used are not too high compared to 125.

We therefore conclude the results are not sensitive to the definition of limit of quantification.

3. We compare results based on SVR determined at Week 72 for a 48-week regimen and Week 48 for a 24-week regimen with results based on the sponsor's SVR determined at the last dose of study drug.

The original standard definition of SVR was having non-detectable viral load 24 weeks after the last dose of study drug. This definition was protocol specified and has been used in the registration trials for currently approved therapies.

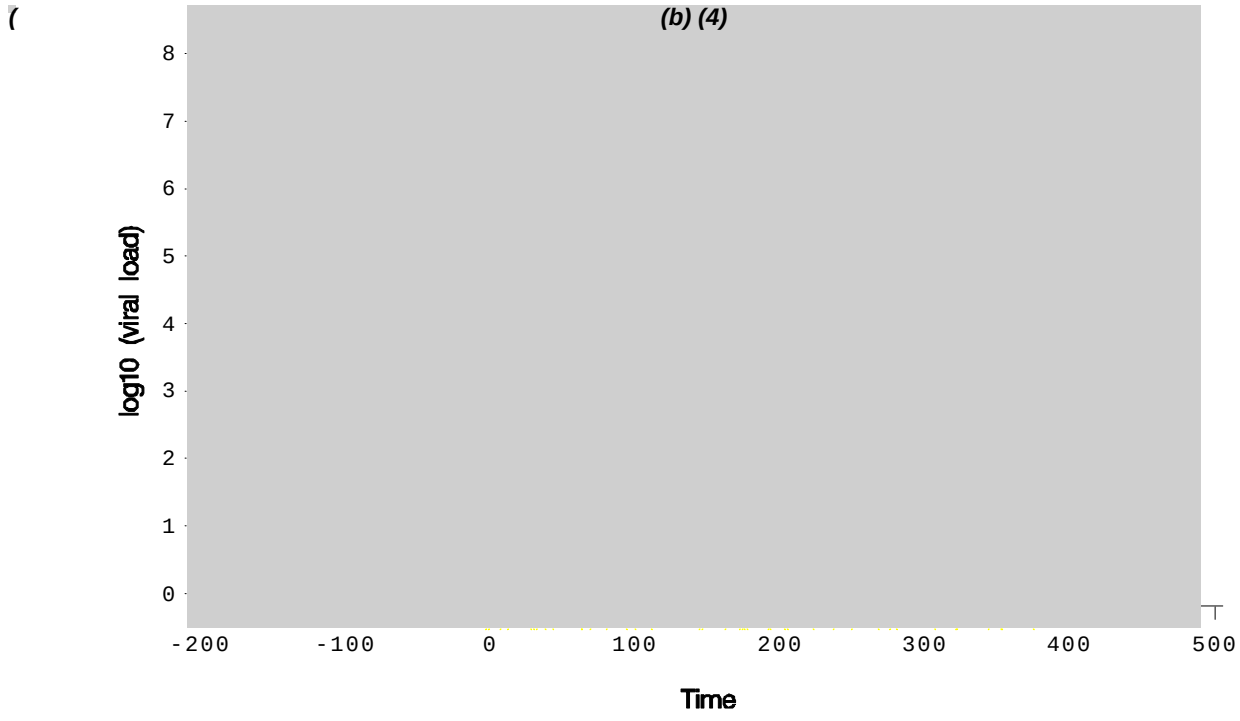
78/107 (73%) subjects completed the treatment phase. Of those who did not complete the treatment phase, 26/29 (90%) were treatment failures and were discontinued per protocol (non-SVR subjects). Only three subjects discontinued the study for a reason other than treatment failure.

Based on this information, we conclude the difference between the two definitions is not a major issue for the analysis.

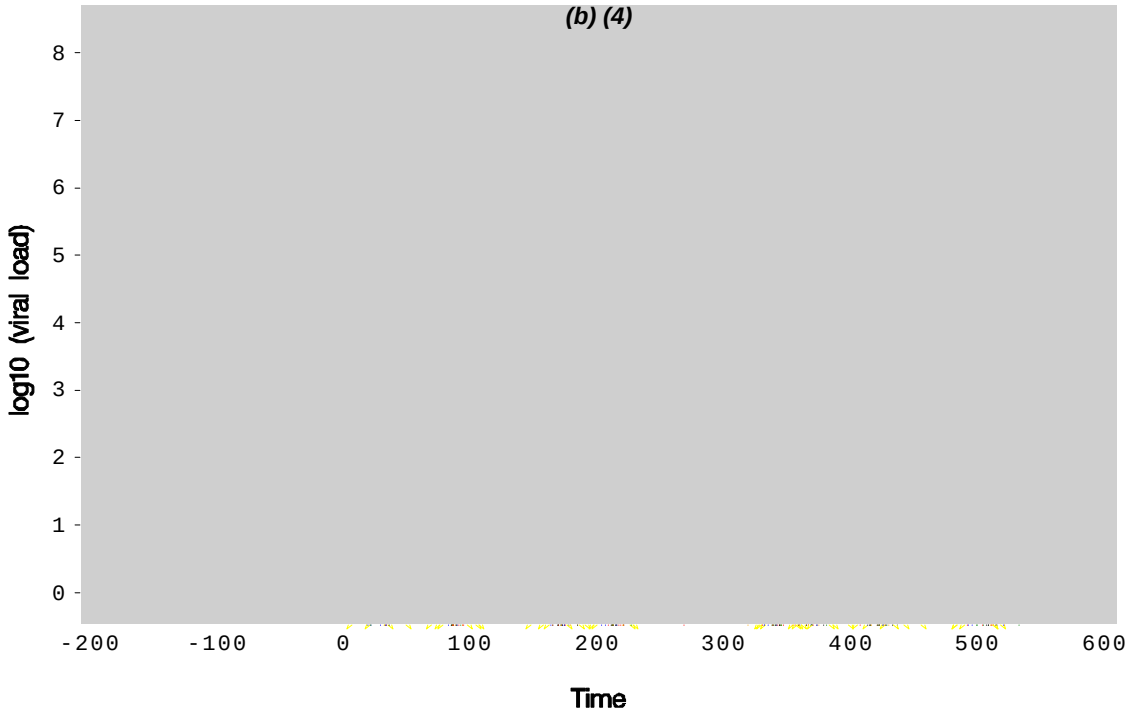
4. It is important to investigate if patients who had SVR by Schering's definition actually achieved sustained viral response. Specifically, we had concerns whether the non-detectable SVR status is stable during a relatively longer period.

For this purpose, we provide the viral load vs time plots for all 107 subjects in three graphs. In these plots, non-detectable viral loads were recorded as 0 in the log10 scale for graphical convenience. From the graphs, we conclude that the SVR status is relatively stable during the follow-up period, particularly for patients who were considered as having SVR according to the definition.

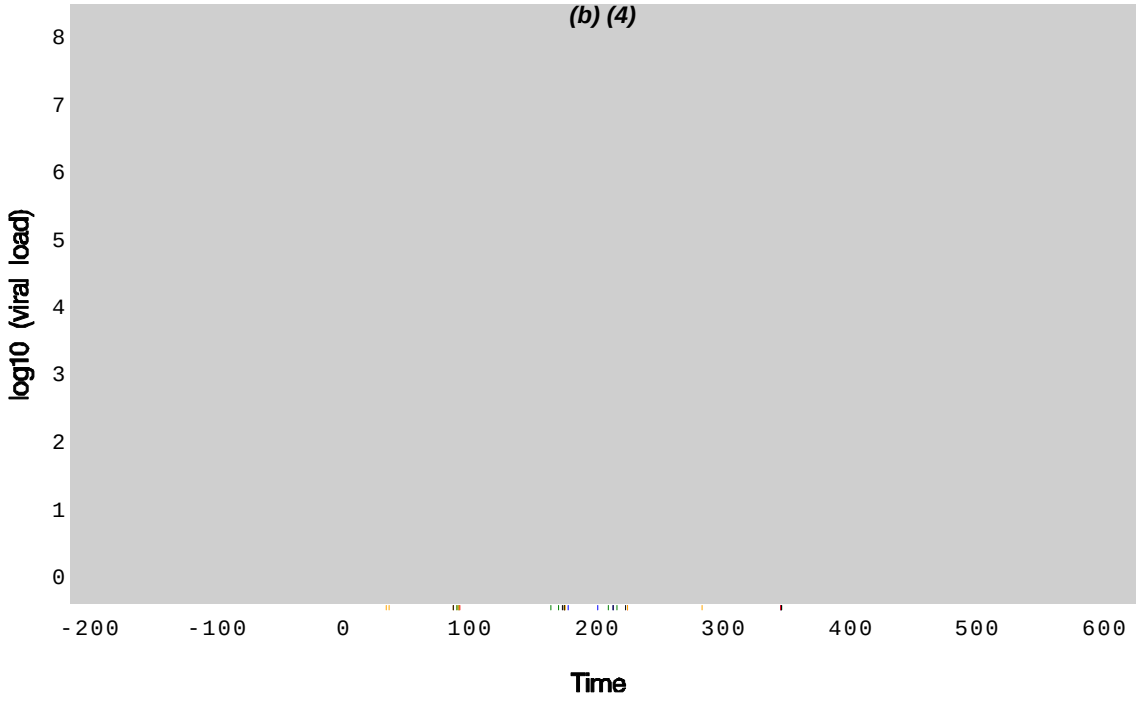
Graph 1: plot for 27 subjects in the 24 week treatment regimen.



Graph 2: plot for 44 subjects who had SVR in the 48 week treatment regimen.



Graph 3: plot for 36 subjects who did not had SVR in the 48 week treatment regimen.



3.1.6 Conclusions

Sponsor's conclusions are as follows:

- The overall SVR rate with PEG2b plus ribavirin in pediatric subjects was 65.4% for all HCV genotypes. Consistent with results previously reported in adults, SVR in pediatric subjects infected with HCV Genotype 1 was lower (52.8%) compared with those infected with HCV Genotypes 2, 3, and 4 (93.3%; 93.3% and 80%, respectively).
- The SVR rates were similar in both younger (3 to 11 years old) and older children (12 to 17 years old) across all genotypes.
- The overall relapse rate was 6.7%. Relapse occurred in subjects who had HCV Genotype 1 and were female. Relapse occurred in these subjects within 4 weeks of treatment discontinuation.
- Eight subjects infected with Genotype 3 and high viral load at baseline all achieved SVR despite being treated for 24 weeks instead of the protocol defined 48 weeks.
- Pediatric subjects with HCV Genotype 1 and low baseline viral load (<600,000 IU/mL) had a higher SVR rate than those with high baseline viral load (71.8% vs 29%, respectively).
- Rapid viral response and early viral response are important predictors of SVR, especially in Genotype 1 subjects. The SVR rate was 88.9% in Genotype 1 subjects who were rapid responders and 83.7% in early responders.
- Early treatment decision rules based on TW 12 and TW 24 HCV RNA results are applicable in treating pediatric subjects assigned to 48 weeks of therapy. Genotype 1 subjects with at least a 2 log drop in HCV RNA at TW 12 had an SVR rate of 75.5%, and subjects with undetectable HCVRNA at TW 24 had an SVR rate of 81.8%.

3.2 Evaluation of Safety

Please refer to the clinical review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Schering presented SVR by baseline demographic data and disease characteristics in Table 5. They reported:

- When accounting for HCV genotype, the SVR rate did not differ appreciably between sex or age groups.
- The SVR rate (71.8%) in subjects with HCV Genotype 1 was much higher in subjects with a baseline low viral load (<600,000 IU/mL) than the SVR rate (20%) in subjects with a baseline high viral load (≥600,000 IU/mL)
- In subjects with Genotypes 2, 3, or 4, SVR rates were high (90.9% to 100%), regardless of baseline viral load.
- Subjects with HCV Genotype 1 who took ribavirin capsules had a higher SVR rate, 68.2%, compared with a SVR rate of 46.0% of those who took oral solution.
- There was no difference in response rate when different weight-based ribavirin doses (mg/kg) were compared. High viral load is associated with lower response rate in Genotype 1 subjects.

Table 5: Sustained Virologic Response by Demographic Data, Baseline Disease Characteristics, and Ribavirin Form

	HCV Genotype 1 n=72		HCV Genotype 2 n=15		HCV Genotype 3 n=15		HCV Genotype 4 n=5	
	Virologic Response		Virologic Response		Virologic Response		Virologic Response	
	n[a]	(%)	n[a]	(%)	n[a]	(%)	n[a]	(%)
Overall Response	38/72	(52.8)	14/15	(93.3)	14/15	(93.3)	4/5	(80)
Sex								
Female	22/39	(56.4)	9/9	(100)	3/4	(75.0)	3/4	(75.0)
Male	16/33	(48.5)	5/6	(83.3)	11/11	(100)	1/1	(100)
Age								
3-11 years	24/47	(51.1)	5/6	(83.3)	9/10	(90.0)	3/4	(75.0)
12-17 years	14/25	(56.0)	9/9	(100)	5/5	(100)	1/1	(100)
Race								
Asian	1/4	(25.0)	1/1	(100)	2/2	(100)	-	-
Black	0/1	-	-	-	-	-	-	-
Multiracial	2/3	(66.7)	-	-	1/1	(100)	-	-
White	35/64	(54.7)	13/14	(92.9)	11/12	(91.7)	4/5	(80.0)
Source of Exposure								
Other	4/5	(80.0)	-	-	2/3	(66.7)	-	-
Parenteral	1/1	(100)	2/2	(100)	2/2	(100)	-	-
Sporadic	4/10	(40.0)	-	-	2/2	(100)	-	-
Transfusion	3/4	(75.0)	2/2	(100)	-	-	1/1	(100)
Vertical Trans	26/52	(50.0)	10/11	(90.9)	8/8	(100)	3/4	(75.0)
Baseline Viral Load								
<600,000 IU/mL	28/39	(71.8)	10/11	(90.9)	5/5	(100)	3/3	(100)
≥600,000 IU/mL	9/31	(29.0)	4/4	(100)	9/9	(100)	0/1	(0)
Missing	1/2	(50.0)	-	-	0/1	(0)	1/1	(100)
Ribavirin Form								
Capsules	15/22	(68.2)	9/9	(100)	3/3	(100)	1/1	(100)
Oral Solution	23/50	(46.0)	5/6	(83.3)	11/12	(91.7)	3/4	(75.0)

HCV = hepatitis C virus; "-" = not applicable.

a: % = Percent response; n = number of responders/number of subjects.

Source: Table 10, Page 62 in the Clinical Study Report.

Predictors of SVR were assessed using logistic regression analysis in logistic regression models (Table 6). The results show that SVR are greatly influenced by HCV genotype, baseline viral load, and liver steatosis.

Table 6: Results of Logistic Regression Analyses

Effect	Odds Ratio	95% CI	P-Value
Univariate Logistic Regression Analysis			
HCV Genotype			0.0088
Genotype (1 vs other)	0.105	0.029, 0.373	0.0005
Log baseline Viral Load	0.421	0.229, 0.774	0.0054
≥600,000 IU/mL vs <600,000 IU/mL	0.250	0.105, 0.592	0.0016
Age	1.074	0.970, 1.190	0.1679
Baseline Weight (kg)	1.021	0.998, 1.046	0.0777
Gender (male vs female)	0.941	0.424, 2.090	0.8820
Race[a]			0.9425
Years Since Exposure	1.013	0.914, 1.124	0.8020
Source of Exposure[a]			0.6100
Metavir Fibrosis Score	0.591	0.215, 1.621	0.3068
Metavir Activity Score	0.897	0.557, 1.444	0.6535
Steatosis	0.372	0.173, 0.801	0.0115
Steatosis ≤5% vs >5%	1.941	0.262, 14.389	0.5164
Treatment Duration Assignment	0.047	0.006, 0.363	0.0034
PEG2b Dose ($\mu g/m^2$)	1.937	0.789, 4.754	0.1492
Ribavirin Dose (mg/kg)	0.825	0.449, 1.516	0.5354
Ribavirin Dose Form (dosing solution vs capsules)	0.350	0.135, 0.906	0.0306
Multivariate Linear Regression Analysis			
Baseline Viral Load (<600,000 vs ≥600,000)	0.201	0.071, 0.568	0.0025
HCV Genotype 1 vs Others	0.035	0.006, 0.212	0.0003
Steatosis (pretreatment score)	0.182	0.063, 0.526	0.0016
Ribavirin Form (dosing solution vs capsules)	0.208	0.060, 0.713	0.0125

CI=confidence interval; HCV=hepatitis C virus; PEG2b = peginterferon alfa-2b; vs = versus.

Note: Mean steatosis score was substituted for any missing steatosis scores.

a: Multiple categories.

Source: Table 11, Page 63 in the Clinical Study Report.

4.2 Other Special/Subgroup Populations: SVR by Baseline Viral Load, ALT, and geographical regions

Low baseline viral load might be associated with good response in the pediatric population with HCV Genotype 1. Twenty-eight of 39 subjects who had a baseline viral load less than 600,000IUml achieved SVR; 10 of 33 subjects (including 2 subjects with missing baseline viral measurements) who had baseline viral load greater or equal to 600,000IUml achieved SVR. 24 of 29 subjects who had baseline viral load less than 400,000IUml achieved SVR; 14 of 43 subjects (including 2 subjects with missing baseline viral measurements) who had baseline viral load greater or equal to 400,000IUml achieved SVR. The mean baseline viral loads of subjects with and without SVR are different, with a statistical significance 0.001.

On the other hand, it is also possible baseline viral load measurement is not a good predictor of SVR. For other genotypes, the baseline viral load was not a determinant of response. The response rates were high irrespective of the baseline viral load (Table 5). Pediatric subjects with

Genotype 3 and high viral load (≥600,000 IU/mL) responded very well to the treatment, and all of them (9/9) attained SVR. We also studied SVR in 10 subjects with the highest baseline viral load measurements among 72 subjects with genotype 1. 7 among these 10 subjects achieved SVR.

There was no apparent difference in SVR rates between subjects with normal baseline ALT levels and subjects with abnormal levels, regardless of HCV genotype.

In general, there are too few subjects to study the treatment effect in each country/region. However, the numerical results, which are listed in Table 7, suggest the treatment is effective across countries/regions.

Table 7: RSV by country/region

Country/region	# of subjects achieved RSV	# of subjects failed to achieve SVR
The United States	21	11
Argentina	8	7
Austria	1	2
Chile	1	0
France	9	2
Germany	7	4
Italy	10	1
Puerto Rico	1	1
Spain	12	9

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

We have no major issues**.**

The SVR rate in the carry-forward analysis was 65.4%. A 99% Confidence interval for this rate is [0.53, 0.77]. A 99.9% Confidence interval for this rate is [0.49, 0.80].

Schering considers the treatment efficacious if the lower bound of a 95% confidence interval of the proportion is greater than 10%**.** According to Guido et al (1998) and Shneider et al (2006), spontaneous viral clearances rarely occur after 3 years of age. We therefore believe that the 10% threshold proposed by Schering is appropriate.

5.2 Conclusions and Recommendations

The overall treatment efficacy, represented by sustained viral response (SVR) in all 107 children enrolled in the study, is consistent with its efficacy reported in adults. The study also demonstrated the treatment efficacy across countries, sex, age, and alanine aminotransferase

(ALT) levels. Although the study demonstrated the treatment efficacy in Caucasians, it has too small a sample size to evaluate its efficacy in other races. The relationship between baseline viral load and SVR is not clear. The data suggested high baseline viral load might be associated with poor SVR response in the pediatric population with HCV Genotype 1. On the other hand, it is also possible baseline viral load measurement is not a good predictor of SVR because this relationship is not demonstrated in subjects with other genotypes or in subjects with genetype 1 and with highest baseline viral load measurements.

Reference:

Shneider BL, González-Peralta R, Roberts EA .Controversies in the management of pediatric liver disease: Hepatitis B, C and NAFLD: Summary of a single topic conference. Hepatology 2006 Nov;44(5):1344-54

Guido M, Rugge M, Jara P, Hierro L, Giacchino R, Larrauri J, Zancan L, Leandro G, Marino CE, Balli F, Bagni A, Timitilli A, Bortolotti F. Chronic hepatitis C in children: the pathological and clinical spectrum. Gastroenterology. 1998 Dec;115(6):1525-9

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