CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-945

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

1 Page(s) Withheld

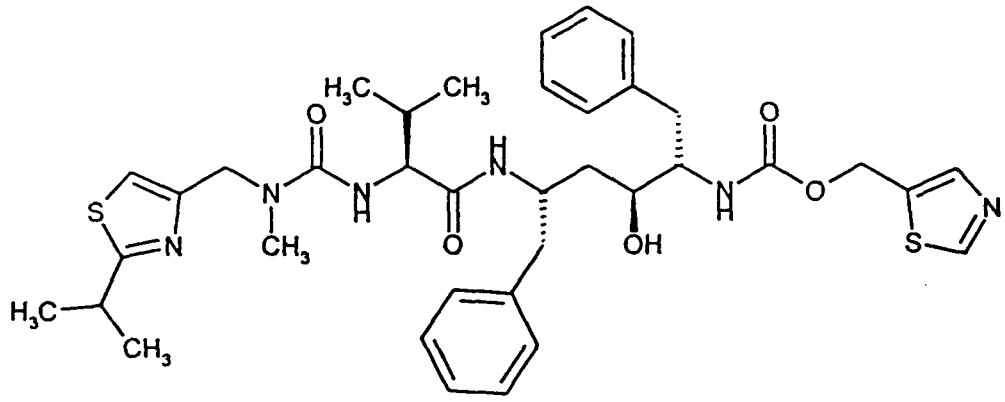
Clinical Pharmacology/Biopharmaceutics Review

Ritonavir soft elastic capsule 100mg: —	Abbott Laboratories
Norvir ———	Abbott Park, IL 60064
Reviewer: A. Noory	Submission Date: November 21, 1997
NDA 20-945	**Draft Date: 6-8-98; Final Date: 8-19-98**

Review of a Bioequivalency Study

I. Background:

Ritonavir (Norvir®) is an HIV protease inhibitor, indicated for the treatment of HIV infection. A solution and a capsule product of Norvir® were approved in March of 1996 (NDA 20-659 and NDA 20-680). Norvir —ritonavir in soft elastic capsule), is a line extension of the capsule product with a change in formulation as well as the capsule shell. The pharmacokinetics and bioavailability section of this NDA consists of a bioequivalenc study between the soft elastic capsule (SEC) formulation of ritonavir and the currently marketed semi-solid capsule formulation (NDA 20-680). The chemical name of Norvir — is 10-hydroy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)]. The empirical formula for ritonavir is $C_{37}H_{48}N_6O_5S_2$ with a molecular weight of 720.95. It is a white to light tan powder and is freely soluble in methanol and ethanol, soluble in isopropanol and insoluble in water. Ritonavir has the following structure:



II. Overview of pharmacokinetics section:

The human pharmacokinetic and bioavailability section of this NDA consists of a randomized 4-way crossover single dose study. In this study the sponsor evaluated the bioequivalency of the new soft elastic capsule formulation Norvir — (100mg ——— , to the currently marketed Norvir® capsule formulation. Also, the applicant assessed the bioavailability of Norvir — when administered in the fasting state.

Formulation:

The formulation of Norvir — (100mg — and the currently marketed Norvir® capsule are shown in pages 9-11 of the appendix.

Analytical:

The analysis of ritovavir (ABT-538) in human plasma was carried out by — — The plasma samples were assayed for ritonavir under the supervision of Abbott Laboratories Drug Analysis Department (D-46W) using an HPLC assay procedure. Ritonavir and A-86093 an internal standard were extracted from human plasma. The assay was shown to be specific for ritonavir and linear over a range of — . The lower limit of quantitation was — Representative chromatograms are included in the appendix, page 12.

III. Bioequivalence:

According to the label, Norvir® should be given with food, if possible. Therefore the bioequivalence study was done under fed conditions. In order to assess the bioavailability of newly formulated soft elastic capsules, Norvir — 100mg — the applicant conducted a randomized four-way crossover study. In this study twenty healthy subjects (male and female) were enrolled as shown in the following table.

[redacted]	No. of Subj.	Mean Age (yr)	Range (yr)	Mean Weight (lb)	Range (lb)
Female	6	29.2	19 - 42	136.7	123 - 148
Male	14	31.3	21 - 45	170.4	146 - 192

The treatments of the study are shown in the following table.

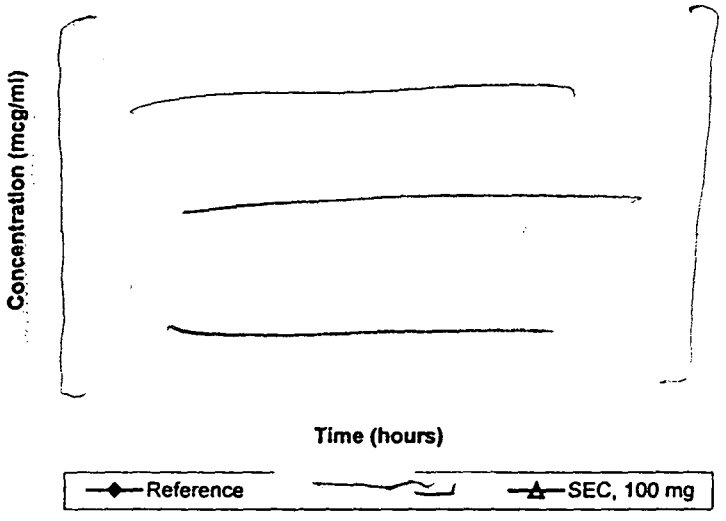
Treatment	Drug Product	Dose	Dosage Form	Mfg. Lot #	Lot Size
A* (Fed)	Norvir® (6X100 mg)	600mg	semi-solid capsule (L)	24-607-AF-21	[redacted]
B (Fed)	Norvir — —	600mg	soft elastic capsule —	23-546-AR-R1/7321N	— of commercial
C (Fasted)	Norvir — —	600mg	soft elastic capsule —	23-546-AR-R1/7321N	
D (Fed)	Norvir — (6X100 mg)	600mg	soft elastic capsule —	23-542-AR-R1/7317N	— of commercial

* - Reference product (currently marketed Norvir® semi-solid capsule)

A summary of results and the plasma concentration time profile are shown below.

Pharmacokinetic Parameters AUC, C_{max}, Tmax; Mean ± SD				
Product	PK-Parameter	Test	Reference	90% Confidence interval
Norvir — 6X100mg	$AUC_{(0-\infty)}$ (µg*h/ml)	108.1 ± 33.0	117.5 ± 33.5	84.7 - 104.5
	C_{max} (µg/ml)	11.98 ± 3.33	12.91 ± 2.71	81.1 - 105.7
	Tmax (hours)	4.8 ± 1.0	3.9 ± 0.3	[redacted]
Norvir — —	$AUC_{(0-\infty)}$ (µg*h/ml)	111.3 ± 39.4	117.5 ± 33.5	84.6 - 103.9
	C_{max} (µg/ml)	12.57 ± 3.83	12.91 ± 2.71	84.0 - 108.8
	Tmax (hours)	4.6 ± 0.9	3.9 ± 0.3	[redacted]

Norvir: Plasma Concentration Time Profile



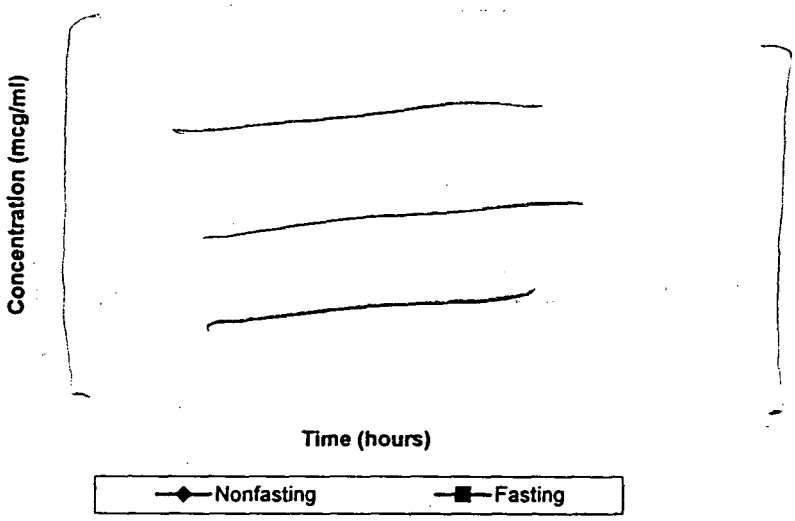
The findings of this study indicate that both 100mg ~~~ Norvir — are bioequivalent to the marketed Norvir® based on the 90% confidence interval for both AUC and C_{max}.

IV. Food Effect:

The applicant also evaluated the bioavailability of the new SEC-formulation under fasting conditions. The following table and graph contain the summary result for treatment B (fed) and treatment C (fasted).

Pharmacokinetic Parameters AUC, C_{max}, T_{max}; Mean ± SD				
Product	PK-Parameter	Nonfasting	Fasting	90% Confidence interval
Norvir — ~~~	$AUC_{(0-\infty)}$ (µg*h/ml)	111.3 ± 39.4	98.0 ± 41.2	84.7-104.5
	C_{max} (µg/ml)	12.57 ± 3.83	13.52 ± 5.88	81.1-105.7
	Tmax (hours)	4.6 ± 0.9	3.5 ± 0.6	

Norvir SEC: Administered Under Fasting and Nonfasting Condition



The data show that when Norvir — is administered with food, the AUC is about 17% ± 28% greater than in the fasting state, based on mean of the difference for each individual. Moreover, the two treatments are bioequivalent based on the 90% confidence interval being within 80 to 125%.

V. Dissolution:

The current quality control dissolution methodology for Norvir® capsules, the reference product is:

Apparatus:
Paddle speed:
Dissolution medium:
Dissolution volume:
Sampling Time
Dissolution Specification: Q= — at —

In order to facilitate a dissolution test with shorter sampling time (—), the applicant has developed a different dissolution test for their new capsule formulation (Norvir —). The equilibrium solubility of ritonavir was determined at — in —. Of all these media, sink conditions were achieved only in —. Testing in — ndicated incomplete release from capsules, around — in —. It was noted that —. This indicated poor dispersion of the — ormulation, making investigation of an alternative medium necessary. Several — were evaluated for testing ritonavir capsules. The effect of the

[redacted] on the dispersion of the formulation was visually observed. [redacted] were found to be most effective for dispersing the formulation. [redacted], is the [redacted] chosen for the dissolution medium because, visually, it dispersed the capsule formulation and did not cause interference in the analytical method. Different concentrations of [redacted] were used to generate dissolution profiles, and based on visual observations and the data, [redacted] was chosen as the final dissolution medium. The solubility of ritonavir in [redacted] was extrapolated from data generated at various concentrations of this [redacted]. The following table contains the solubility of ritonavir in some of the media tested.

Medium	Solubility (mg/ml)
[redacted]	
[redacted]	

* - Solubility was determined by extrapolation.

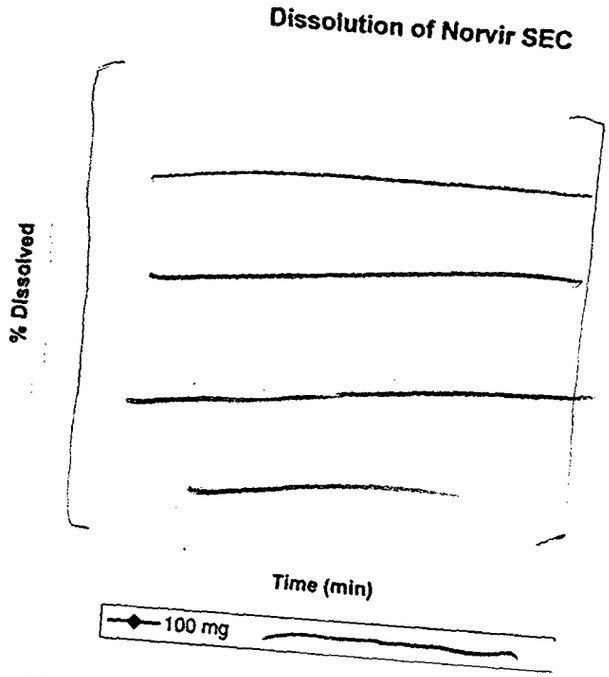
The proposed dissolution methodology and specification by the sponsor is:

Apparatus: [redacted]
Paddle Speed: [redacted]
Dissolution Medium: [redacted]
Dissolution Volume: [redacted]
Dissolution Specification: Q = Not Less Than [redacted] at [redacted]

The results of the dissolution tests are located in pages 13-25 of the appendix and the summary results for the products used in the bioequivalence study and proposed market product are shown in the following table and graph.

Dissolution Profile of Norvir SEC® Used in the Bioequivalence Study: N=12; Mean (%CV)			
Time (min.)	100 mg (23-542-AR-RI)*	[redacted]	[redacted]
10	73.8 (26.6)	[redacted]	[redacted]
20	100.0 (1.0)	[redacted]	[redacted]
30	100.9 (0.0)	[redacted]	[redacted]

* - Batches used in the bioequivalence study.



The results indicate that the dissolution of Norvir [redacted] in [redacted] is [redacted] soft elastic capsules meet the requirements for approval. The 100mg [redacted]

V1. Labeling Comment: (To be sent to the applicant)

Under heading of Pharmacokinetics second paragraph [redacted] should be replaced with **After a single 600 mg dose under non-fasting condition,** [redacted] Also in the same paragraph sentence eight, change [redacted] (based on mean of individual difference ± SD).

VII. Conclusions/Recommendation:

In support of the pharmacokinetics and bioavailability portion of this NDA, the applicant submitted the result of a bioequivalency study. This study demonstrates that the reformulated oral capsule (Norvir —— is bioequivalent to the marketed capsule product, Norvir®. Also, this study further demonstrates that the bioavailability of Norvir —— will decrease by about 12% when it is administered under fasting conditions compared to administration with food. NDA 20-945 meets the requirements for approval under section §14.50 (d) (3) of title 21 of the Code of Federal Regulation (CFR).

Note: It is noted that additional dissolution data are likely to be submitted prior to the regulatory action on this submission. Such data, will be the subject of a separate review.

8/19/98

Assadollah Noory
Pharmacokineticist
Division of Pharmaceutical Evaluation III

Team Leader: Janice Jenkins, Ph.D

8/20/98

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CC: NDA 20-945 (ORIG),
HFD-530/DIV. File
HFD-530/Prj. Mgr./Gump
HFD-880 (Noory)
HFD-880 (Jenkins)
HFD-880 (Lazor)
(CDR. Attn. B. Murphy)
HFD-344 (Viswanathan)

Appendix

Table 1. List of Ingredients - Standard Amounts and Ranges of Each Ingredient in Ritonavir [redacted] Soft Elastic Capsules (List 3994)

[redacted] Ingredients	[redacted] Item Number	Amount per Capsule (Standard)	Amount per Capsule (High)	Amount per Capsule (Low)
[redacted] USP	[redacted]	[redacted] mg	[redacted] mg	[redacted] mg
Butylated Hydroxytoluene (BHT), NF, EP	[redacted]	[redacted] mg	[redacted] mg	[redacted] mg
Oleic Acid [redacted], NF, EP[1]	[redacted]	[redacted] mg	[redacted] mg	[redacted] mg
Ritonavir	[redacted]	[redacted] mg	N/A mg	N/A mg
Polyoxyl 35 Castor Oil, NF, EP	[redacted]	[redacted] mg	[redacted] mg	[redacted] mg
[redacted] NF	[redacted]	N/A	N/A	N/A
Encapsulation and [redacted] Ingredients				
[redacted]		[redacted] mg	[redacted] mg	[redacted] mg
[redacted]		[redacted]	N/A	N/A
[redacted]		[redacted]	N/A	N/A
[redacted]		[redacted]	N/A	N/A
[redacted]	[redacted]	[redacted]	N/A	N/A
or				
[redacted]	[redacted]	[redacted]	N/A	N/A

(1) [redacted]
(2) [redacted]

Table 2. List of Ingredients - Standard Amounts and Ranges of Each Ingredient in Ritonavir 100 mg Soft Elastic Capsules (List 3990)

Ingredients	Item Number	Amount per Capsule (Standard)	Amount per Capsule (High)	Amount per Capsule (Low)
USP		mg	mg	mg
Butylated Hydroxytoluene (BHT), NF, EP		mg	mg	mg
Oleic Acid NF, EP[1]		mg	mg	mg
Ritonavir		100.0 mg	N/A mg	N/A mg
Polyoxyl 35 Castor Oil, NF, EP		mg	mg	mg
NF		N/A	N/A	N/A
Encapsulation and Ingredients				
		mg	mg	mg
			N/A	N/A
			N/A	N/A
			N/A	N/A
			N/A	N/A
or				
			N/A	N/A

(1)
(2)

marketed Norvir Capsule

Component	Amount Per Capsule
Capsule Fill:	
Ethanol, USP,	mg
Polyoxyl 35 Castor Oil, NF[b]	mg
Ritonavir[c]	mg
Propylene glycol, USP	100 mg= of fill
Caprylic/Capric Triglycerides	mg
Polysorbate 80, NF	mg
Citric Acid, , USP	mg
Capsules, Gelatin,	mg
Total fill weight =	mg
Components[a]:	
Polysorbate 80	mg
Ethanol, USP,	

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Figure 2: Representative Chromatogram of ABT-538 in Human Plasma, Human Plasma Blank

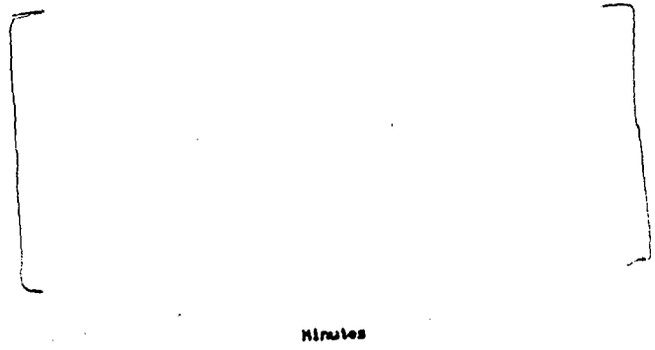

Figure 3: Representative Chromatogram of a Test Sample

Figure 4: Representative Chromatogram of a —— ng/ml Calibration Standard

Figure 5: Representative Chromatogram of a —— ng/ml Calibration Standard

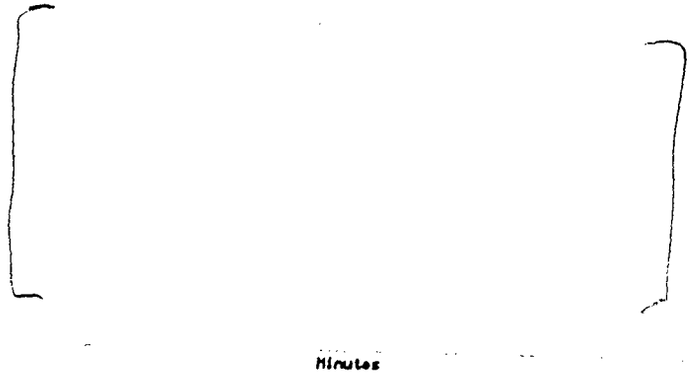

Table IV. Mean Dissolution Profiles of Ritonavir Soft Elastic Capsules in ——— ——— n=12)

Dosage Strength	Lot #	% Released (SD) 10	20	30 min.
100 mg	23-542-AR-R1*	73.8 (19.6) 26.6	100.0 (1.0) 1.0	100.9 (0.6) 0.6
	24-566-AR-R1	48.1 (31.2)	98.6 (2.5)	100.5 (1.8)
	25-583-AR-R1	65.2 (22.0)	98.0 (0.8)	98.8 (0.7)
———	23-544-AR-R1	[		]
	24-568-AR-R1			
	25-585-AR-R1			
———	23-546-AR-R1*	[		]
	24-570-AR-R1			
	25-586-AR-R1			

* Evaluated in bioavailability study M96-617.

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Table V. Ritonavir SEC 100 mg, Dissolution Test Data

Test Method: USP Dissolution one capsule/run, HPLC assay.

Lot 23-542-AR-R1

Run	% Released 10	20	30 min.
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean	73.8	100.0	100.9
SD	19.6	1.0	0.6

Lot 24-566-AR-R1

Run	% Released 10	20	30 min.
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean	48.1	98.6	100.5
SD	31.2	2.5	1.8

Table V (cont'd)

Lot 25-583-AR-R1.

Run	% Released 10	20	30 min.
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean	65.2	98.0	98.8
SD	22.0	0.8	0.7

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Table IX. Ritonavir SEC 100 mg, Lot 23-541-AR-R1, Dissolution Data in

Test Method: USP Dissolution
dissolution medium at , one capsule/run, HPLC assay.

0.1 N HCl

Run	% Released 10	20	30 min.
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean	32.8	46.0	52.1
SD	11.3	7.0	6.1

Water

Run	% Released 10	20	30 min.
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean	3.5	6.5	6.3
SD	3.9	1.0	1.7

Table IX (cont'd)

Run	% Released 10	20	30 min.
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean	6.8	9.3	11.0
SD	3.0	3.0	5.3

Run	% Released 10	20	30 min.
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean	4.6	9.5	10.4
SD	3.8	1.6	3.6

Table IX (cont'd)

Run	% Released 10	20	30 min.
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean	0.6	3.5	5.3
SD	1.4	0.9	0.9

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Clinical Pharmacology & Biopharmaceutics Review

NDA 20-945	**Submission Date:** 03/01/99
Ritonavir Soft-Elastic Capsules (SEC)	**Draft Review:** 05/10/99
Abbott Laboratories	**Final Review:** 06/03/99
Type of Submission: New NDA	**Reviewer:** Brad Gillespie, PharmD

Background The original clinical safety and efficacy trials for ritonavir were conducted using the currently marketed 80 mg/mL liquid which was linked to the 100 mg semi-solid capsule (SSC) through bioequivalency testing. Although the NDA is still active for the SSC formulation, the sponsor is not currently manufacturing or marketing it. In an effort to increase patient compliance, the sponsor began development of new 100 ——— soft-elastic capsules (SEC). During the review of that application, the sponsor confirmed that a Form II polymorphic crystal had spontaneously appeared during the course of manufacturing. This crystal dramatically reduced the solubility of ritonavir to the point that they could no longer manufacture the proposed SEC or SSC formulations. As a result of these solubility concerns, the sponsor received a non-approval (NA) letter for their SEC NDA. The sponsor has conducted further research on this formulation problem and has submitted a new NDA for their refined 100 mg ritonavir SEC formulation. It has a —— drug load (100 mg versus —— and contains a ——— of solubility-enhancing excipients.

Synopsis The important pharmacokinetic features of this application are presented below. More detailed individual study reviews begin on Page 9.

Bioequivalence: In support of this application, the sponsor has conducted bioequivalence trials comparing this formulation to the currently marketed liquid and semi-solid capsule. In both trials, the bioavailability of the SEC formulation was significantly higher than that of the reference formulation. Since all of the original clinical trials were conducted with the liquid formulation, the sponsor has chosen Study M98-966 as their pivotal comparison. In this trial, when the SEC was compared to the liquid, the resultant confidence intervals were 1.036-1.762 and 1.028-1.773 for C_{max} and AUC, respectively. Nevertheless, based on a number of factors, the difference observed between formulations does not appear to be clinically important. For a detailed discussion, see the individual study report evaluation in this review (pages 12 - 26). When the SEC was compared to the semi-solid capsule (Study M98-916), the analysis yielded confidence intervals of 1.029-1.374 and 1.136-1.511 for C_{max} and AUC, respectively.

Food Effect: Study M98-966 demonstrated that food does not have an appreciable effect on the bioavailability of the ritonavir SEC formulation (C_{max}: -6%, AUC +12%).

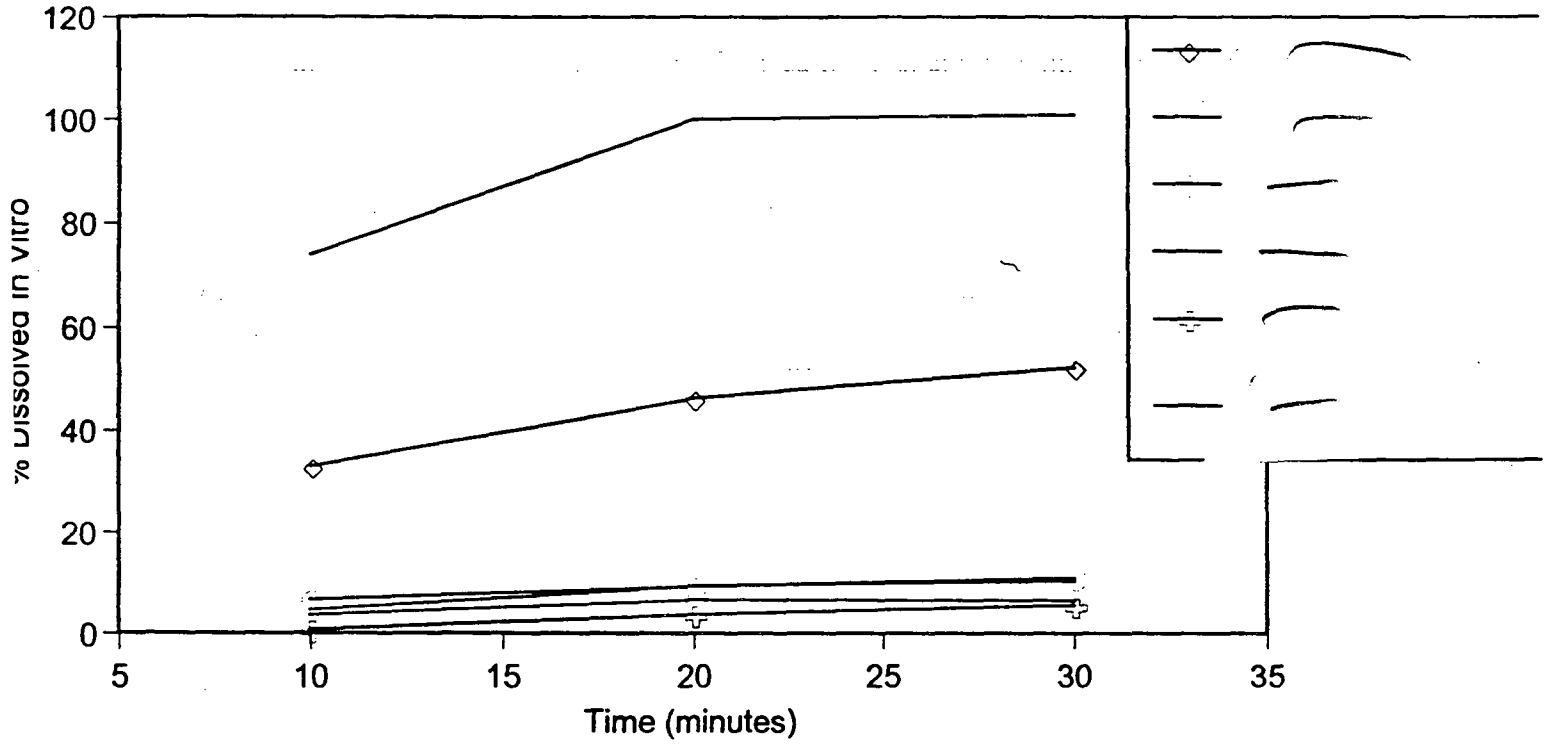
Effect of Crystals, ——— on Bioavailability: In Study M98-991, soft-elastic capsules were formulated with varying levels of Form II crystals. The first

formulation contained [redacted] of dissolved ritonavir and [redacted] of the Form II crystal. The second formulation had [redacted] of dissolved ritonavir and [redacted] of the Form II crystal. These extemporaneously prepared capsules were compared to the currently marketed liquid. Although the presence of the crystals clearly decreased the SEC's bioavailability, the capsules were bioequivalent to the liquid. Although this information is useful, it is critical to note that these capsules were manually compounded not using the proposed manufacturing equipment. Since the method of manufacture could also influence the product's bioavailability, it may not be appropriate to set a specification [redacted]. Instead, this information is best suited to demonstrate that the formation of some crystals may not largely impact the product's bioavailability. In addition, the sponsor conducted Study [redacted] This study report was not evaluated in this review.

Dissolution Methodology: It should be noted that all of the following dissolution method development was conducted using a formulation quantitatively different than that proposed for marketing. Differences in the formulations included the following (new versus former formulation): [redacted] mg [redacted] vs [redacted] oleic acid, [redacted] vs [redacted] polyoxyl 35 castor oil and [redacted] vs [redacted] mg [redacted] It appears that this new formulation should exhibit a higher degree of solubility. While it is unclear what effect these changes would have on the product's *in vitro* performance, it is possible that they may accelerate its dissolution rate.

The sponsor conducted dissolution testing in the following media using [redacted] Dissolution profiles in these media are presented in Figure A, below.

Figure A. Mean Dissolution Profiles of Ritonavir 100 mg Soft-Elastic Capsules in Various Media



These data suggest that a [redacted] needed to fully dissolve the ritonavir SEC formulation. In a second series of experiments, the sponsor used varying concentrations of [redacted] These mean dissolution profiles are presented in Figure B. Of these combinations, [redacted] provided the most uniform degree of variability at the different time points. Based on these findings, the sponsor's choice of [redacted] seems appropriate. Although the proposed formulation is different than that tested in these experiments, its qualitative similarities suggest that the method should be appropriate for either formulation. Dissolution specifications, though, need to be based on dissolution data obtained from batches representative of that proposed for marketing. The individual data from the three stability lots (to include the biobatch) are presented below, in Figure C. It is evident that although there is a great deal of variability at the [redacted] timepoint, nearly complete dissolution is observed at [redacted] The sponsor has proposed a [redacted] specification of [redacted] dissolved in [redacted] which is supported by these data. All three stability batches would pass at [redacted]

Figure B. Mean Ritonavir Soft-Elastic Capsule Dissolution Profiles in Varying Concentrations of

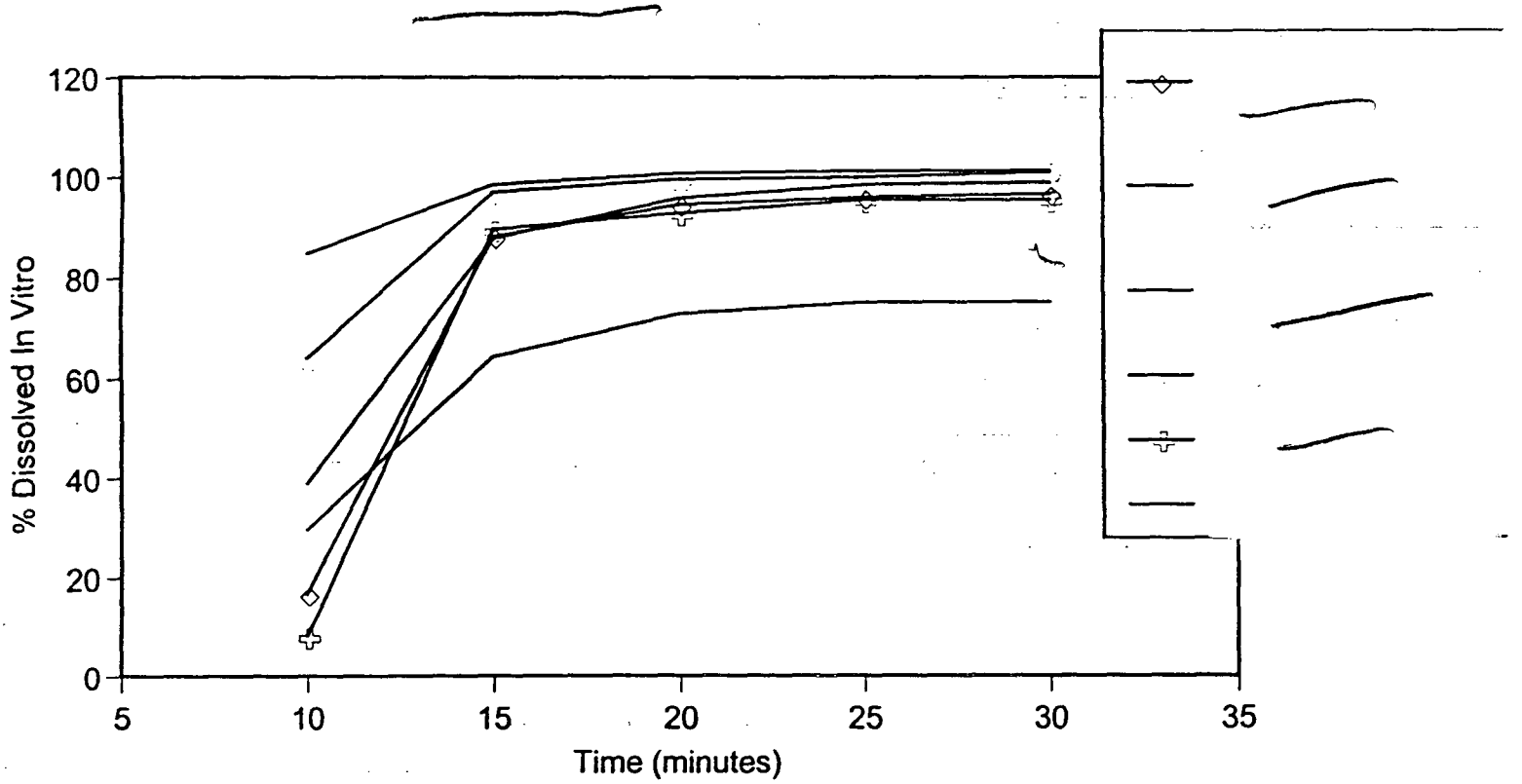


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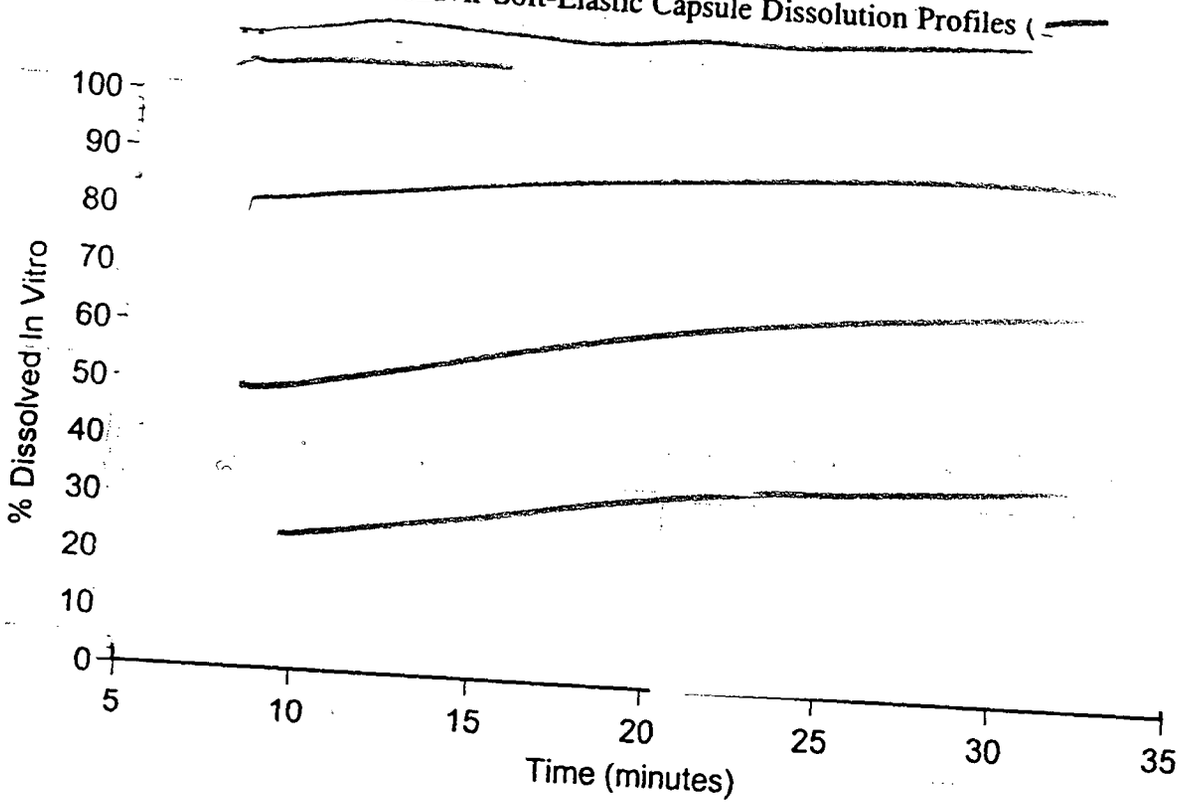
Figure C. Individual Ritonavir Soft-Elastic Capsule Dissolution Profiles (



Recommendation Although the pivotal bioequivalence study indicates that the ritonavir SEC formulation is more bioavailable than the currently marketed liquid, it is not expected that these differences would be clinically meaningful. Therefore, the Office of Clinical Pharmacology & Biopharmaceutics supports the approval of this application. For a clinical interpretation, see the Medical Officer's review of this NDA.

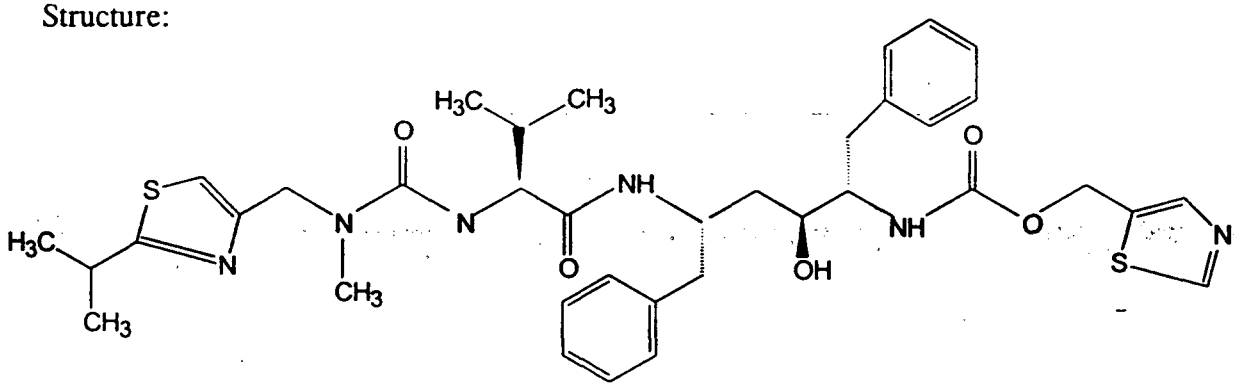
Clinical Pharmacology & Biopharmaceutics Briefing The briefing for this product was held on May 20, 1999 and was attended by Drs. Reynolds, Lazor, Uhl, Chen, Mehta, Lesko, Miller, Lo and Struble.

Table of Contents

I. Chemistry Overview

Chemical name: 1—Hydroxy-2-methyl-5(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R*, 8R*, 10R*, 11R*)]

Structure:



Molecular Formula: $C_{37}H_{48}N_6O_5S_2$

Solubility: Freely soluble in ethanol and methanol, practically insoluble in water

II. Formulation

Ingredients	Amount per capsule (mg)
[illegible]	[illegible]
Butylated Hydroxytoluene (BHT), NF, EP	[illegible]
Oleic Acid [illegible], NF, EP	[illegible]
Ritonavir	[illegible]
[illegible]	[illegible]
Polyoxyl 35 Castor Oil, NF, EP	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]

The inclusion of ethyl alcohol does create the risk of a possible Antabuse-type interaction. This possibility is discussed in the package insert. Rare instances of this interaction have been recorded by the spontaneous events reporting system.

III. Indication Ritonavir is indicated in combination with other antiretroviral agents for the treatment of HIV-infection.

IV. Dosage and Administration The recommended adult dose is 600 mg twice daily, by mouth.

Assessment of the effects of ethanol levels and ritonavir crystals on the bioavailability of two ritonavir soft-elastic capsule formulations compared to the marketed liquid formulation (K-5)
Study No. M98-991 **Volumes** 8.1- 8.4
Investigator

Clinical Dates 01/11/99 - 03/04/99
Analytical Facility Abbott Laboratories Drug Analysis Department
Analytical Dates 1/29/99 - 2/23/99

Objectives To assess the bioavailability of two modified soft-elastic capsule formulations (SEC), one containing — of dissolved ritonavir and — undissolved ritonavir Form II crystals and one containing — of dissolved ritonavir and — undissolved ritonavir Form II crystals, relative to the currently marketed liquid ritonavir formulation (K-5).

Formulations

Ritonavir Test Formulation T3:	Modified SEC capsules: — dissolved ritonavir and — Form II ritonavir crystals
Ritonavir Test Formulation T4:	Modified SEC: — dissolved ritonavir and — Form II ritonavir crystals
Ritonavir Reference Liquid (K-5)	80 mg ritonavir/mL

Study Design A total of 72 healthy, non-smoking adult male and female subjects were included in this open-label, randomized, single-dose, 3-treatment, 3-period crossover study. After a standardized breakfast, subjects received a single, 600 mg dose of study medication. Regular, standardized meals were served throughout the confinement period. A washout interval of 6 days separated each of the three dosing periods. Subjects were confined throughout each study phase and abstained from the consumption of xanthine containing foods and beverages.

Sampling
Blood samples were obtained for plasma ritonavir determinations just prior to (zero hour), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 32 and 40 hours after study drug administration.

Assay An HPLC — ethod was used for plasma ritonavir determinations

Assay Performance
Linearity
Accuracy

Precision Satisfactory: CV- 10% at [redacted] 10% at [redacted] ; 11% at [redacted]

Sensitivity LOQ: [redacted]
Specificity [redacted]

Data Analysis
Pharmacokinetic: - $C_{max.}$, T_{max}, $AUC_{0-\infty}$, $t_{1/2}$, CL/F
Statistical: An ANOVA, which included effects for sequence, subject within sequence, period and treatment was used to compare the naturally log-transformed pharmacokinetic parameters. The bioavailability of the test formulations relative to the reference formulation was assessed by using the two one-sided test procedure.

Results A total of 68 subjects completed all three phases of the study. The mean plasma concentration versus time profiles for the first 40 hours after dosing are presented in Figure 1. Pharmacokinetic parameters are presented in Table 1. Bioavailability assessments are presented in Table 2.

Figure 1. Mean Ritonavir Plasma Concentrations After a Single, Oral 600 mg Dose (Test Formulations T3 and T4, reference liquid).

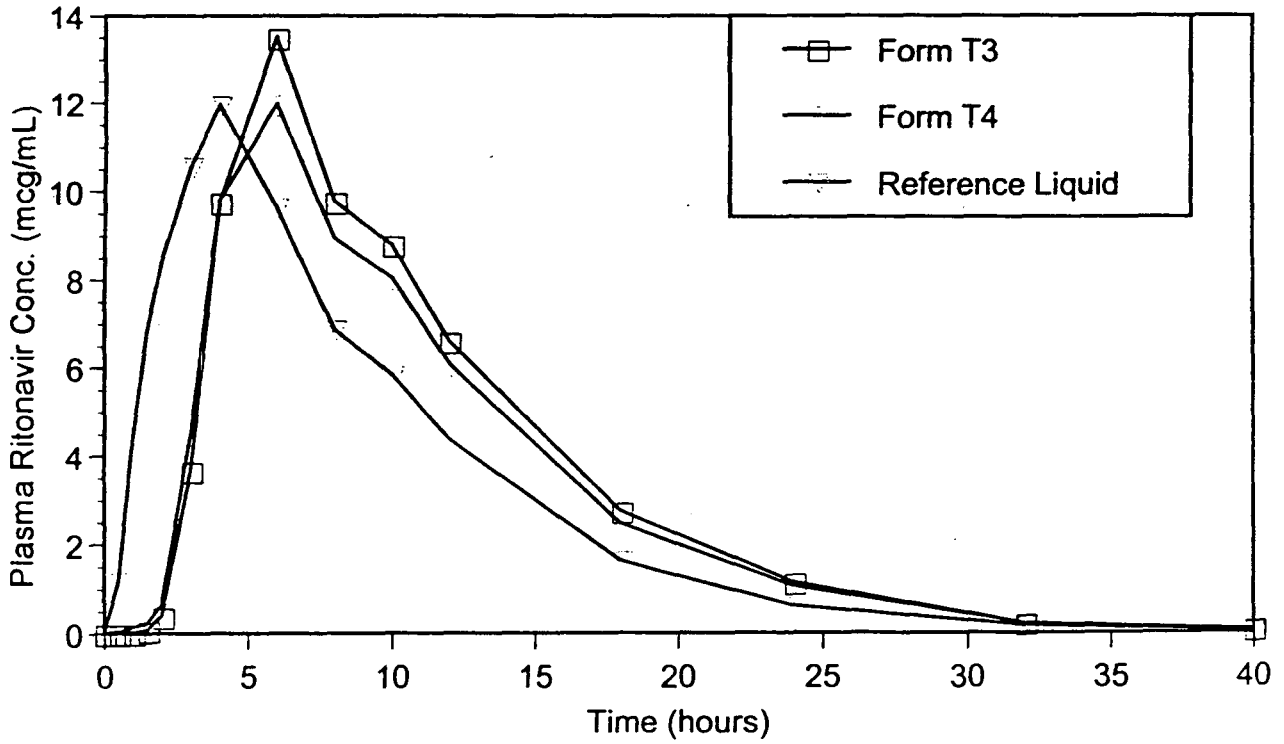


Table 1. Mean (%CV) Ritonavir Plasma Pharmacokinetic Parameters After a Single, Oral 600 mg Dose (Test Formulations T3 and T4, reference liquid)

	Test Formulation T3	*Test Formulation T4*	*Reference Liquid*
T_{max} (h)	5.8 (28)	5.5 (29)	4.2 (33)
C_{max} (μg/mL)	14.7 (34)	14.0 (30)	12.4 (25)
$AUC_{0-\infty}$ (μg·h/mL)	136.0 (35)	126.7 (36)	119.2 (38)
$t_{1/2}$ (h)	3.96	4.06	4.51
CL/F (L/h	5.0 (40)	5.3 (34)	5.8 (41)

Table 2. Confidence Interval Analysis to Assess Relative Bioavailability of Capsule Formulations T3 and T4

	C_{max}		$AUC_{0-\infty}$	
	Point Estimate	90% CI	Point Estimate	90% CI
Capsule T3 vs. Liquid	1.171	1.095 - 1.253	1.169	1.100 - 1.242
Capsule T4 vs Liquid	1.118	1.046 - 1.195	1.073	1.011 - 1.139

Discussion These data suggest that the Form II crystals are less bioavailable than Form I. If the assumption is made that both crystal forms contribute to total exposure based on their individual bioavailability, the following equations can be used:

$45x + 5y = 136.0$ (Formulation T3)
$40x + 10y = 126.7$ (Formulation T4)
Where x is the bioavailability of Form I and y is the bioavailability of Form II and total exposure is measured by AUC.

When the first equation is solved for x, and the second for y, the following values are derived:

$x = 3.02 - 0.111y$
$y = 12.67 - 4x$

Through algebraic substitution, values of 2.90 and 1.06 are calculated for x and y, respectively. Since these values represent bioavailability coefficients, this procedure estimates that the bioavailability of Form II is approximately 37% relative to Form I (y/x). Naturally, this estimate is based on a number of assumptions and is intended only as a guide to the approximate relative bioavailability of the Form II crystal.

Conclusion It is evident that the addition of Form II crystals to ritonavir soft elastic capsules decreases their bioavailability. Nevertheless, the two formulations containing approximately — and — of ritonavir as Form II crystals are bioequivalent to the currently marketed liquid. From a regulatory standpoint, the relevance of these findings is unclear.

Assessment of the bioequivalence of and the effect of food on a new ritonavir soft-elastic capsule formulation compared to the marketed liquid formulation

Study No. M98-966 **Volumes** 7.7-7.10
Investigator [redacted]
Clinical Dates 11/05/98 - 11/20/98
Analytical Facility Drug Analysis Department, Abbott Labs
Analytical Dates 11/11/98 - 12/8/98

Objectives To assess the bioequivalence of the 100 mg ritonavir soft elastic capsule (SEC) formulation to the currently marketed liquid formulation (K-5) under non-fasting conditions and to evaluate the effect of food on the bioavailability of the SEC formulation.

Formulations
Ritonavir Oral Liquid: 80mg/mL, Bulk Lot 44-565-AW, Expiration Date 4/1/99
Ritonavir Soft Elastic Capsule: 100 mg, Bulk Lot 44-992-AR-R1, Expiration Date 2/1/99

Regimen A: 7.5 mL Ritonavir Liquid (600 mg) administered under fed conditions
Regimen B: Six 100 mg SECs (600 mg) administered under fed conditions
Regimen C: Six 100 mg SECs administered under fasting conditions

Study Design A total of 60 healthy, non-smoking adult males and females were included in this open-label, randomized, single-dose, 3-treatment, 3-period crossover study. Subjects receiving Regimens A and B ate a low fat breakfast approximately 30 minutes before receiving a single, 600 mg dose of study medication. The agency prospectively agreed that it was acceptable to dose subjects in a fed state to avoid emesis. During Regimen C, volunteers were served breakfast approximately 4 hours after dosing. All subjects remained ambulatory for at least 2 hours after study drug administration. A washout interval of at least 6 days separated the dosing periods. Subjects were confined throughout each study phase and abstained from the consumption of alcohol, grapefruit and xanthine containing foods and beverages.

Sampling
Blood samples were obtained for plasma ritonavir determinations just prior to (zero hour), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 32 and 40 hours after study drug administration.

Assay An HPLC [redacted] method was used for plasma ritonavir determinations.

Assay Performance
Linearity [redacted]
Accuracy [redacted]

Precision Satisfactory: CV-8% at [redacted], 8% at [redacted] 8% at [redacted]

Sensitivity LOQ: [redacted]
Specificity [redacted]

Data Analysis
Pharmacokinetic: C_{max}, T_{max}, $AUC_{0-\infty}$, $t_{1/2}$
Statistical: Due to a non-normal distribution of the pharmacokinetic parameters, the sponsor used a non-prospectively defined, non-parametric analysis. This approach is evaluated in Dr. Chuanpu Hu's attached QMR consult review (beginning on Page 20).

Results A total of 57 subjects completed all phases of the study. Subject 32 did not return to the study facility for dosing in Periods 2 or 3, while subjects 15 and 28 were terminated due to positive drug screens. The mean plasma concentration versus time profiles for the first 40 hours after dosing are presented in Figure 2. Pharmacokinetic parameters are presented in Table 3. According to Dr Hu's QMR consult review, the shift from normality observed in this study was not sufficient to warrant the use of a non-parametric procedure. As a result, the sponsor's analysis is inappropriate for determining bioequivalence. Traditional 90% bioequivalence confidence intervals derived from the two one-sided procedure are presented in Table 4. Individual plots of C_{min}, C_{max} and AUC are presented in Figures 3 – 5. Individual subject bioavailability parameter ratios are plotted in Figures 6 – 8 (does not include extremely low levels discussed below). Although not normally included in single-dose studies, C_{min} was included at the request of the medical officer to predict if there would be any efficacy problems at the end of the dosing interval.

Discussion After ingestion of the reference liquid, Subjects 40 and 43 had extremely low plasma ritonavir concentrations (C_{max}: [redacted] µg/mL, respectively), while subject 51's observed plasma concentrations were inconsistent with one another (all concentrations ≤0.080 µg/mL with the exception of the 12 hour timepoint [[redacted] µg/mL]). After taking the SEC under fed conditions, Subject 44's plasma concentrations were low (C_{max} [redacted] µg/mL) while Subject 51's levels were also low (C_{max} [redacted] µg/mL) after taking the SEC under fasting conditions. These type of results have not been observed in earlier trials using the liquid or SSC formulation. Nevertheless, since the sponsor was unable to provide good explanations for these observations, their values were included in the analysis. Moreover, it is important to be aware of several critical points: (1) The low values probably cannot be attributed to dosage form inconsistencies since several subjects were dosed from the same bottle; (2) Subjects 40, 43 and 51 all achieved plasma ritonavir concentrations within the expected range (C_{max}: [redacted] µg/mL) after ingestion of the SEC (all subjects mean

13.64±5.4 μg/mL), thus eliminating the probability that these subjects are rapid metabolizers of ritonavir; (3) It appears that rather than having a high test (SEC) bioavailability, this trial may have a relatively low reference (liquid) bioavailability. This is supported by a review of previous trials dosing the liquid formulation in similar populations under similar conditions, with C_{max} and AUC values averaging 14.2 μg/mL and 136.0 μg·hr/mL, respectively. It is important to note that similar low values have never been reported in any of these previous trials. Although it appears unlikely that the SEC bioavailability is actually higher than that of the liquid after a single 600 mg dose, it is important to note that even if it is, in practice, many patients are dosed at a level of 400 mg BID, or less. Therefore levels achieved would be certainly less than that observed after administration of 700 mg BID doses in Study M94-229 (included in original NDA). Although this dose was poorly tolerated, i.e., gastrointestinal safety concerns, it was not substantially worse than a 600 mg regimen; (4) Although the company is unable to confirm that these subjects with low values did or did not vomit, this seems like a likely explanation for the unusually low bioavailability observed (vomiting is a common adverse event with ritonavir); (5) If the extremely low values are eliminated from the analysis, the SEC and liquid formulations are bioequivalent according to the conventional criteria (C_{max}: 0.972 - 1.204; AUC: 0.957 - 1.193).

Conclusion This study clearly shows that the new SEC and liquid formulations are not bioequivalent. Nevertheless, it appears that multiple anomalous data points may be skewing the results. Visual inspection of individual plots of the bioavailability parameters shows that each distribution is similar between the different treatment groups. Based on this similarity, it seems unlikely that there is a clinically meaningful difference between the treatment groups. The Medical Officer assigned to this application (Dr. Kim Struble) concurs with this assessment. This study also showed that food did not have a significant effect on the bioavailability of the SEC formulation (C_{max} -6%, AUC +12%).

Figure 2. Mean Ritonavir Plasma Concentrations After Oral Ingestion of 600 mg Ritonavir

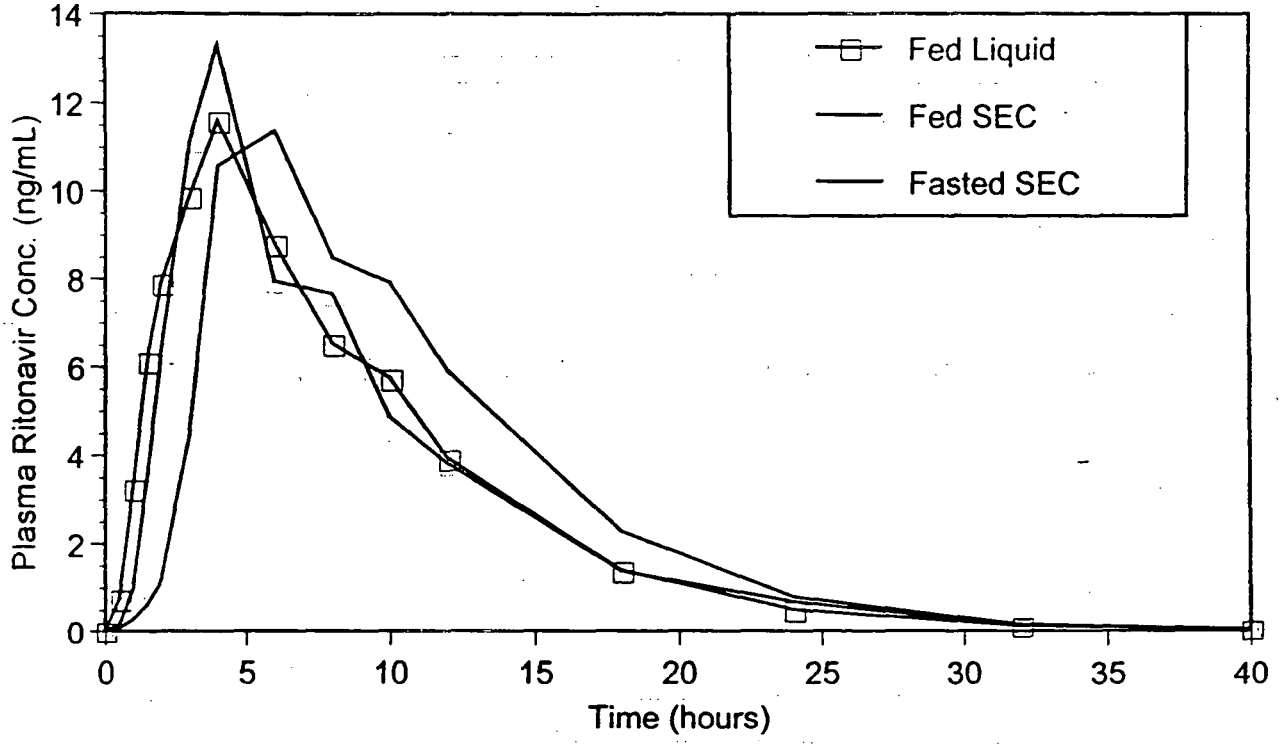


Table 3. Mean (%CV) Ritonavir Pharmacokinetic Parameters After Administration of a Single 600 mg Dose

	Fed Liquid	*Fed SEC*	*Fasted SEC*
T_{max} (h)	4.1 (39)	5.5 (36)	4.4 (70)
C_{max} (µg/mL)	11.92 (45)	13.64 (40)	14.53 (40)
$AUC_{0-\infty}$ (µg·h/mL)	109.6 (54)	121.7 (44)	108.7 (48)
$t_{1/2}$ (h)	4.23	3.96	4.21

Table 4. Ritonavir Bioequivalence Estimates After 600 mg Single-Dose Oral Administration of Soft Elastic Capsules and the Currently Marketed Liquid

	Parameter	Point Estimate of Ratio	90% C.I.
SEC (fed) vs Liquid (fed)	Cmax	1.351	1.036 - 1.762
	AUC_t	1.351	1.027 - 1.775
	AUC_{inf}	1.350	1.028 - 1.773
SEC (fasted) vs SEC (fed)	Cmax	1.060	0.812 - 1.382
	AUC_t	0.887	0.675 - 1.167
	AUC_{inf}	0.887	0.675 - 1.165

Figure 3. Individual and Mean C_{max} Values (mean values denoted by horizontal line)

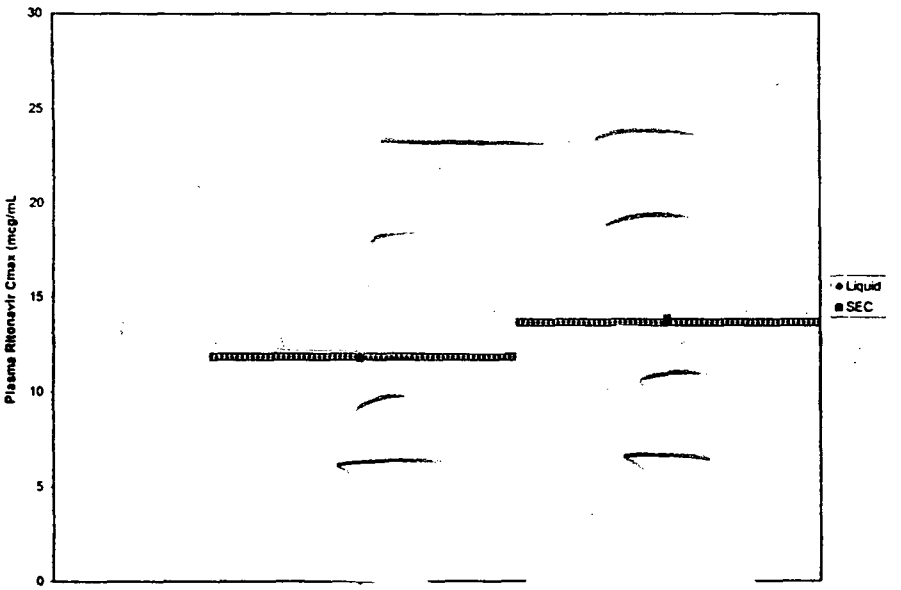


Figure 4. Individual and Mean AUC Values (mean values denoted by horizontal line)

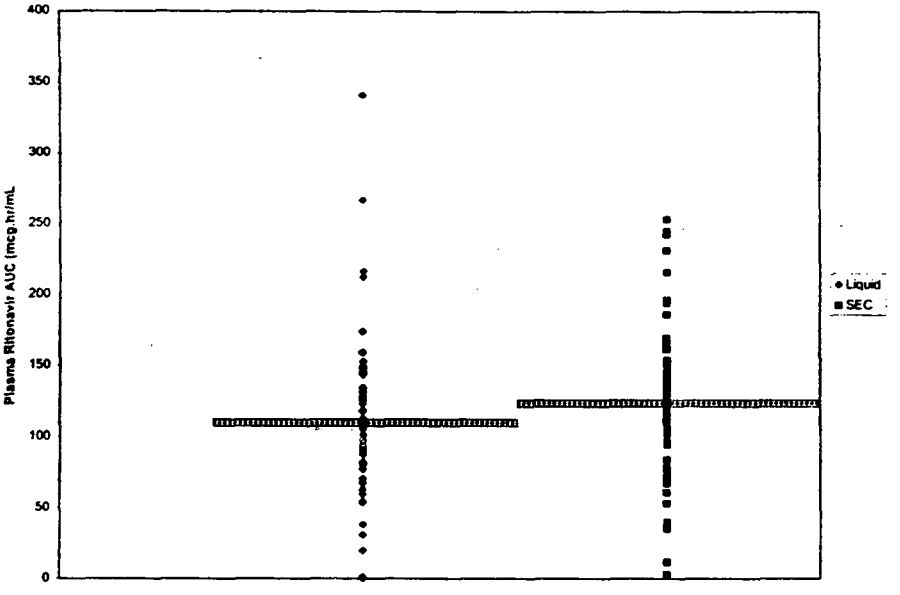


Figure 5. Individual and Mean C_{min} (concentration at end of dosing interval) Values (mean values denoted by horizontal line)

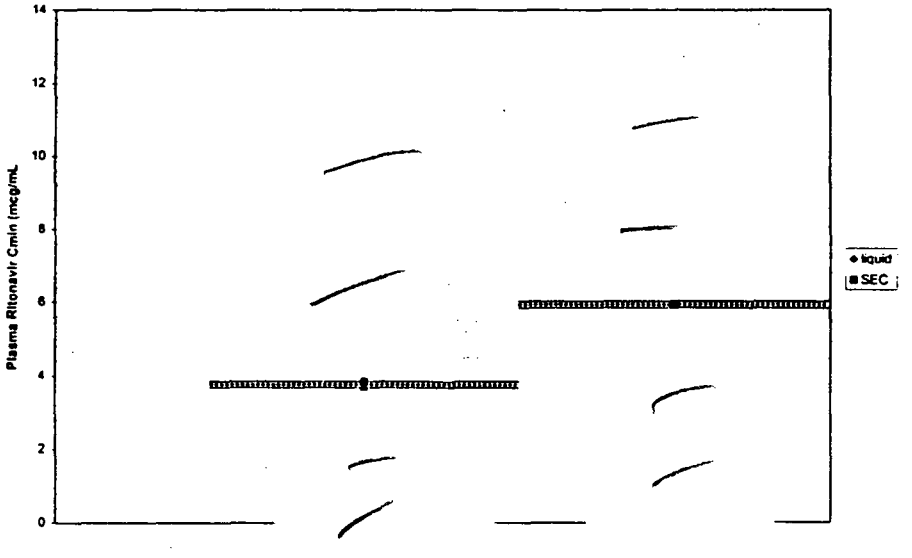


Figure 6. Individual Subject C_{max} Ratios (SEC/Liquid)

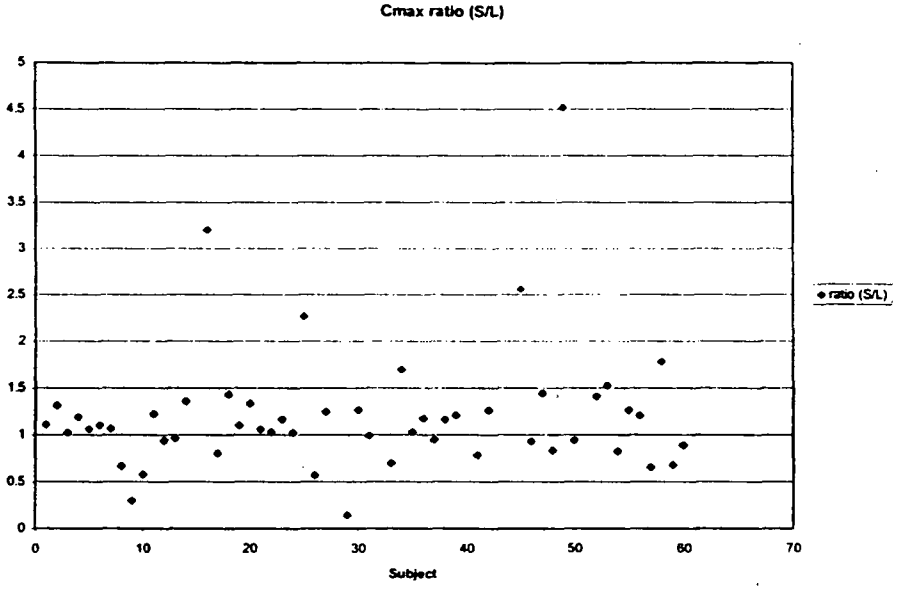


Figure 7. Individual Subject C_{min} Ratios (SEC/Liquid)

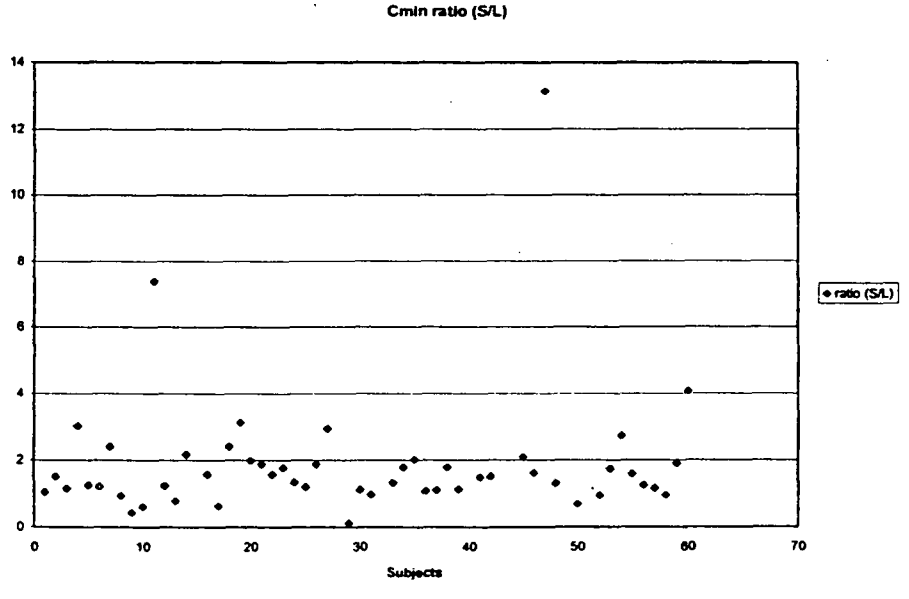
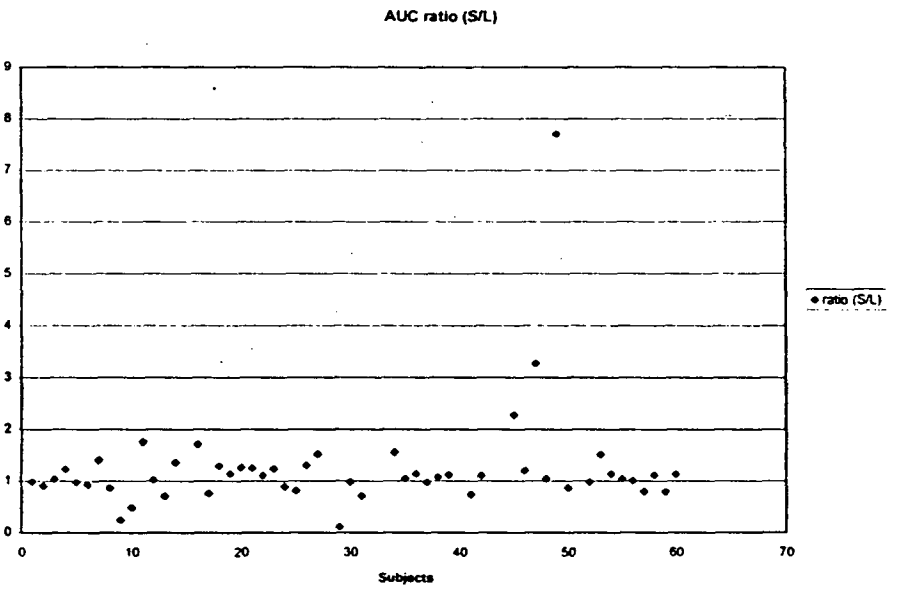


Figure 8. Individual Subject AUC Ratios (SEC/Liquid)



Statistical Report: Ritonavir;
OCPB NDA 20-945, Abbott Laboratories

OCPB reviewer: Bradley Gillespie

QMR is requested to assess the appropriateness of the sponsor's nonparametric analysis in study M98-966.

Study Design:

This was a Phase I, randomized, single-dose, fasting and nonfasting, open-label, three treatment, three-period crossover study, comparing the capsule formulation vs. the marketed liquid formulation of ritonavir. The regimens were (A) liquid (reference) formulation administered under nonfasting conditions, (B) test formulation administered under nonfasting conditions, and (C) test formulation administered under fasting conditions. Sixty healthy volunteers participated in the study, with 57 subjects completed all three periods. Subjects were randomized to the following three sequences.

Sequence	Subject
ABC	1, 5, 8, 10, 15(a), 16, 20, 23, 26, 28(a), 31, 35, 38, 42, 44, 48, 49, 54, 56, 58
BCA	2, 4, 7, 11, 14, 18, 19, 22, 27, 29, 32(a), 34, 37, 40, 45, 47, 51, 52, 55, 59
CAB	3, 6, 9, 12, 13, 17, 21, 24, 25, 30, 33, 36, 39, 41, 43, 46, 50, 53, 57, 60
(a)	Did not participate in periods 2 and 3.

The following endpoints were analyzed: AUC_t, AUC_{inf}, and Cmax on the log scale.

Sponsor's Analysis

The three subjects who did not participate in periods 2 and 3 were excluded from the analysis. The parametric analysis showed the following result:

	Parameter	Point Estimate of Ratio	90% C.I.
B vs. A	Cmax	1.351	1.036 - 1.762
	AUC_t	1.351	1.027 - 1.775
	AUC_{inf}	1.350	1.028 - 1.773
C vs. A	Cmax	1.060	0.812 - 1.382
	AUC_t	0.887	0.675 - 1.167
	AUC_{inf}	0.887	0.675 - 1.165

The sponsor acknowledged that the point estimates and 90% confidence intervals lie outside the (0.8, 1.25) range. However, they argued that the distributions of Cmax and AUC for all three regimens had long left tails, and therefore the normality assumption is violated. They then argued that a nonparametric sign test was more appropriate for assessing bioequivalence, and conducted two one-sided tests for the median of the distribution of the test value over the reference value. Ignoring the period effect, the nonparametric sign test produced 90% confidence intervals lie inside the (0.8, 1.25) range. The sponsor argued for excluding the period effect because of (1) results of ANOVA tests on period effects were marginally insignificant (0.053 or higher), (2) if there were period effect, not accounting for them would not favor bioequivalence. The sponsor also conducted a nonparametric test for sequence effects.

Comments on Sponsor's Analysis

Normality assumptions and ANOVA for assessing bioequivalence have been widely used. In particular, using ANOVA on log transformed endpoints is recommended by the FDA (Guidance: Statistical Procedures for Bioequivalence Studies Using A Standard Two-treatment Crossover Design, July 1, 1992). Nonparametric analysis procedures require minimal distributional assumptions, but compromise on efficiency when normality assumptions hold. Interpretation of the results is also different: the traditional bioequivalence analysis compares the means of the test and reference product, whereas the sponsor's sign test procedure aims to compare the medians. We currently discourage nonparametric bioequivalence analyses.

The appendix contains some plots, showing distributions of the data. Figures 1-3 show log(Cmax) by treatment. They show 2-5 points on the left tail, out of total 59 observations. log(AUC_t) and log(AUC_{inf}) showed similar distribution characteristics. (AUC_t and AUC_{inf} were almost identical.) Figures 4-5 show differences of log(Cmax) between the test formulations and the reference formulation by subject. The skewness was somewhat less although still appeared present. However, in regulatory assessment of bioequivalence, the mere appearance of some deviation from normality, in this magnitude, does not justify shifting to a nonparametric procedure that is more robust to outliers than the parametric precedure. In particular, it is to be noted that the nonparametric analysis would unlikely be conducted at all, had the parametric analysis concluded bioequivalence.

Another inconsistency in the sponsor's nonparametric analysis is that the period effects were tested with ANOVA, but the sequence effects were tested with a nonparametric test.

Figure 6-7 show that the apparent lean to the left of the distribution was due to a few low values that are not consistent across subjects. It is not clear why these low values occurred. Note that we also discourage the deletion of "outliers" for pure statistical

reasons (see the above-cited FDA guidance).

Conclusion

The nonparametric analysis conducted by the sponsor is not appropriate for determining bioquivalence.

Chuanpu Hu, Ph.D.
Mathematical Statistician
06/04/99

Concur:

Stella G. Machado, Ph.D.
Director, QMR
06/04/99

CC:

HFD-880	Bradley Gillespie
HFD-880	Kellie Reynolds
HFD-705	QMR Chron

3 Page(s) Withheld

Assessment of the bioequivalence of and the effect of food on a new ritonavir soft-elastic capsule formulation compared to the marketed semi-solid capsule formulation
Study No. M98-916 **Volume** 131.1 - 131.3 (submitted to IND 43,718)
Investigator [redacted] Abbott Clincial Research Unit, Victory Memorial Hospital; 1324 N. Sheridan Rd; Waukegan, IL 60085
Clinical Dates 9/28/98 - 10/16/98
Analytical Facility Abbott Laboratories, Abbott Park, IL
Analytical Dates 10/1/98 - 10/27/98

Objectives To assess the bioequivalence of the ritonavir soft-elastic capsule (SEC) formulation compared to the currently marketed semi-solid capsule and to determine the effect of food on the bioavailability of the SEC formulation.

Formulations
100 mg ritonavir semi-solid capsule, bulk lot no. 41-284-AF-22
100 mg ritonavir soft-elastic capsule, bulk lot no. 44-992-AR-R1

Study Design A total of 28 healthy, non-smoking adult male and female subjects were included in this open-label, randomized, single-dose, 3-treatment, 3-period crossover study. Subjects receiving Regimens A and B ate a low fat breakfast approximately 15 minutes before receiving a single, 600 mg dose of study medication. During Regimen C, volunteers were served breakfast approximately 4 hours after dosing. All subjects remained ambulatory for at least 2 hours after study drug administration. A washout interval of at least 6 days separated the dosing periods. Subjects were confined throughout each study phase and abstained from the consumption of alcohol, grapefruit and xanthine containing foods and beverages.

Sampling
Blood samples were obtained for plasma ritonavir determinations just prior to (zero hour), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 32 and 40 hours after study drug administration.

Assay An HPLC [redacted] method was used for plasma ritonavir determinations.

Assay Performance
Linearity [redacted]
Accuracy [redacted]

Precision Satisfactory: CV-6% at [redacted] 7% at [redacted] 3% at

Sensitivity LOQ: [redacted]
Specificity [redacted]

Data Analysis

Pharmacokinetic: $C_{max.}$, T_{max}, $AUC_{0-\infty}$, $t_{1/2}$, CL/F

Statistical: Naturally log-transformed bioavailability parameters were compared using an ANOVA model including effects for sequence, subject within sequence, period and treatment. Confidence intervals were constructed using the two one-sided test procedure to compare treatment means.

Results A total of 27 subjects completed all phases of the study. Subject 12 voluntarily withdrew from the study during Period 1 for personal reasons. The mean plasma concentration versus time profiles for the first 40 hours after dosing are presented in Figure 9. Pharmacokinetic parameters are presented Table 5, while bioequivalence estimations are presented in Table 6.

Figure 9. Mean Plasma Ritonavir Concentration vs. Time Profile After Oral Administration of A Single 600 mg Dose

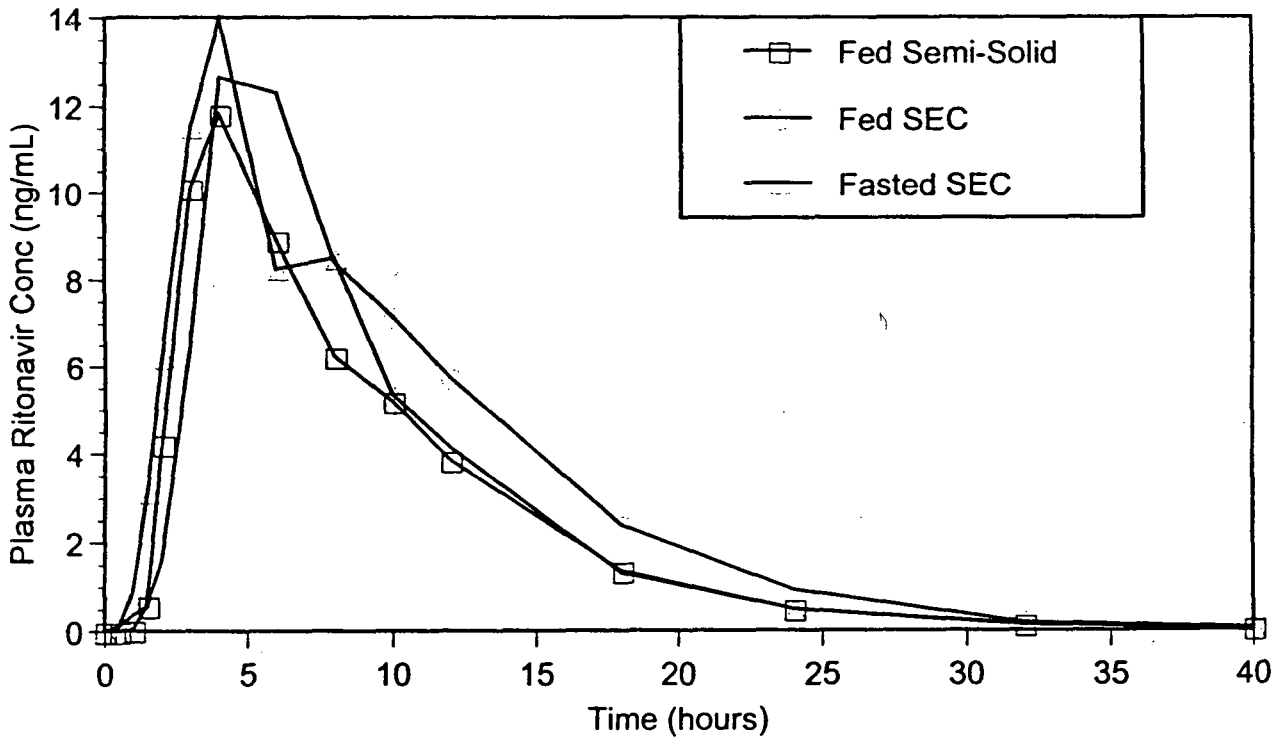


Table 5. Mean (%CV) Pharmacokinetic Parameters After Oral Administration of Single 600 mg Doses of Ritonavir Semi-Solid Capsules (SSC) and Soft-Elastic Capsules (SEC)

	Fed SSC (reference)	*Fed SEC (test)*	*Fasted SEC (test)*
T_{max} (h)	4.2 (24)	5.0 (22)	4.4 (32)
C_{max} (μg/mL)	12.33 (32)	14.43 (34)	14.70 (37
$AUC_{0-\infty}$ (μg·h/mL)	100.6 (37)	128.7 (35)	112.7 (33)
$t_{1/2}$ (h)	4.12	3.94	4.19
CL/F (L/h)	7.39 (63)	5.36 (42)	5.96 (35)

Table 6. Bioequivalence and Food Effect Estimates of SEC After Oral Administration of Single 600 mg Doses of Ritonavir Semi-Solid Capsules (SSC) and Soft-Elastic Capsules (SEC)

	Parameter	Point Estimate of Ratio	90% C.I.
SEC (fed) vs SSC (fed)	Cmax	1.071	0.964 - 1.301
	AUC_t	1.235	1.073 - 1.309
	AUC_{inf}	1.236	1.072 - 1.309
SEC (fasted) vs SEC (fed)	Cmax	0.959	0.844 - 1.096
	AUC_t	0.895	0.789 - 1.036
	AUC_{inf}	0.893	0.789 - 1.034

Conclusion This study demonstrates that the SEC formulation is not bioequivalent to the currently marketed semi-solid capsule. Total exposure, as measured by AUC, and peak plasma concentrations (C_{max}) were approximately 24% and 7% higher after administration of the SEC. While the effect of food did not significantly blunt peak plasma concentrations after administration of the SEC, AUC was reduced by approximately 11%.

/S/

6/4/99

Bradley K. Gillespie, PharmD
Reviewer, Pharmacokinetics
Division of Pharmaceutical Evaluation III

Concurrence: /S/ 6/4/99

Kellie Schoolar Reynolds, PharmD
Team Leader, Antiviral Drug Products Section

cc:

HFD-530	/IND 43,718
	/MO/Struble
	/CSO/Lynche
HFD-880	/Gillespie
	/TL/Reynolds
	/DPE III
HFD-340	/Viswanathan
CDR	/Barbara Murphy

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