CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 21-546

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21546	Submission Date(s): January 29, 2003
Brand Name	REBETOL Oral Solution
Generic Name	Ribavirin
Reviewer	Yuanchao (Derek) Zhang, Ph.D.
Team Leader	Kellie Reynolds, Pharm.D.
OCPB Division	DPE III
ORM division	DAVDP
Sponsor	Schering Corporation
Relevant IND(s)	IND 49923
Submission Type; Code	Priority (P1)
Formulation; Strength(s)	Oral Solution, 40 mg/mL
Indication	Treatment of chronic hepatitis C [redacted]

1 Executive Summary

The sponsor submitted a New Drug Application for REBETOL oral solution to be used as part of combination therapy with INTRON A for the treatment of chronic hepatitis C in previously untreated pediatric patients at least three years of age. The dosing regimen was approved with NDA 20903 SE8-013, for Rebetol capsules. The regimen is ribavirin 15 mg/kg/day (divided in 2 daily doses) with INTRON A 3 MIU/m^2 tiw.

1.1 Recommendation

The Clinical Pharmacology and Biopharmaceutics information provided by the applicant is acceptable. There are no major clinical pharmacology and biopharmaceutics issues related to the approval of this application.

However, the pharmacokinetic information is not ideal for the following reasons:

1. The study design of P00392 is not a cross-over but rather a cross-study comparison of relative bioavailability of ribavirin in oral solution vs. capsule formulation in healthy adults.
2. The application does not include a full characterization of ribavirin pharmacokinetics following administration of Rebetol oral solution to pediatric patients. The pharmacokinetics of ribavirin were characterized following administration of Rebetol capsules in children 5 years of age and older (NDA 20903, SE8-013). The current application included ribavirin Cmin data following administration of Rebetol oral solution and capsules to pediatric patients.

1.2 Phase IV Commitments

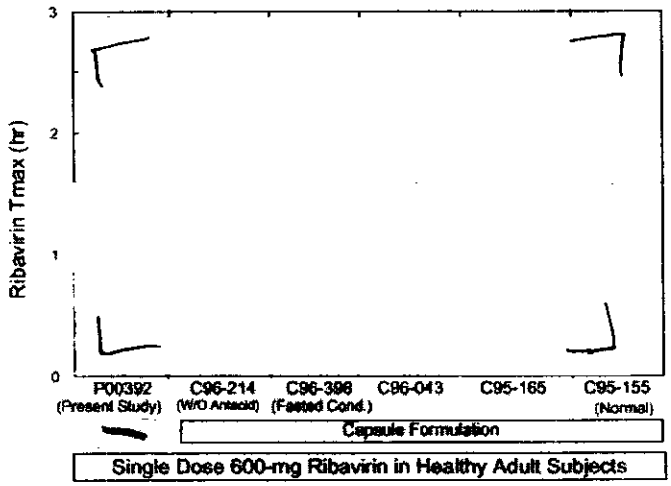
None

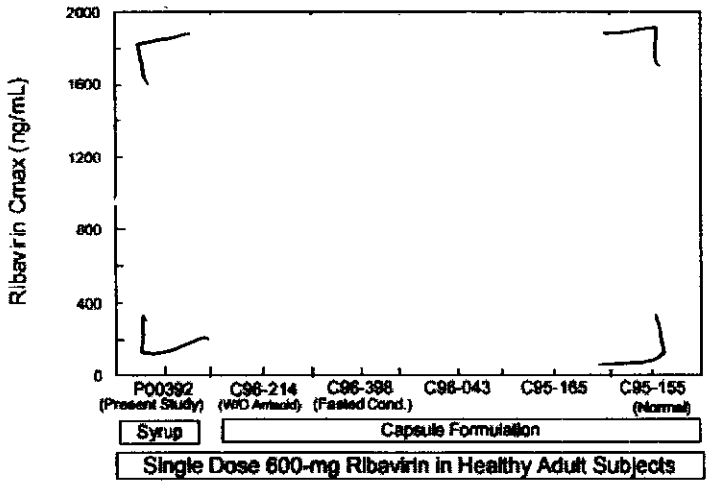
2 Table of Contents

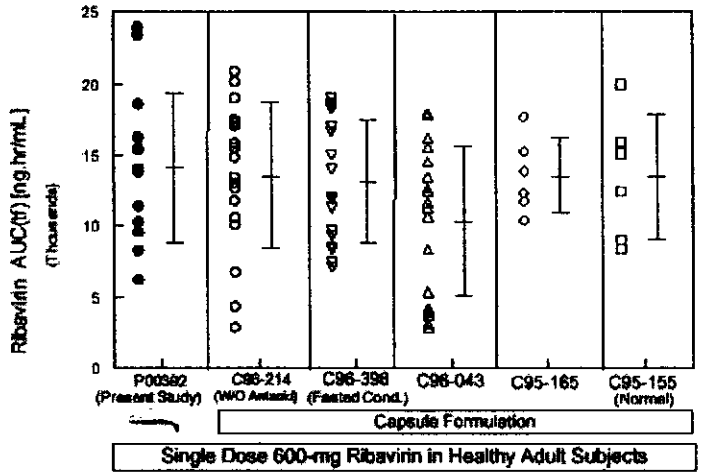
3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Ribavirin is a purine analog that is approved (in combination with INTRON A and PEG-INTRON) for the treatment of chronic hepatitis C (CHC) in adults and children only with INTRON A. The mechanism for antiviral activity against HCV-RNA and the mechanism for synergistic activity observed with INTRON A is unknown. The only available strength and formulation are oral 200 mg capsules. At the present time, because of this limitation, ribavirin (12-15 mg/kg/day) is only labeled for children > 25 kg who are able to swallow capsules. Availability of the liquid formulation would allow dosing in smaller children.

The applicant conducted a single dose bioavailability study in adults (P00392) to demonstrate comparable exposure with the oral solution to that of the same dose of the capsule. Ribavirin was rapidly absorbed following oral administration as oral solution formulation. Maximum plasma concentrations were achieved within 0.5 to 2 hr post-dose. Ribavirin Cmax and AUC values after administration of ribavirin oral solution were comparable to data obtained in previous ribavirin capsule studies in healthy adults.







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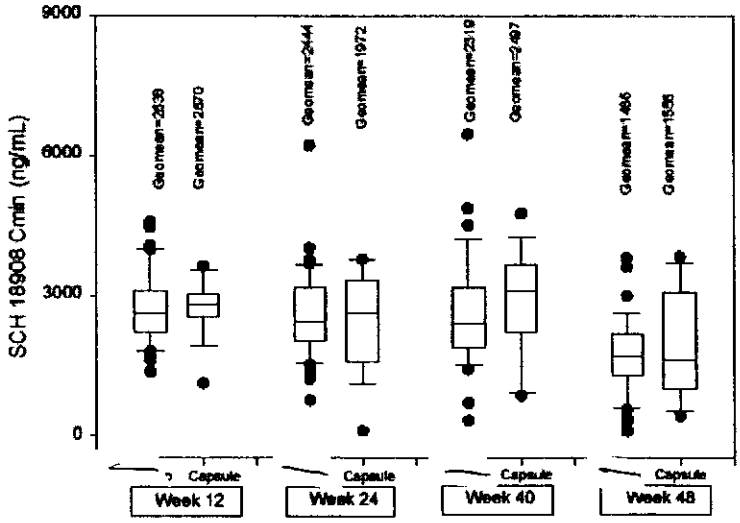
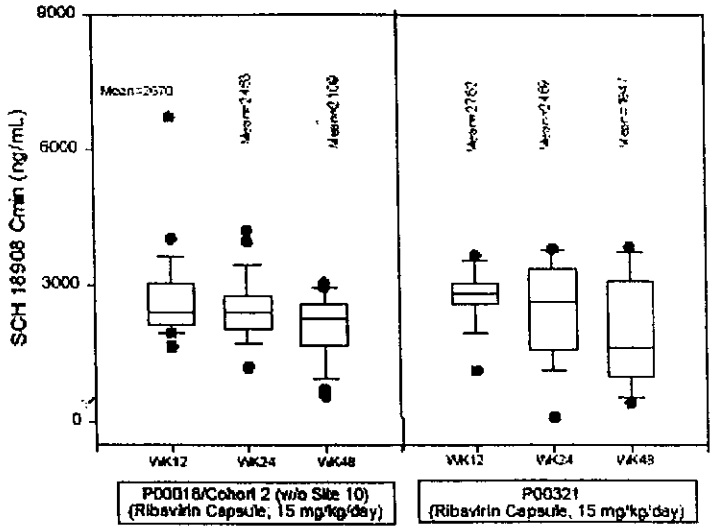
The sponsor conducted two clinical studies evaluating ribavirin plus INTRON A in pediatric patients. P00018 was a clinical trial to determine the dose and pharmacokinetics of ribavirin and the safety and efficacy of ribavirin and INTRON A in pediatric patients (age range: 5-16 years) with CHC. The study was conducted in 2 parts. The Cohort 1 was a dose-ranging PK/PD study to select a REBETOL dose based on pharmacokinetic and pharmacodynamic assessments (HCV RNA at Week 12 and hemoglobin at Week 4) for further evaluation of safety and efficacy in pediatric patients in Cohort 2 of Study P00018 and in Study P00321.

Study P00018 was reviewed by Dr. Jooran Kim. Please refer to Dr. Kim's review of Ribavirin Pediatric Supplement (NDA 20-903, SE8-013) in 2001. Briefly, in P00018, the pharmacokinetics, safety and efficacy of ribavirin 8, 12 and 15 mg/kg/day (divided in two daily doses) were initially evaluated at week 4. At week 4, ribavirin 8, 12 and 15 mg/kg/day yielded mean (%CV) Cmax and AUC values that appeared generally dose proportional. These PK parameters in pediatric patients were comparable to adult PK values observed with adult ribavirin doses of 800, 1000 and 1200 mg/day (divided in two daily doses), respectively. Mean ribavirin clearance in children ranged between 0.23-0.27 L/h/kg (16-26%) for all dose groups. In terms of activity, at Weeks 4 and 12, the 15 mg/kg/day dose produced the greatest reduction in HCV RNA and hemoglobin levels, compared to the 8 and 12 mg/kg/day doses. Because the decline in hemoglobin levels was not worse than the reduction observed in adults, ribavirin 15 mg/kg/day was the dose selected for further development in Cohort 2 of P00018 and in P00321.

P00321 evaluated the safety, tolerability and efficacy of ribavirin 15 mg/kg (ribavirin 200 mg capsules or 40 mg/mL oral solution) and INTRON A 3 MIU/m^2 for 48 weeks in pediatric patients (age range: 3-16 years) with CHC. Patients <5 years of age received REBETOL Oral Solution and those ≥5 years of age received either REBETOL Oral Solution or Capsules (age ranges: 9 – 16 years for subjects receiving capsules, and 3-16 years for subjects receiving oral solution). Week 12 to Week 48 ribavirin Cmin values following administration of Rebetol oral solution to pediatric patients were similar to Cmin values following administration of Rebetol capsules to pediatric patients. The mean REBETOL Cmin at Treatment Weeks 12, 24, and 48 for subjects who received REBETOL capsules in P00321 were similar to those in the P00018 Cohort 2, who also received REBETOL capsules.





4 Question Based Review

4.1 General Attributes

4.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

REBETOL Oral Solution is a clear, colorless to pale or light yellow bubble gum-flavored liquid. Each milliliter of the solution contains 40 mg of ribavirin and the inactive ingredients sucrose, glycerin, sorbitol, propylene glycol, sodium citrate, citric acid, sodium benzoate, natural and artificial flavor for bubble gum #15864, [redacted] and water.
For chemistry and physical-chemical properties of the drug substance, please refer to Dr. Rajagopalan's review of ribavirin in 1998.

4.1.2 What is the proposed mechanism of drug action and therapeutic indication?

Ribavirin (in combination with interferon alfa-2b) was approved in 1998 for the treatment of chronic hepatitis C (CHC). There has been in vitro evidence since the 1970s of antiviral activity against some DNA and RNA viruses; the mechanism of action, however, has not yet been fully determined.

4.1.3 What is the proposed dosage and route of administration?

[redacted]

4.1.4 What efficacy and safety information contribute to the assessment of clinical pharmacology and biopharmaceutics study data?

P00018:
Age range: 5-16 years
Study duration: 48 weeks

Cohort 1 (n=61): Dose-ranging trial of ribavirin (8-15 mg/kg/day) and INTRON A in pediatric patients with CHC: PK, safety and efficacy (50 mg capsules)
Cohort 2 (n=35): Safety, efficacy and tolerability evaluation of ribavirin 15 mg/kg/day + INTRON A (50 mg capsules)

P00321 (n=70):
Age range: 3-16 years
Study Duration: 48 weeks
Phase III: Safety, efficacy and tolerability evaluation of ribavirin 15 mg/kg/day + INTRON A (ribavirin 200 mg capsules, 40 mg/mL oral solution)

4.2 General Clinical Pharmacology

4.2.1 What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

Please refer to Dr. Kim's review of Ribavirin Pediatric Supplement (NDA 20-903, SE8-013) in 2001

4.2.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?

Please refer to Dr. Kim's review of Ribavirin Pediatric Supplement (NDA 20-903, SE8-013) in 2001.

4.2.3 What is the basic PK of ribavirin oral solution in adults?

Ribavirin is rapidly absorbed following oral administration as oral solution formulation. Maximum plasma concentrations are achieved within 0.5 to 2 hr post-dose. Ribavirin Cmax and AUC values after administration of ribavirin oral solution are comparable to data obtained in previous ribavirin capsule studies in healthy adults.

TABLE 1. Mean (% CV) Pharmacokinetic Parameters for REBETOL When Administered Individually to Adults

Parameter	REBETOL		
	Single Dose 600 mg Oral Solution (N=14)	Single Dose 600 mg Capsules (N=12)	Multiple Dose 600 mg BID Capsules (N=12)
T_{max} (hr)	1.00(34)	1.7 (46) ***	3 (60)
C_{max} *	872 (42)	782 (37)	3680 (85)
AUC_{tf} **	14098 (38)	13400 (48)	228000 (25)
$T_{1/2}$ (hr)		43.6 (47)	298 (30)
Apparent Volume of Distribution (L)		2825 (9) †	
Apparent Clearance (L/hr)		38.2 (40)	
Absolute Bioavailability		64% (44) ††	

* ng/mL
** ng.hr/mL
*** N = 11
† data obtained from a single-dose pharmacokinetic study using ^{14}C labeled ribavirin; N = 5
†† N = 6

4.2.4 How does the PK of ribavirin in children compare to that in adults?

The PK parameters in pediatric patients receiving ribavirin as capsule at 8, 12 and 15 mg/kg/day (divided in two daily doses) were comparable to adult PK values observed with adult ribavirin doses of 800, 1000 and 1200 mg/day (capsule, divided in two daily doses), respectively.

4.2.5 What is the basic PK of ribavirin oral solution in children?

Full pharmacokinetic profiles of ribavirin oral solution have not been studied in children. However, Week 12 to Week 48 ribavirin Cmin values following administration of Rebetol oral solution to pediatric patients were similar to Cmin values following administration of Rebetol capsules to pediatric patients.

4.2.6 What dose was selected for pediatric patients and how was this dose selected?

Based on ribavirin pharmacokinetic and pharmacodynamic assessments in Cohort 1 in P00018, ribavirin 15 mg/kg was chosen as the dose for evaluation in the second cohort of P00018 and Study P00321, which evaluated the safety, efficacy and tolerability of ribavirin 15 mg/kg with INTRON A. Based on these safety and efficacy data, ribavirin 15 mg/kg/day was selected as the dose in pediatric patients with CHC. Please also refer to Dr. Kim's review of Ribavirin Pediatric Supplement (NDA 20-903, SE8-013) in 2001.

4.3 Intrinsic Factors

4.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics? What dosage regimen adjustments, if any, are recommended for each of these subgroups?

Please refer to Dr. Kim's review of Ribavirin Pediatric Supplement (NDA 20-903, SE8-013) in 2001.

4.4 Extrinsic Factors

4.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

Extrinsic factors in pediatric patients have not been evaluated in this submission.

4.4.2 Drug-Drug Interactions

In general, a significant drug interaction has not been observed with concomitant administration of ribavirin and INTRON A.

4.5 General Biopharmaceutics

In adults, the bioavailability of ribavirin increased significantly (70%) with food. Because subjects took ribavirin without regard to food in previous clinical trials, the pediatric studies were conducted the same way, but patients were instructed to take ribavirin consistently with respect to food.

4.6 Analytical

All plasma samples were assayed for ribavirin concentration using a validated high performance liquid chromatography [redacted] method. The lower limit of quantitation (LOQ) of the assay was established at [redacted] for ribavirin. All assays were performed at [redacted]

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6 Appendix

6.1 Individual Study Reviews (2)

TITLE: Bioavailability of A Oral solution Formulation of Ribavirin (Protocol P00392)

BACKGROUND: The current oral solid dosage formulation of ribavirin is a 200 mg capsule. As part of a development program for new formulations, a 40 mg/mL oral solution formulation is being developed for use in pediatric patients with chronic hepatitis C. This open-label study in healthy, adult subjects was designed to assess the bioavailability of the oral solution formulation, prior to using it in pediatric patients.

OBJECTIVES: To assess the bioavailability of a 40 mg/mL oral solution formulation of ribavirin in healthy adult male and female subjects.

SUBJECTS AND STUDY DESIGN: Phase I, open-label, uncontrolled, single-dose bioavailability study. Fourteen subjects received treatment. A single 600mg (15 mL) dose of 40 mg/mL oral solution was administered to each subject in the morning after fasting for a minimum of 10 hours.

INVESTIGATOR AND STUDY LOCATION:

FORMULATION: 40 mg/mL ribavirin oral solution, batch No. 39609-023-A

SAMPLE COLLECTION: Blood samples were collected for determination of the plasma pharmacokinetic profile of ribavirin. Ten milliliters (10 mL) of blood were collected just prior to drug administration (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 16, 24, 48, 72, 96 and 120 hours after dosing.

ASSAY: All plasma samples were assayed for ribavirin concentration using a validated high performance liquid chromatography (HPLC) method. The lower limit of quantitation (LOQ) of the assay was established for ribavirin. All assays were performed at

PHARMACOKINETIC DATA ANALYSIS: Non-compartmental methods were used. The area under the plasma concentration-time curve from Time 0 to the time of the final quantifiable sample (AUC(tf)) was calculated using the linear trapezoidal method.

PHARMACOKINETIC RESULTS:

Table 1. Mean ribavirin pharmacokinetic parameters in healthy adults following a single oral dose of 600mg (15 mL) of 40 mg/mL oral solution

	Mean	%CV
Cmax (ng/mL)	872	42
Tmax (hr)	1.0	34
AUC(tf) (ng-hr/mL)	14098	38

Figure 1. Mean plasma ribavirin concentration-time profiles in healthy adults after a single oral dose of 600 mg as oral solution

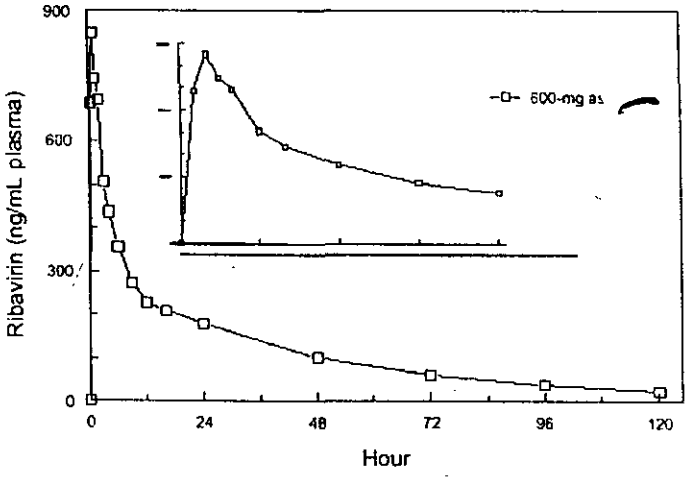
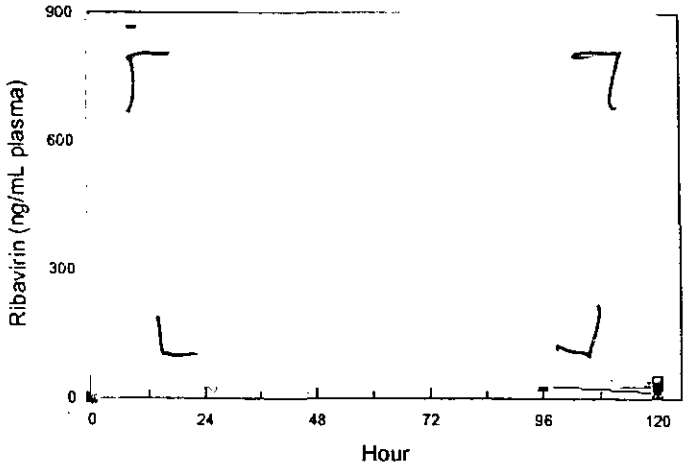


Figure 2. Comparison of ribavirin concentration-time profiles, obtained from six studies [P00392 (Present Study), C96-214, C96-398, C96-043, C95-165 and C95-155] in healthy adults administered 600-mg ribavirin as oral solution or capsule



Note: The time period of insert in Figures 1 and 2 was from 0 to 8 hours post dose (2 hours/unit on X-axis).

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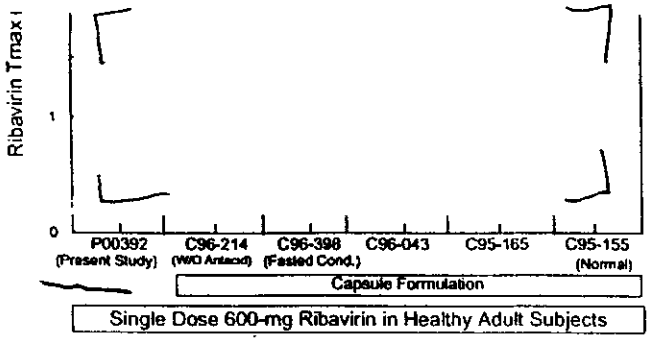

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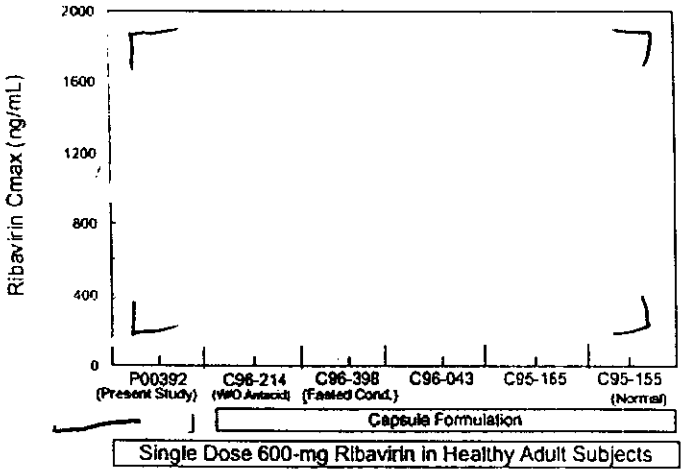

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SAFETY RESULTS: Five of 14 (36%) subjects reported at least one adverse event during the treatment period. The most common adverse event (regardless of association to treatment) was headache. All adverse events were mild in severity except one report of constipation that was moderate in severity. No serious or unexpected adverse events were reported. No subject discontinued participation in the study due to adverse events.

CONCLUSIONS AND DISCUSSIONS: Plasma ribavirin concentrations reflected high inter-subject variability as shown by the high %CV (30-42%) of pharmacokinetic parameters (Table 1). Ribavirin pharmacokinetic parameters from the present study (P00392) were compared with those obtained in healthy adults
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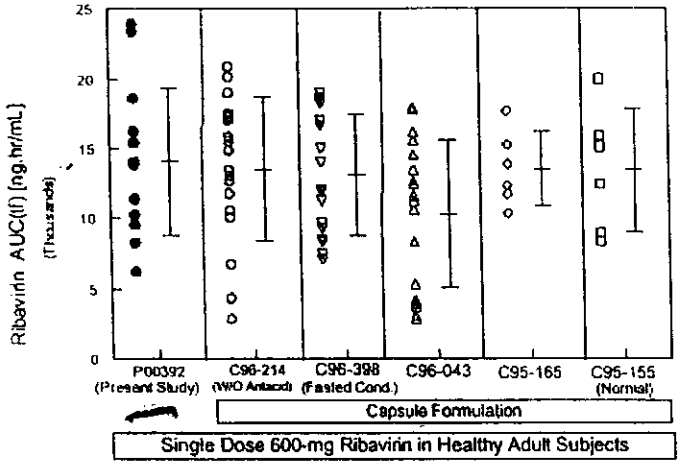

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plasma concentrations were achieved within 0.5 to 2 hr post-dose. Ribavirin Cmax and AUC values after administration of ribavirin oral solution were comparable to data obtained in previous ribavirin capsule studies in healthy adults.

NOTE: The study design is not a cross-over but rather a cross-study comparison of relative bioavailability of ribavirin in oral solution vs. capsule formulation in healthy adults.

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TITLE: 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 (Protocol No. P00321)

BACKGROUND: Schering-Plough conducted a REBETOL dose-ranging study in pediatric CHC subjects who had not been treated with interferon previously or who had relapsed following prior interferon treatment. The objective of the study was to assess the pharmacokinetics/pharmacodynamics and safety of the combination of INTRON A plus REBETOL and to select a dose of REBETOL for further evaluation of efficacy in children (P00018). All subjects received INTRON A 3 MIU/m^2 SC TIW in combination with REBETOL 8, 12, or 15 mg/kg/day. Based on pharmacokinetic and pharmacodynamic assessments at Treatment Weeks 4 and 12, a REBETOL dose of 15 mg/kg/day was selected as the optimal dose to be used in combination with INTRON A. The current study, P00321 was conducted to further assess the efficacy, safety and tolerability of the combination of INTRON A 3 MIU/m^2 SC TIW plus REBETOL 15 mg/kg/day orally for 48 weeks in pediatric subjects with chronic hepatitis C.

OBJECTIVES: To assess the efficacy, safety and tolerability of the combination INTRON A 3 MIU/m^2 three times weekly plus REBETOL 15 mg/kg/day for 48 weeks in pediatric subjects with chronic hepatitis C.

SUBJECTS AND STUDY DESIGN: Phase III, fixed dose, single arm, open-label, multinational, 48 weeks treatment and 24 weeks follow-up. 70 subjects who had not been previously treated with interferon, ribavirin or combination interferon plus ribavirin (3-16 years old) were enrolled and treated. Patients <5 years of age received REBETOL Oral Solution and those ≥5 years of age received either REBETOL Oral Solution or Capsules. Demographic data of the subjects enrolled in the study are listed below.

Protocol No. P00321

	INTRON A 3MIU/m^2 TIW and REBETOL 15 mg/kg/day		
	All Subjects (n=70)	Capsules (n=15)	(n=55)
Age (years)			
Mean	10.2	13.7	9.2
Median	10.5	14.0	10.0
Range (min-max)	3-16	9-16	3-16
Age Range (n, %)			
3-6 yr	17 (24)	0	17 (31)
7-9 yr	11 (16)	1 (7)	10 (18)
10-12 yr	19 (27)	3 (20)	16 (29)
13-15 yr	16 (23)	7 (47)	9 (16)
>15 yr	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)	10-92	49-92	10-87
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)	87-179	152-179	87-167
HCV Genotype (n, %)[a]			
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

INVESTIGATOR AND STUDY LOCATION: Multicenter

FORMULATION: [redacted]

SAMPLE COLLECTION: Serum samples were collected at Treatment Weeks 12, 24, 40 and 48 for a trough serum concentration analysis for interferon alfa-2b and ribavirin.

ASSAY: All plasma samples were assayed for ribavirin concentration using a validated high performance liquid chromatography- [redacted] method. The lower limit of quantitation (LOQ) of the assay was established at [redacted] for ribavirin.

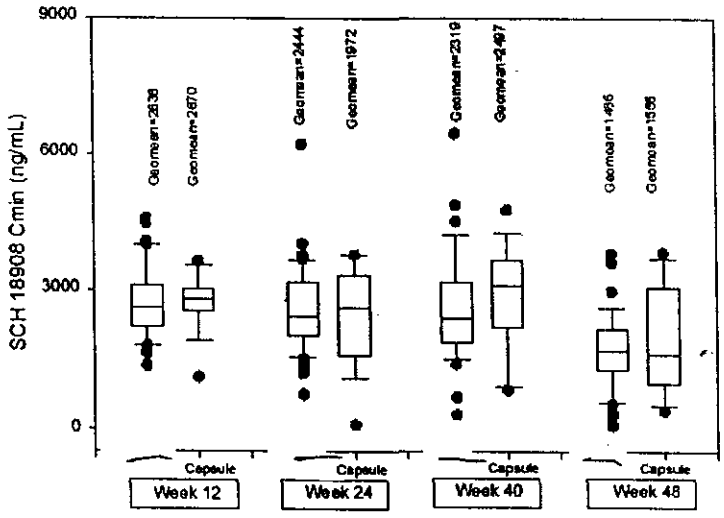
PHARMACOKINETIC DATA ANALYSIS: Summary statistics of C_{trough} were provided.

PHARMACOKINETIC RESULTS:

Table 1. Mean Plasma REBETOL Cmin Values Following Oral solution or Capsule Treatment

	[redacted]		Capsule	
Week	Arithmetic Mean (%CV)	Geometric Mean	Arithmetic Mean (%CV)	Geometric Mean
12	2735 (28)	2638	2762 (24)	2670
24	2592 (35)	2444	2469 (47)	1972
40	2607 (48)	2319	2828 (52)	2497
48	1756 (46)	1486	1947 (56)	1556

Figure 1. Mean Plasma Ribavirin Cmin Values Following Oral solution or Capsule Treatment



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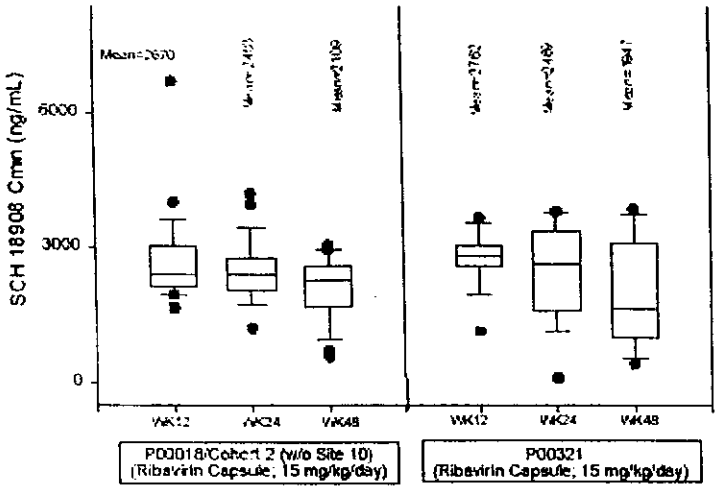

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Table 2. Mean Serum Interferon alfa-2b Cmin Values for P00321

Dose	Week	Time (hr)	Cmin, IU/mL	%CV
15 mg/kg/day	12	0	22.8	168
REBETOL +	24	0	26.2	134
3 MIU/m^2	40	0	53.0	134
INTRON A TIW	48	0	41.8	152

Table 3. Mean Serum Interferon alfa-2b Cmin Values for Cohort 1 of P00018

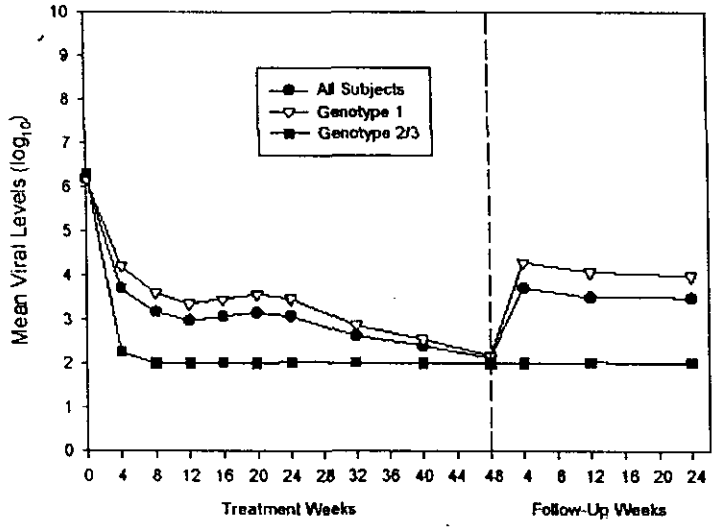
			n		Cmin, IU/mL		%CV	
Dose	Week	Time (hr)	With Site 10	Without Site 10[a]	With Site 10	Without Site 10[a]	With Site 10	Without Site 10[a]
REBETOL	12	0	60	56	24.2	25.6	180	175
15 mg/kg/day +	24	0	52	49	38.3	39.1	156	157
INTRON A	36	0	34	31	49.8	53.0	120	116
3 MIU/m^2 TIW	48	0	41	38	40.7	42.1	120	120

a: Excluding data for subjects P00018-10/220, P00018-110/222, P00018-10/224 and P00018-10/226.

EFFICACY RESULTS: INTRON A 3 MIU/m^2 TIW plus REBETOL 15 mg/kg/day therapy was effective in inducing loss of HCV-RNA in previously untreated pediatric subjects with chronic hepatitis C (CHC). Sustained virologic response with Interferon alfa-2b /Ribavirin (15) in pediatric subjects was 49%, 38% and 82% for all genotypes, Genotype 1 and Genotype 2/3, respectively. These sustained virologic response rates in pediatric subjects were similar to the corresponding rates for adults (41-47%, 29-33% and 65-79%). For subjects with an abnormal ALT at entry, normalization was correlated with sustained virologic response.

Figure 3. Mean Viral Levels (log10)

All subjects (n=70), Genotype 1 (n=52), Genotype 2/3 (n=17)
Number of subjects at Treatment Week 48: all (39), Genotype 1 (27), Genotype 2/3 (12)



SAFETY RESULTS: Combination INTRON A/REBETOL therapy was well tolerated in pediatric CHC subjects. The most common AEs were fever, headache, fatigue, anorexia, vomiting, abdominal pain, myalgia, weight decrease, rigors, and nausea. The flu-like adverse events and gastrointestinal complaints decreased with time, as typically observed with interferon treatment. Rash and pruritus, which are known side effects of REBETOL, decreased slightly over time with INTRON A/REBETOL treatment, while pharyngitis, acne, alopecia and lymphadenopathy increased in incidence over time. AEs were primarily mild to moderate in severity and not treatment limiting. Discontinuation due to AEs was infrequent (7%) and the reasons varied.

CONCLUSIONS AND DISCUSSIONS: The mean Cmin of ribavirin on Treatment Week 12 to Treatment Week 48 following administration oral solution or capsule formulation were similar. Relative bioavailability (geometric mean ratio as %) of oral solution-to-capsule, for Treatment Weeks 12, 24, 40, and 48 were 99, 124, 93, and 95, respectively. The mean ribavirin Cmin at Treatment Weeks 12, 24, and 48 for subjects who received ribavirin capsules in P00321 study were similar to those in the P00018 Cohort 2, who also received ribavirin capsules. The mean trough interferon alfa-2b concentrations for P00321 and P00018 Cohort 1 (with and without Site 10 data) at Treatment Weeks 12, 24, and Week 48 were similar.

6.2 Cover Sheet and OCPB Filing /Review Form

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-546**	**Brand Name**	**Rebetol**
OCPB Division (I, II, III)	**DPE III**	**Generic Name**	**Ribavirin**
Medical Division	**HFD-530**	**Drug Class**	**Purine Analog**
OCPB Reviewer	**Derek Zhang**	**Indication(s)**	
OCPB Team Leader	**Kellie Reynolds**	**Dosage Form**	**Oral solution (40 mg/mL)**
		Dosing Regimen	**15 mg/kg/day (divided in two daily doses), (for children < 25 kg)**
Date of Submission	**January 29, 2003**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**June 30, 2003**	**Sponsor**	**Schering**
PDUFA Due Date	**July 30, 2003**	**Priority Classification**	**Priority Review**
Division Due Date	**June 30, 2003**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				

fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	2		
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
No reference:	X	1		
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Other Studies				
Pediatric development plan				
Literature References				
Total Number of Studies		3		
Filability and QBR comments				

–	"X" if yes	Comments
Application filable ?	X	If the application is not filable,
Comments sent to firm ?		applicable
QBR questions (key issues to be considered)	1. Are adequate PK data provided in pediatrics with oral solution formulation?	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-546, HFD-850 (P. Lee), HFD-860 (M. Mehta)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Derek Zhang
7/28/03 04:47:20 PM
BIOPHARMACEUTICS

Kellie Reynolds
7/29/03 08:15:01 AM
BIOPHARMACEUTICS

APPEARS THIS WAY
ON ORIGINAL