# OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-659 (oral solution) 20-945 (capsule)	Submission Date(s): 04-06-2005
Brand Name	Norvir
Generic Name	Ritonavir
Reviewer	Yuanchao (Derek) Zhang, Ph.D.
Team Leader	Kellie S. Reynolds, Pharm.D.
OCPB Division	Division of Pharmaceutical Evaluation III
OND Division	DAVDP
Sponsor	Abbott
Other NDA(s)	20-680 (original capsule, no longer marketed)
Relevant IND(s)	43-718
Submission Type; Code	SE5 (Pediatric Exclusivity); Priority
Indication	Treatment of HIV-1 infection

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	Executive Summary Recommendation Post Marking Commitments Summary of Important Clinical Pharmacology and Biopharmaceutics Findings Question Based Review General Attributes of the Drug General Clinical Pharmacology Intrinsic Factors Extrinsic Factors General Biopharmaceutics Analytical Section Labeling Recommendations Appendices Individual Study Review.

# 1 Executive Summary

# 1.1 Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has concluded that the clinical pharmacology information submitted to this NDA supplement is adequate to support the claim for Pediatric Exclusivity for Norvir and to make the relevant labeling revisions. Based on the submitted pharmacokinetic data, it is acceptable to expand the pediatric age range from > 2 years of age to > 1 month of age. The dosing regimen for HIV-infected pediatric patients does not change (350 to 400 mg/m<sup>2</sup> BID).

# 1.2 Post Marking Commitments

None

# **1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings**

## Application Contents

Two studies provide pharmacokinetic data in HIV infected patients <2 years old of age.

Study PACTG 345 is the main study to support the Pediatric Exclusivity claim. The ritonavir dose regimens studied were 350 and 450 mg/m<sup>2</sup> BID. The number of subjects with pharmacokinetic data in each age group are as follows:

1 month to < 3 months:	18
3 months to < 6 months:	10
6 months to < 2 years:	13

Study PACTG 366 is a supportive study to the Pediatric Exclusivity claim. The ritonavir dose regimen studied was 350 mg/m<sup>2</sup> BID. The number of subjects with pharmacokinetic data in the age range of >6 months to 2 year was 9.

## Pharmacokinetics of Ritonavir in Pediatric Patients

In Study PACTG 345, ritonavir exposures in infants and children < 2 years of age after 350 or 450 mg/m<sup>2</sup> BID dosing were similar to historical data in older children after 250 to 350 mg/m<sup>2</sup> BID dosing, with the exception that steady-state trough concentrations were lower in children < 2 years of age. There was high variability in ritonavir exposure. Higher ritonavir exposures were not evident with 450 mg/m<sup>2</sup> BID dose compared to the 350 mg/m<sup>2</sup> BID dose.

	1	month - 2 yrs		Childre	n > 2 yrs		Adults	
	350 mg/m <sup>2</sup> (N = 14)	450 mg/m <sup>2</sup> (N = 27)	250 mg/m <sup>2</sup> (N = 7)	300 mg/m <sup>2</sup> (N = 9)	350 mg/m <sup>2</sup> (N = 11)	$400 \text{ mg/m}^2$ (N = 10)	400 mg (N = 13)	600 mg
C <sub>max</sub> ,ss (µg/mL)	10.1 ± 7.9 (5.6)	8.2 ± 6.8 (6.9)	9.7 ± 4.9 (9.6)	10.9 ± 3.7 (9.8)	11.4 ± 4.2 (12.4)	16.0 ± 9.9 (11.4)	7.1 ± 2.7 (6.0)	11.2 ± 3.6 (10.9)
C <sub>trough,</sub> ss (µg/mL)	1.4 ± 1.8 (0.86)	1.4 ± 1.9 (0.75)	3.3 ± 3.4 (2.3)	2.2 ± 1.4 (1.7)	2.1 ± 1.9 (2.0)	5.5 ± 4.0 (5.9)	1.8 ± 0.9 (1.5)	3.5 ± 2.5 (2.8)
AUCss (µg∙h/mL)	61 ± 53 (40)	66 ± 54 (50)	58 ± 33 (56)	63 ± 27 (56)	60 ± 27 (52)	100 ± 64 (97)	49 ± 21 (46)	77 ± 32 (69)
CL/F (L/h)	3.0 ± 1.6 (2.9)	3.1 ± 2.0 (2.7)					95+37(87)	88+32/84
CL/F (L/h/m <sup>2</sup> )	8.4 ± 5.2 (7.8)	8.9 ± 5.7 (7.8)	6.0 ± 3.9 (4.4)	5.7 ± 2.7 (5.3)	7.4 ± 4.0 (6.8)	6.4 ± 5.2 (4.2)	5.2 ± 2.0* (4.8)	4.9 ± 1.7* (4.8)

Table 1. Mean ± SD (Median) Pharmacokinetic Parameters of Ritonavir at Steady State Across Different Age Groups (All BID Regimens)

Data for infants and children (1 month - 2 yrs.) are from the current study using Week 4 values.

Data for children > 2 yrs. are from Study M95-310 as previously submitted in NDA 20-659/S-008, approved 3/14/97.

Data for adults are from Study M93-112 as previously submitted in IND 43,718, Serial No. 99 in support of NDA 20-659, approved 3/1/96. BSA of 1.818 m<sup>2</sup> was used to calculate the normalized values of CL/F (L/h/m<sup>2</sup>)

In Study PACTG 366, ritonavir exposures in children  $\leq 2$  years of ago were lower than in older children receiving 350 mg/m<sup>2</sup> BID dose, and also were lower than those observed in the PACTG 345 study.

The data submitted with this sNDA adequately describe the RTV exposure in HIV-infected pediatric patients. It appears that increasing the RTV dose beyond 400 mg  $/m^2$  will not lead to increased RTV concentrations.

Pending on the DSI's inspection results (bioanalytical assay results), Study 366 may need to be excluded from the review. However, it will have no impact on the overall conclusions of this review.

Yuanchao (Derek) Zhang, Ph.D. Pharmacokinetics Reviewer, DPE III Office of Clinical Pharmacology and Biopharmaceutics

Concurrence:

Kellie S. Reynolds, Pharm. D. Pharmacokinetics Team Leader, DPE III Office of Clinical Pharmacology and Biopharmaceutics

## 2 Question Based Review

## 2.1 General Attributes of the Drug

Please refer to the original NDA review 20-659 and 20-680.

## 2.2 General Clinical Pharmacology

Please refer to the original NDA review 20-659 and 20-680.

## 2.3 Intrinsic Factors

Please refer to the original NDA review 20-659 and 20-680 for factors other than pediatric age range.

#### 2.3.1. Pediatric Patients

In Study PACTG 345, ritonavir exposures in infants and children < 2 years of age after 350 or 450 mg/m<sup>2</sup> BID dosing were similar to historical data in older children after 250 to 350 mg/m<sup>2</sup> BID dosing, with the exception that steady-state trough concentrations were lower in children < 2 years of age. There was high variability in ritonavir exposure. Higher ritonavir exposures were not evident with 450 mg/m<sup>2</sup> BID dose compared to the 350 mg/m<sup>2</sup> BID dose.

Table 1. Mean ± SD (Median) Pharmacokinetic Parameters of Ritonavir at Steady State Across Different Age Groups (All BID Regimens)

	1	month - 2 yrs		Childre	n > 2 yrs		Adults			
	350 mg/m <sup>2</sup> (N = 14)	450 mg/m <sup>2</sup> (N = 27)	250 mg/m <sup>2</sup> (N = 7)	300 mg/m <sup>2</sup> (N = 9)	350 mg/m <sup>2</sup> (N = 11)	$400 \text{ mg/m}^2$ (N = 10)	400 mg (N = 13)	600 mg		
C <sub>max</sub> ,ss (µg/mL)	10.1 ± 7.9 (5.6)	8.2 ± 6.8 (6.9)	9.7 ± 4.9 (9.6)	10.9 ± 3.7 (9.8)	11.4 ± 4.2 (12.4)	16.0 ± 9.9 (11.4)	7.1 ± 2.7 (6.0)	11.2 ± 3.6 (10.9)		
C <sub>trough,</sub> ss (µg/mL)	1.4 ± 1.8 (0.86)	1.4 ± 1.9 (0.75)	3.3 ± 3.4 (2.3)	2.2 ± 1.4 (1.7)	2.1 ± 1.9 (2.0)	5.5 ± 4.0 (5.9)	1.8 ± 0.9 (1.5)	3.5 ± 2.5 (2.8)		
AUCss (µg•h/mL)	61 ± 53 (40)	66 ± 54 (50)	58 ± 33 (56)	63 ± 27 (56)	60 ± 27 (52)	100 ± 64 (97)	49 ± 21 (46)	77 ± 32 (69)		
CL/F (L/h)	3.0 ± 1.6 (2.9)	3.1 ± 2.0 (2.7)					95+37(87)	88+33/84		
CL/F (L/h/m <sup>2</sup> )	8.4 ± 5.2 (7.8)	8.9 ± 5.7 (7.8)	6.0 ± 3.9 (4.4)	5.7 ± 2.7 (5.3)	7.4 ± 4.0 (6.8)	6.4 ± 5.2 (4.2)	5.2 ± 2.0* (4.8)	6.6 ± 5.2 (8.6) 4.9 ± 1.7* (4.8)		

Data for infants and children (1 month - 2 yrs.) are from the current study using Week 4 values.

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In Study PACTG 366, ritonavir exposures in children  $\leq 2$  years of ago were lower than in older children receiving 350 mg/m<sup>2</sup> BID dose, and also were lower than those observed in the PACTG 345 study.

Age/Weight Group	C0 (µg/mL)	C8 (µg/mL)	C <sub>max</sub> (µg/mL)	T <sub>max</sub> (h)	AUC <sub>0-8</sub> (μg•h/mL)	AUC <sub>0-τ</sub> (μg•h/mL)	CL/F (L/h/m <sup>2</sup> )	CL/F (L/h)
A (n = 9)	0.6 ± 0.7 (0.4)	$2.7 \pm 2.8$ (1.2)	7.2 ± 6.6 (4.4)	3.9 ± 2.5 (4.0)	34 ± 33 (20)	40 ± 39 (22)	31±37 (11)	14 ± 18 (4.7)
B (n = 12)	7.5 ± 6.9 (6.5)	7.7 ± 5.4 (6.5)	14 ± 6.1 (14)	2.7 ± 1.8 (2.1)	87 ± 41 (79)	111 ± 63 (98)	3.9±2.1 (3.4)	$3.0 \pm 1.4 (2.7)$
C (n = 10)	2.4 ± 1.8 (2.5)	4.1 ± 1.8 (3.7)	6.9 ± 2.2 (6.7)	4.5 ± 2.9 (5.5)	32 ± 14 (36)	$48 \pm 11^{\ddagger}(49)$	7.3±2.8 <sup>‡</sup> (7.0)	$10 \pm 3.6^{\ddagger}(11)$
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Table 2. Mean + SD (Median) Pharmacokinetic Parameters of Ritonavir Following 350 mg/m<sup>2</sup> BID Dosing

‡ n=9.

Age/Weight Group A: 6 months ≤ age ≤ 2 yrs. Group B: age 2 yrs. and weight ≤ 30 kg Group C: age 2 yrs. and weight > 30 kg.

#### 2.4 Extrinsic Factors

Please refer to the original NDA review 20-659 and 20-680.

## 2.5 General Biopharmaceutics

Please refer to the original NDA review 20-659 and 20-680.

## 2.6 Analytical Section

Please refer to reviews of Studies PACTG 345 and PACTG 366.

## 3. Labeling Recommendations

The sponsor proposed the following major labeling changes related to Clinical Pharmacology and Biopharmaceutics:

1. CLINICAL PHARMACOLOGY: Special Populations: Pediatric Patients:

Steady-state pharmacokinetics were evaluated in 37 HIV-infected patients ages 2 to 14 years receiving doses ranging from 250 mg/m2 twice-daily to 400 mg/m<sup>2</sup> twice-daily in PACTG Study 310, and in 41 HIV-infected patients ages 1 month to 2 years at doses of 350 and 450 mg/m<sup>2</sup> twice-daily in PACTG Study 345. Across dose groups, ritonavir steady-state oral clearance (CL/F/m<sup>2</sup>) was approximately 1.5 to 1.7 times faster in pediatric patients than in adult subjects. Ritonavir concentrations obtained after 350 to 400 mg/m<sup>2</sup> twice-daily in pediatric patients > 2 years were comparable to those obtained in adults receiving 600 mg (approximately 330 mg/m<sup>2</sup>) twice-daily. The following observations were seen regarding ritonavir concentrations after administration with 350 or 450 mg/m<sup>2</sup> twice daily in children < 2 years of age. Higher ritonavir exposures were not evident with 450 mg/m<sup>2</sup> twice-daily compared to the 350 mg/m<sup>2</sup> twice daily. Ritonavir trough concentrations were somewhat lower than those obtained in adults receiving 600 mg twice daily. The area under the ritonavir plasma concentration-time curve and trough concentrations obtained after administration with 350 or 450 mg/m<sup>2</sup> twice-daily in children < 2 years were approximately 16% and 60% lower, respectively, than that obtained in adults receiving 600 mg twice daily.

#### 2. DOSAGE AND ADMINISTRATION: Pediatric Patients:

The recommended dosage of ritonavir in children > 1 month is 350 to 400 mg/m<sup>2</sup> twice daily by mouth and should not exceed 600 mg twice daily.

The above changes are acceptable. They are supported by results of Studies PACTG 345 and PACTG 366.

## 4. Appendices

# 4.1 Individual Study Review (2)

## PACTG 345

**TITLE**: A phase I/II dose finding, open label trial to assess the safety, tolerance and activity of ritonavir therapy alone and in combination with lamivudine (3TC) and zidovudine (ZDV) in HIV-1 infected infants and children between the ages of 1 month and 2 years

**OBJECTIVES**: The primary objectives of this study were to assess the pharmacokinetics, safety and tolerance of single and multiple oral doses of ritonavir monotherapy and in combination with 3TC and ZDV in HIV-1 infected infants and children less than 2 years of age and to assess potential age related differences in ritonavir exposure parameters.

**SUBJECTS AND STUDY DESIGN**: This was a phase I/II study to assess safety, tolerance, pharmacokinetics and activity of RTV alone and in combination with 3TC (and ZDV) in HIV-1 infected male and female infants and children. Two ritonavir dose cohorts were studied.

Cohort I: RTV dose was 350 mg/m<sup>2</sup> BID. The choice of this dose was based on the anticipated pharmacokinetic equivalence to the 600-mg dose given in adults and preliminary data from older children in the National Cancer Institute study with a RTV dose between 350 and 400 mg/m<sup>2</sup>.

Cohort II: RTV dose was 450 mg/m<sup>2</sup> BID.

Subjects were stratified by age in each dose cohort and dosed as follows:

Group 1: >6 months to 2 years. On Day 0, a single dose of RTV was taken for pharmacokinetic study. RTV BID monotherapy began 12 hours after the single dose. On Day 7, RTV, 3TC and ZDV combination therapy was started.

Group 2: 3-6 months. Dosing was the same as Group I.

Group 3: 1 month to < 3 months. On Day 0, a single dose of RTV was taken for pharmacokinetic study. RTV, 3TC and ZDV combination therapy was started once the RTV pharmacokinetic results were available (Day 7-10).

51 HIV-1 infected male and female infants and children were enrolled (18 in Cohort 1 and 33 in Cohort II)

Number of subjects with PK information are as follows:

Cohort 1:	Group 1:	6
	Group 2:	2
	Group 3:	6
Cohort 2:	Group 1:	7
	Group 2:	8
	Group 3:	12

	PID	Weight	Height	Gender	Race	BSAcalo	Initial Dose	Dose mg/m
Group I	280740	11.7	82.5	2	2	0.518	182	351
	400312	8.3	72.2	1	1	0.408	144	353
	503065	8.5	68.0	2	2	0.401	128	319
	503070	8.2	64.0	1	2	0.382	136	356
	503228	7.6	70.0	1	3	0.384	136	354
	700060	13.0	90.5	2	1	0.572	200	350
	Mean	9.6	74.5	3M/3F	3B / 2W	0.444	154	347
	SD	2.2	10.0		1H	0.080	29	14
And Brants	A > 4	The second second	机、花花的	5. 2. 34 NG	S. S. Fast	the second	14447	Serve and the serve
Group II	650411	4.8	58.0	2	2	0.278	104	374
	650379	5.0	57.1	1	2	0.282	104	369
	Mean	4.9	57.6	1M/1F	2B	0.280	104	372
	SD	0.1	0.6			0.002	0	3
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Group III	410436	7.0	62.5	2	2	0.349	112	321
	503073	6.0	61.5	1	2	0.320	96	300
	503088	4.8	60.0	. 1	1	0.283	98	346
	503302	4.9	55.0	1	6	0.274	95	347
	650413	4.2	58.7	1	2	0.262	88	336
	504085	2.7	44.5	1	2	0.183	64	350
	Mean	4.9	57.0	5M / 1F	4B / 1W	0.278	92	334
	SD	1.5	6.7		/10	0.057	16	20
			TOTAL:	9M / 5F	9B/3W 1H/1U			
Sender Co	des:	1 = male; 2	= female	at an	AN (1996)	Sec. 1	- 1995	
ace Code	s:	1 = White, n	on-Hispar	nic;	2 = Black,	non-Hispa	nic;	
		3 = Hispanic	/ Latino;		4 = Asian.	inder.		
		5 = America	n Indian /	Inuit:	6 = Unknor	WD		

Demographic and RTV Dose Information for Cohort 1 Subjects with Evaluable PK (n=14)

	PID	Weight	Height	Gender	Race	BSAcalc	Initial Dose	Dose mg/m <sup>2</sup>
Group I	290210	14.8	91.8	1	2	0.614	279	454
	400444 *	8.7	75.1	2	2	0.426	176	413
	690412	6.6	68.6	2	2	0.355	152	429
	460731	7.5	65.0	1	3	0.368	176	478
	670182	6.8	65.0	2	2	0.350	160	457
	504353	8.8	70.3	2	2	0.415	200	482
	400805	11.9	78.0	2	2	0.508	208	410
	Mean	9.3	73.4	2M/5F	6B/1H	0.43	193	446
	SD	3.0	9.5	1		0.10	43	30
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Group II	400393*	6.3	61.0	1	11	0.327	128	392
	400365*	6.2	58.2	2	2	0.317	128	404
	504357	7.9	63.5	1	2	0.373	168	450
	290207	4,1	54.0	2	1	0.248	112	452
	411027	4.9	57.4	2	2	0.280	104	372
	504343**	6.3	61.0	1	2	0.327	120	367
	504352	5.7	60.0	2	2	0.308	128	415
	410424	7.2	65.0	2	3	0.361	144	399
	Mean	6.1	60.0	3M / 5F	58/2W/1H	0.32	129	406
	SD	1.2	3.5			0.04	13	32
	* Dose of	420 mg/m	12 prior to p	rotocol ame	endment.			
·	** PK par	ameters e	stimated fro	m week 1 c	lata.			
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Group III	690414	5.4	57.8	2	3	0.294	120	408
	400412	3.5	51.0	2	2	0.223	96	431
	504346	4.5	54.0	2	2	0.260	112	431
	504761	6.6	57.0	1	2	0.323	144	445
	440228	5.4	54.0	1	2	0.285	112	394
	504366	5.4	58.0	2	3	0.295	128	434
	690529	4.5	53.3	2	3	0.258	112	434
	650694	4.4	53.8	1	2	0.255	120	468
	440243	6.4	62.0	2	2	0.332	144	434
	440244	5.4	57.5	2	2	0.294	128	436
	505284	5.4	57.2	1	3	0.293	128	437
	650744	5.9	53.0	1	2	0.295	135	458
	Mean	5.2	55.7	5M / 7F	8B / 4H	0.28	123	434
	SD	0.9	3.0			0.03	14	20
Weight & he	ight are Wk4	data;	TOTAL:	10M / 17F	19B / 6H / 2W			
BSAcalc bas	ed on Wk4							
weight and h	eight							

#### Demographic and RTV Dose Information for Cohort 2 Subjects with Evaluable PK (n=27)

## INVESTIGATOR AND STUDY LOCATION: Multicenter

**FORMULATION**: Ritonavir (RTV) 80 mg/mL liquid formulation, Lamivudine 10 mg/mL syrup and Zidovudine 10 mg/mL syrup.

**SAMPLE COLLECTION**: Blood samples for the determination of ritonavir were collected as follows:

- Cohort 1: Day 1 and Week 4: pre-dose, 1, 3, 5 and 8 hrs post-dose Day 7: pre-dose, 1 and 3 post-dose Weeks 8, 12 and 16: pre-dose and 2 hrs post-dose
- Cohort 2: Day 7 and Week 4: pre-dose, 1, 3, 5 and 8 hrs post-dose Weeks 8, 12 and 16: pre-dose and 2 hrs post-dose

ASSAY: Plasma concentrations of ritonavir were determined using a validated HPLC assay (b) (4) The lower limit of quantification of ritonavir was 7.5 ng/mL using 1.0 mL plasma. Overall precision and accuracy for quality control samples were less than 8.0% (measured by %RSD) and 6.69% (measured by %RE), respectively.

**PHARMACOKINETIC DATA ANALYSIS**: One-compartment model with first order absorption and a lag time was used to fit the pharmacokinetic data. Summary statistics of pharmacokinetic parameters such as means and standard deviations for Cmax, Tmax and AUC were provided for each group.

# PHARMACOKINETIC RESULTS:

Table 1. Mean ± SD (Median) Pharmacokinetic Parameters for Ritonavir at Steady State Across Different Age Groups (All BID Regimens)

	1	month – 2 yrs		Childre	n > 2 yrs		Adults			
	350 mg/m <sup>2</sup> (N = 14)	450 mg/m <sup>2</sup> (N = 27)	250 mg/m <sup>2</sup> (N = 7)	300 mg/m <sup>2</sup> (N = 9)	350 mg/m <sup>2</sup> (N = 11)	$400 \text{ mg/m}^2$ (N = 10)	400 mg (N = 13)	600 mg		
C <sub>max</sub> ,ss (µg/mL)	10.1 ± 7.9 (5.6)	8.2 ± 6.8 (6.9)	9.7 ± 4.9 (9.6)	10.9 ± 3.7 (9.8)	11.4 ± 4.2 (12.4)	16.0 ± 9.9 (11.4)	7.1 ± 2.7 (6.0)	11.2 ± 3.6 (10.9)		
C <sub>trough,</sub> ss (µg/mL)	1.4 ± 1.8 (0.86)	1.4 ± 1.9 (0.75)	3.3 ± 3.4 (2.3)	2.2 ± 1.4 (1.7)	2.1 ± 1.9 (2.0)	5.5 ± 4.0 (5.9)	1.8 ± 0.9 (1.5)	3.5 ± 2.5 (2.8)		
AUCss (µg•h/mL)	61 ± 53 (40)	66 ± 54 (50)	58 ± 33 (56)	63 ± 27 (56)	60 ± 27 (52)	100 ± 64 (97)	49 ± 21 (46)	77 ± 32 (69)		
CL/F (L/h)	3.0 ± 1.6 (2.9)	3.1 ± 2.0 (2.7)					05+37(87)	88,22 (B ()		
CL/F (L/h/m <sup>2</sup> )	8.4 ± 5.2 (7.8)	8.9 ± 5.7 (7.8)	6.0 ± 3.9 (4.4)	5.7 ± 2.7 (5.3)	7.4 ± 4.0 (6.8)	6.4 ± 5.2 (4.2)	5.2 ± 2.0* (4.8)	8.8 ± 3.2 (8.6) 4.9 ± 1.7* (4.8)		

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										Grou	ID III			All Gr	oups	
		Gre	up I			Grou	ip IL		Pre	dore	2-h P	ostdose	Pre	dose	2-h Pe	stdose
t	Pres	lose	2-h Po	stdose	Pred	ose	2-h P	ostaose	Ma	dian	Median		Median		Me	dian
t	Me	dian	Me	dian	Med	lian	M	edian	Min	Max	Min	Max	Min	Max	Min	Max
1	Min	Max	Min	Max	Min	Max	Min	Max	Paris 1	TLAA						
								Week B	206	(1006)	4057	(n=6)	857	(n=14)	5726	(n=14)
Cohort I	1679	(n=6)	8084	(n=6)	863 (	(n=2)	320	7 (n=2)	300	1220	\$62	11147	79	4139	562	18678
Contra	853	4139	895	18678	79	1647	580	5835	188	(1329	709	(Pmn) 6	587	(n=21)	4986	(n=21)
Cabert II	188	(n=4)	4658	(n=4)	399	(n=7)	440	5 (n=8)	113	(1-10)	873	18465	0	5383	0	18465
Conorta	45	1921	2512	7157	0	1034	0	12111	98	2282	0/5	10405	, , , , , , , , , , , , , , , , , , ,			
	42	1741						Weck 12			452	(m=6)	1587	(n=12)	5484	(n=14)
C.L. HT	1749	(==5)	6528	(n=6)	3553	(n=2)	147	13 (n=2)	584	(n=5)	432	T 15314	118	4161	2437	24387
Cohorti	1002	3783	2437	16164	2944	4161	5039	24387	118	1829	2/20	10014	769	(n=25)	8225	(n=24)
	1092	(277)	512	5 (n=6)	769	(n=7)	83	94 (n=7)	959	(n=11)	85/4	1 16645	1 0	8020	414	25159
Cohort II	143	1 2142	2281	25159	0	8020	3241	16845	517	4360	414	13043	<u> </u>	0020		
	00	3143	2201					Week 16				1 ( 1)	668	(nal?)	8737	(n=12)
		(	888	1 (026)	628	(n=2)	48	00 (n=2)	61	5 (n=4)	674	(n=4)	000	2398	88	12599
Cohort I	830	2308	90	17599	0	1255	367	9234	111	843	3288	9/80	116	0 (0=25)	1141	8 (n=24)
	1 0	2398	00	7 (n=7)	867	(n=6)	10	840 (n≕6)	142	4 (n=12)	1339	2 (nat1)	110	1 11757	772	24362
Cohort I	782	(n≃/)	772	1 14490	14	2419	2669	13635	73	6440	10350	24362	14	111/5/		1.000
	229	11/57	1 112	14450			Avera	ge Week 8, 1	2, and 1	64			1 00	( / 28)	1 650	7 (n=40)
				( -18)	168	1 (1975)	7	74 (n=6)	49	1 (n=15)	513	8 (n=16)	98	5 (n=36)	1000	1 12157
Cohort I	148	1 (n=17)	787	6 (n=18)	1008	2354	1995	13152	2.04	980	2529	11598	204	3181	199	e (am(0)
	700	3181	2310	12/95	588	(0=20)	81	58 (n=21)	16	32 (n=33)	121	71 (n=31)	74	U (n=71)	- 613	112071
Cohort I	1 740	) (n=18)	645	0 (n=17)	300	2751	639	11355	534	3078	5863	13626	15	7450	039	13973
	210	7450	1526	13973		3/31	1 000	1 1 1 1 1	d and a							

# Table 2. Ritonavir Concentrations (ng/mL) at Weeks 8, 12 and 16

Numbers in parentheses (n) are numbers of subjects with available samples in each dose cohort and age group Numbers in parentheses (n) are numbers of subjects.

Cardenary 1710 College			_				_	_		
Group ] (n=13).	Cohort	BSAcal	(c Weigt	CLIF ILING	CL/F (L/hrim2	VEID	V/F /L (helm 2)	T 12	C	AUCINE
										(b) (4)
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t										
t							1 10.00			
- Insan	+	0.40	9.03	2.90	0.09	8.97	19.87	3.18	10999	68.38
50	1	80.0	244	211	3,78	3.65	8.81	2.17	10214	67.34
Median		0.44	8.70	2.33	4.42	8.65	17.84	2.46	5422	78.04
min		0.37	6.80	0.69	1.57	5.79	12.37	0.91	126	27.84
max		0.63	14,60	7.47	14.65	20.49	46.20	8.74	31654	280.60
St. Martin College St.	arbana.	a bialtante	13444	Contraine to Pro-	A STATE A DEST- HA	West Statistics	Survey and the state of the	A Manufacture	Talkey all the start	1 208.09
TO VER HALL BE STONE	in the second	Property of			and the second second	1	COLOR DATE SHOW NO	SCALES OF STATE	2 Service and the service of the ser	No Constitution and the State
Group If (D=10)	Cohort	BSAcalo	Weight	CL/F (L/hr)	CL/F (L/hr/m2)	V/F (L/hr)	V/F (L/brim2)	T 1/2	Cmar	ALLC (method )
										(b) (4)
										1
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mean		0.34	6.2	2.93	9.14	8.27	24.65	2.45	8200	54.88
SD		0.04	1.1	1.54	6.10	0.62	3.47	1.21	5762	3271
Median		0.34	6.4	2.73	7.61	8.50	24.75	2.08	7386	47.06
min		0.26	4 10	1 35	3 91	7.01	10.77	0.01	120	47.00
		- W-6.0	4,10	1.35	10.0	7.01	18.72	0.93	125	17.57
i may		0.41	8.00	634	33.07		20.05	407		
max		0.41	8.00	6.34	23.97	8.84	32.25	4.27	17351	124.44
max Self-File Colores	15.5526A3	0.41	8.00	6.34	23.97	8.84	32.25	4.27 248794.53	17351	124.44
max Group films (Country) Group fill transferrer	Cobot	0.41	8.00	6.34	23.97	8.84 53382533	32.25	4.27	17351	124.44
max Group ()L (m=18)=	Cohort	0.41 MSAcalc	8.00 Weight	6.34 April 2 proto	23.97 CL/F (L/hrim2)	8.84 States and V/F (L/her)	32.25 String L/ scie L/s V/F (L/hr/m2)	4.27 29/27≩53 T 1/2	17351 Comer	124.44
max Group ()L (m=18)	Cohort	0.41 Marito and BSAcalc	8.00 Weight	6.34 Sprint of the	23.97 CL/F (L/hr/m2)	8.84 States and V/F (L/hy)	32.25 String L/ actor Fil V/F (L/hrim2)	4.27 29:73 € 75 5 5 5 T 1/2	17351 Comar	124.44 124.44 124.44 124.44 (b) (4)
Group ()L (m*18)	Cohort	0.41 BSAcalc	8.00 Septimized Weight	6.34 Sprint of the	23.97 CL/F (L/hr/m2)	8.84 StateState	32.25	4.27 77 - 1/2 T 1/2	17351	124.44
Group (1) (m*18)	Cohort	0.41 BSAcalc	8.00 Byesto Auto Weight	6.34 Sgall 2 - FO	23.97 CL/F (L/hrim2)	8.84 States and VIF (Linc)	32.25 String Watter 24 V/F (L/heim2)	4.27 27 - 7 - 7 - 7 - 7 - 7 - 7 - 7 - 7 - 7 -	17351 Constant State	124.44
Group (1) (m=18)	Cohort	0.41 SSAcalc	Weight	6.34 Agentia Society CLUF (L/hr)	23.97 CL/F (L/hr/m2)	8.84 Turking and	32.25 Strang La Stree File V/F (L.Ibrim2)	4.27 2016 7 (2) (2) T 1/2	17351 Const	124.44
max	Cohort	0.41 Here and the second s	8.00 Bersonau Weight	6.34 CLIF (Uhm	23.97 Stranger and Stranger CL/F (L/holm2)	8.84 States and	32.25 String Laster Eve V/F (L/helm2)	4.27 25년7年第33 T 1/2	17351 Const	124.44
Group (1) (m <sup>2</sup> 18)	Cohort	0.41 BSAcalc	8.00 Bersonson Weight	6.34 April 2010 CLIF (Uhm	23.97 CL/F (L/hr/m2)	8.84 TURES AN	32.25 String L/stree Eve V/F (L/hr/m2)	4.27 7 1/2	17351 Const	124.44
Group til (me 18)	Cohort	0.41 BSAcalc	8.00 Bersonan Weight	6.34 Ruff (Unin	23.97 Attacharterite CL/F (L/hv/m2)	8.84 TuildSuide	32.25 Strang Wards File V/F (L/br/m2)	4.27	17351 Const	124.44
Group SIL (m=18)	Cohort	0.41 BSAcalc	8.00 BerSchotz Weight	6.34 Nga Sarang CLIF (L/hm	23.97 Regenerations CL/F (L/hurim2)	8.84 Trilligen der	32.25 Strang Water File VIF (L.Ihrim2)	4.27	17351 Creat	124.44
Group (1) (m <sup>2</sup> 18)	Cohort	0.41 BSAcalc	8.00 Weight	6.34 Starting	23.97	8.84 States and V/F (Line)	32.25 Strang Wards En	4.27	17351 Const	124.44
Group 111 mm 180	Cohort	0.41 BSAcalc	8.00 Weight	6.34 South Strategy	23.97 Stranger Holder Holder CL/F (L/hor/m2)	8.84 Transformer V/F (Liher)	32.25 Strate Line Line VIF (Lihelm2)	4.27	17351 Constant	124.44
Group SIL (mr 18)	Cohort	0.41 BSAcalc	Weight	6.34 Ruff (L/hm	23.97 Regenerations	8.84 States and V/F (Liber)	32.25 Strang Watter VIF (L.Ihrim2)	4.27 ₩ 7 1/2	17351 Const	124.44
Group 111 (m=10)	Cohort	0.41 BSAcalc	8.00 Weight	6.34 GLIF (L/hm	23.97 Strategisticstanded CL/JF (L/Indim2)	8.84 Standardson	32.25 Strang Life Sector VIP (Liferim2)	4.27 ₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩	17351 Const	124.44
Group 111 mm 180	Cohort	0.41 BSAcalc	8.00	6.34 Ruff an Server CL/F (L/hm	23.97 Regenerations	8.84 Standard V/F (Linct	32.25 Strate Life Entry V/F (L/heim2)	4.27 ₩ 7 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	17351 Const	124.44
Group (1) (m <sup>2</sup> 18)	Cohort	0.41 BSAcalc	8.00 Berschart Weight	GL/F (L/hm	23.97 Regenerations	8.84 Statistics and V/F (L/her)	32.25 Strang Watter VIF (L.Ihrim2)	4.27 ₩₹795,500 T 1/2	17351 Const	124.44
Group 111 (m=10)	Cohort	0.41 BSAcalc	8.00 Berschart Weight	6.34 Staff and the second	23.97	8.84 Statistical VF (Lind	32.25 V/F (L/hrim2)	4.27 第1日日 〒 1/2	Cmax	124.44
Group 111 mm 180	Cohort	0.41 BSAcalc	8.00 Berschart Weight	6.34 References	23.97 Regenerations	8.84 Tradicio de Vil <sup>e</sup> (Liber)	32.25 Strate Line Line VIF (L.Inelm2)	4.27 112 T 1/2	17351 Const	124.44
Group (1) (m <sup>2</sup> 18)	Cohort	0.41 BSAcalc	8.00 Berdshitt	GL/F (L/hm	23.97 Regenerations CL/F (L/brim2)	8.84 States and V/F (Liber)	32.25 Strang Watter VIF (L.Ihrim2)	4.27 ₩₹795,500 T 1/2	17351 Const	124.44
Group 111 m 180	Cohort	0.41 BSAcalc	8.00 Berdshin	6.34 CL/F (L/hm	23.97	8.84 Tradicio de VIE (Liber	32.25 V/F (L/hrim2)	4.27 第1日日 〒 1/2	Cmax	124.44
Group 111 mm 180	Cohort	0.41 BSAcalc	8.00	6.34 Ruff an or the CL/F (L/hm	23.97 Regenerations	8.84 Statistica and	32.25 Strang La Contra VIF (L.fhrim2)	4.27 112 T 1/2	Conav	124.44
Group 111 (m=10)	Cohort	0.41 BSAcalc	8.00 Berdshitt	6.34 Staff and the	23.97	8.84 TURBED A	32.25 V/F (L/hrim2)	4.27 ₩679 <b>1</b> 12	Cmax	124.44
Group 111 m 180	Cohort	0.41 BSAcak	8.00	GL/F (L/hm	CL/F (L/hr/m2)	8.84 Tradici de Vil <sup>e</sup> (Liber)	32.25 V/F (L/hrim2)	4.27 10 〒 1/2	Cmax	124.44
max Group 111 m=180	Cohort	0.41 BSAcak	5.75	3.35	23.97 State State State CL/F (L/br/m2)	8.84 51959 at VF (Libra)	32.25 Strate Line Line VIF (L.Inelm2) 28.34	4.27 ₩/27 (2.5 (2.5 (2.5 (2.5 (2.5 (2.5 (2.5 (2.5	7674	124.44
max Group 11 (m=10) mean SO	Cohort	0.41 BSAcalc	5.75 ( 0.98	6.34 2004 85 - FE CL/F (L/hm 3.35 1.89	23.97 CL/F (L/hr/m2) CL/F (L/hr/m2) 10.32 5.70	8.94 10.2550 at V/F (Liter) 2.38	28.34 8.37	4.27 ₩/€/7क,537 T 1/2 2.82 2.48	7674 4947	124.44 127.55 All C 10000000 (b) (4) 53.19 46.27
max Group 111 me 180	Cohort	0.41 85Acak 0.32 0.03 0.33	5.76 0.98 5.95	6.34 3494355769 CL/F (L/hm 1.89 2.93	23.97 214255-4-354 CL/F (L/br/m2) 10.32 5.70 8.96	8.94 V/F /L/he1 2.38 8.78	28.34 28.34 28.34 8.37 26.25	2.82 2.48 2.24	7674 7674 4947	53.19 46.27 36.10
max Group 11 meta SO Median min	Cohort	0.41 BSAcalc 0.32 0.33 0.24	5.76 0.98 5.95 0.98 5.95	6.34 (ApaHastorree) CL/F (L/hm 1.89 2.93 0.31	23.97 CL/F (L/br/m2) 10.32 5.70 8.96 1.29	8.94 V/F /L/hr1 2.38 5.72	22.25 V/F (L/br/m2) V/F (L/br/m2) 28.34 8.37 26.25 21.56	4.27 ₩/27 = 5 = 5 = 5 = 5 = 5 = 5 = 5 = 5 = 5 =	7674 7674 4947 6542 2925	124.44 124.44 At 10 <sup>-</sup> Jone West (b) (4) 53.19 46.27 36.10 15.22
max Signal State Group 11 (m=18) SO Median min max	Cohort	0.41 14-07-3-5 BSAcalc 0.32 0.03 0.33 0.24 0.37	5.75 0.98 5.95 5.95 3.50 7.20	6.34 CL/F (L/hm CL/F (L/hm 2.93 0.31 6.07	23.97 CL/F (L/hr/m2) CL/F (L/hr/m2) 5.70 8.96 1.29 18.77	8.94 2.38 2.38 8.78 5.12	28.34 8.37 26.25 21.56 57	4.27 2.82 7 1/2 2.82 2.48 2.24 0.96 11 58	7674 7674 4947 6542 2926	124.44 127.35 AHIC Jacobins (b) (4) 53.19 46.27 38.10 15.22 208.40
max Group 111 me 180 Broup 111 me 180 Br	Cohort	0.41 BSAcalc 0.03 0.33 0.24 0.37	5.76 0.98 3.50 7.20	6.34 349435 FEB CL/F (L/hm 1.89 2.93 0.31 6.07	23.97 CL/F (L/br/m2) CL/F (L/br/m2) 5.70 8.96 1.29 18.77 18.77	8.84 5082529 ak V/F /L/he1 2.38 8.78 5.12 17.71	22.25 V/F (L/hrim2) V/F (L/hrim2) 28.34 8.37 26.25 21.56 59.57 20.25	4.27 ■ 2.82 2.82 2.48 2.24 0.96 11.56	7674 7674 4947 6542 2926 18706	124.44 124.44 110 January (b) (4) 53.19 46.27 38.10 15.22 208.40
max Group 111 (m=10) Group 111 (m=10) Median min max Used an one	Cohort	0.41 14-07-3-5 BSAcalc 0.32 0.03 0.33 0.24 0.37 0.37 0.37	5.76 ( 0.98 5.95 5.95 5.95 7.20	6.34 3.35 CL/F (Uhm) 3.35 1.89 2.93 6.07 3.31 6.07	23.97 The second secon	8.94 10.2550 at V/F /L/hv1 2.38 8.78 5.12 17.71 17.71	22.25 V/F (L/hr/m2) V/F (L/hr/m2) 28.34 8.37 26.25 21.56 59.57	4.27 ■ (27 = 5 = 5 = 5 = 5 = 5 = 5 = 5 = 5 = 5 =	7674 7674 4947 6542 2925 18706 2934 18706	124.44 124.44 110 1
mean SO Median min max SD Median max SD Median min	Cohort Cohort	0.41 BSAcalc 0.32 0.33 0.24 0.33 0.24 0.33	5.76 5.95 5.95 5.95 5.95 3.50 7.20 Weight	6.34 CL/F (L/hm) CL/F (L/hm) 3.35 1.69 2.93 6.07 245/1429/354 CU/F (L/hm)	23.97 CL/F (L/br/m2) CL/F (L/br/m2) 10.32 5.70 8.96 1.29 18.77 Set Sistemation CL/F (L/br/m2)	8.54 10.2550 at V/F (Liber) 2.38 8.78 5.12 17.71 17.71 17.71 17.71 17.71 17.71 17.71 17.71 17.71 17.71 17.71 17.71 17.75 17	22.25 V/F (L/hr/m2) V/F (L/hr/m2) 28.34 9.37 26.25 21.55 21.55 21.55 21.55 7.55 7.55 7.55 7.55 7.55	4.27 2.82 2.48 2.24 0.95 11.56 11.56 11.56	7674 7674 6542 2926 18706 2926 2026 20 2026 2	53.19 46.27 38.10 15.22 208.40 52.22 208.40 52.22 208.40 53.29 53.19 55.20 55.19 55.20
max Group 111 me 180 Group 111 me 180 Median min max Electrosteretere ALL GROUPS (mean	Cohort Cohort Internet Ermetration	0.41 BSAcalc 0.32 0.03 0.24 0.37 ESAcalc 0.37	5.75 5.75 0.98 5.95 3.50 7.20 Weight 7.10	6.34 3.35 CL/F (L/hm) 1.89 2.93 0.31 6.07 245/32/324 CL/F (L/hm) 3.11	23.97 21.97 21.07 21	8.94 V/F /L/hc1 2.38 5.12 17.71 V/F (L/hc1 8.79 5.12 17.71 V/F (L/hc1 8.79	28.34 V/F (L/hr/im2) V/F (L/hr/im2) 28.34 8.37 26.25 21.56 59.57 V/F (L/hr/im2) V/F (L/hr/im2) 24.75	4.27 2.82 2.82 2.48 2.24 0.96 11.56 11.56 11.56 11.56 11.56	7674 Cmax Cmax Cmax 6542 2926 18706 29265 555555	124.44 124.44 110 January (b) (4) 53.19 46.27 38.10 15.22 208.40 54.527 208.40 55.22 55.22 208.40 55.22 55.22 55.20 55.22 55.20 55.22 55.20 55.22 55.20 55.
max Group 11 (m=18) SO Median min max Ubication SD ALL GROUPS (n=4 mean SD	Cohort Cohort	0.41 85Acalc 0.32 0.03 0.33 0.24 0.37 15Acalc 0.09	5.76 0.98 5.95 3.50 7.20 Weight 7.10 2.36	6.34 CL/F (Uhn) CL/F (Uhn) 3.35 1.89 2.93 0.31 6.07 2402/234 CUF (Uhr) 3.11 1.85	23.97 21.97 21.97 21.07 21	8.94 2.38 2.38 8.78 5.12 17.71 57.12 17.71 57.12 17.71 57.12 17.71 57.12 17.71 57.12 17.71 57.12 17.71 57.12 17.71 57.12 17.71 57.12 17.71 57.12	28.34 28.34 V/F (L/hrim2) 26.25 21.56 59.57 V/F (L/hrim2) 24.75 8.32	4.27 2.82 2.82 2.48 2.24 0.96 11.56 37 M-950 7 1/2 2.85 2.11	7674 7674 Cmax Cmax Cmax 6542 2926 18706 2926 Cmax 8856.55 7160 08	124.44 124.44 110 January (b) (4) 53.19 46.27 38.10 15.22 208.40 Statistics (5) 44.27 38.10 15.22 208.40 Statistics (5) 44.27 38.10 15.22 208.40 Statistics (5) 44.27 38.10 15.22 208.40 Statistics (5) 44.27 38.10 15.22 208.40 Statistics (5) 44.27 38.10 15.22 208.40 Statistics (5) 44.27 38.10 15.22 208.40 Statistics (5) 44.27 208.40 Statistics (5) 44.75 57 57 57 57 57 57 57 57 57
mean SO Median Median ALL GROUPS (n= SO Median	Cohort I I I I I I I I I I I I I I I I I I I	0.41 85Acalc 0.32 0.03 0.33 0.24 0.33 0.24 0.37 0.09 0.34	5.76 0.98 5.95 5.95 7.20 7.10 2.36 6.60	6.34 CL/F (L/hm) CL/F (L/hm) 2.93 0.31 0.31 CL/F (L/hm) 3.11 1.85 2.65	23.97 CL/F (L/hr/m2) CL/F (L/hr/m2) 5.70 8.96 1.29 18.77 5.70 2.95 1.29 18.77 5.70 8.96 1.29 18.77 1.29 18.77 1.29 18.77 7.2	8.54 10:25:00 al 0:25:00 al 0:25:00 al 2.38 8.78 5.12 17.71 8.79 5.71 8.79 2.57 4.72	22.25 V/F (L/hr/m2) V/F (L/hr/m2) 28.34 8.37 26.25 21.56 59.57 21.56 59.57 24.75 8.32 24.75 8.32 24.75 8.32	4.27 2.82 2.82 2.48 2.24 0.96 11.56 3.50 3.50 1.56 3.50	7674 7674 6497 6542 2926 18705 18705	124.44 124.44 110 January (b) (4) 53.19 46.27 38.10 15.22 208.40 53.19 46.27 38.10 15.22 208.40 53.19 40.27 50.10 15.22 208.40 53.19 64.76 52.70 54.76
max Group III (meta) SO Median min max SUIDE (meta) Median SD Median SD Median min max SUIDE (meta) SD Median Median SD Median Median	Cohort Kettersteinen Ketterste	0.41 14-07-3-5 BSAcalc BSAcalc 0.03 0.33 0.24 0.37 ACCESSION 0.37 0.	5.76 ( 0.98 5.95 5.95 5.95 5.95 7.20 Weight 7.20 Weight 7.20	6.34 3.35 CL/F (Uhr) 1.89 2.93 0.31 6.07 2.45 CUF (Uhr) 3.11 1.85 2.68	23.97 CL/F (L/hr/m2) CL/F (L/hr/m2) 5.70 8.96 1.29 18.77 Strift (L/hr/m2) 6.59 CL/F (L/hr/m2) 6.59 5.77 7.78	8.94 2.38 8.74 2.38 8.78 5.12 17.71 5.12 17.71 5.12 17.71 5.12 17.71 5.12 17.71 5.12 5.12 17.71 5.12 5.2 5.2 5.2 5.2 5.2 5.2 5.2 5.	28.34 28.34 V/F (L/hr/m2) 28.37 26.25 21.56 59.57 V/F (L/hr/m2) 24.75 8.32 24.78 8.37	4.27 ■ (C) (P = 10 T 1/2 T 1/2 2.82 2.48 2.24 0.96 11.56 11.56 11.56 11.56 11.56	7674 Cmax Cmax Cmax Cmax Cmax Cmax Cmax 6542 2926 18706 2019/06/06/00 Cmax 8856.56 7156.08 6829.00	53.19 46.27 38.10 15.22 208.40 3.50 46.27 38.10 15.22 208.40 3.50 46.27 30.10 15.22 208.40 3.50 46.27 50.03
mean Group 111 me183 SO Median min max Tissicar(s)295 seeks ALL GROUPS (new mean SO Median min max	Cohort Cohort	0.41 85Acalc 0.32 0.33 0.24 0.37 0.09 0.34 0.37 0.09 0.34 0.34 0.37 0.09 0.34 0.34 0.34 0.37 0.09 0.34 0.34 0.34 0.34 0.35 0.37 0.3	5.76 5.95 5.95 5.95 3.50 7.20 Weight 7.10 2.360 3.60 3.60	6.34 CL/F (L/hm) CL/F (L/hm) 3.35 1.89 2.93 6.07 2.93 6.07 2.93 CL/F (L/hm) 3.11 1.85 2.66 0.31	23.97 CL/F (L/hr/m2) CL/F (L/hr/m2) 5.70 8.96 1.29 18.77 Set Size(12) 6.69 5.47 7.78 1.29 1.29	8.94 5.94 2.38 8.78 5.12 5	22.25 V/F (L/hr/m2) V/F (L/hr/m2) 28.34 8.37 26.25 21.56 21.56 21.57 V/F (L/hr/m2) 24.75 8.32 24.78 12.37	4.27 2.82 2.48 2.24 0.96 11.56 11.56 11.56 11.56 11.56 11.20 0.91	7674 Cmax Cmax Cmax 2926 18706 2926 18706 2926 18706 2926 18706 2926 18706 2926 18706 2926 2926 18706 2926 2027 2926 2027 2926 2027 2926 2027 2926 2027 2926 2027 2926 2027 2027 2027 2027 2027 2027 2027 20	124.44 127.55
max Group 111 me 180 SO Median min max SO Median min max SO Median min max	Cohort Cohort (1) E	0.41 85Acalc 85Acalc 0.03 0.24 0.33 0.24 0.37 0.24 0.37 0.24 0.37 0.09 0.34 0.24 0.37	5.76 0.98 5.95 3.50 7.20 90 90 90 90 90 90 90 90 90 90 90 90 90	6.34 3.35 CL/F (L/hm 1.89 2.93 0.31 6.07 2.83 0.31 3.11 1.85 2.66 0.31 7.47	23.97 21.97 21.97 21.97 21.97 21.97 21.97 23.97 23.97 23.97 23.97 23.97 23.97 23.97 23.97 23.97 23.97 23.97	8.94 5.9252 al V/F (L.he) 2.38 8.78 5.12 17.71 5.12 17.71 5.12 17.71 5.12 17.71 5.12 17.71 5.12 1.72 5.12 1.72 5.12 1.72 5.12 1.57 1.72 5.12 1.57	28.34 V/F (L/hrim2) V/F (L/hrim2) 28.37 26.25 21.56 59.57 V/F (L/hrim2) 24.75 8.32 24.75 8.32 24.75 8.32 24.75	4.27 2.82 2.82 2.82 2.48 2.24 0.96 11.56 37.102 2.85 2.11 2.20 0.91 11.56	7674 Cmax Cmax Cmax Cmax Cmax Cmax Cmax 6542 2926 18706 2825 Cmax 8855.55 7169.08 6825.00 125.00 31654.00	124.44 124.44 110 January (b) (4) 53.19 46.27 38.10 15.22 208.40 52.70 50.03 15.22 265.69
max Group III (m=18) Group III (m=18) SO Median min max SD Median min max SD Median min max	Cohort	0.41 14-07-3-25 BSAcalc BSAcalc 0.32 0.03 0.33 0.24 0.37 0.37 0.37 0.37 0.37 0.37 0.37 0.34 0.34 0.34 0.53 0.54 0.55	5.76 0.98 5.95 3.50 7.20 9000443 Weight 7.10 2.36 6.60 3.60 14.60	6.34 244 CL/F (L/hm) CL/F (L/hm) 3.35 1.89 2.93 0.31 6.07 245 2.68 0.31 1.85 2.68 0.31 7.47	23.97 23.97 24.95 24.75 24.75 2.70 8.96 1.29 18.77 29 18.77 29 20 20 21 29 23.57 23.57 23.57	8.94 2.38 8.94 2.38 8.78 5.12 17.71 5.12 17.71 8.79 2.57 8.72 5.12 20.49	28.34 V/F (L/hr/m2) V/F (L/hr/m2) 26.25 21.56 59.57 V/F (L/hr/m2) 24.75 8.32 24.76 12.37 59.57	4.27 2.82 2.82 2.48 2.24 0.96 11.56 37.40 3	7674 4947 6542 2926 18706 2016 2017 2017 2017 2017 2017 2017 2017 2017	124.44 124.44 110 January (b) (4) 110 January (b) (4) 15.22 208.40 15.22 208.40 15.22 208.69 AUC (mg*hr/L) 64.76 52.70 50.03 15.22 286.69 200.50 2

Table 3. Ritonavir Pharmacokinetic Parameters by Age Groups For both Dose Cohorts

**SAFETY RESULTS**: No new safety concerns compared to adults and old children. See Medical Officer's review for more detailed information.

**CONCLUSIONS AND DISCUSSION**: In Study PACTG 345, ritonavir exposures in infants and children < 2 years of age after 350 or 450 mg/m<sup>2</sup> BID dosing were similar to historical data in older children after 250 to 350 mg/m<sup>2</sup> BID dosing, with the exception that steady-state trough concentrations were lower in children < 2 years of age. There was high variability in ritonavir exposure. Higher ritonavir exposures were not evident with 450 mg/m<sup>2</sup> BID dose compared to the 350 mg/m<sup>2</sup> BID dose.

**Note:** One study center, the <sup>(b)(4)</sup> was found noncompliant with ethical standards in several clinical trials including PACTG 345. Three subjects with pharmacokinetic data were enrolled at the Columbia site. One subject was in Cohort I, Group III (ID 410436) and two subjects were in Cohort II, Group II (ID 411027 and ID 410424).

After reviewing the pharmacokinetic data, we concluded that excluding these three subjects from the study has little impact on the overall pharmacokinetic conclusions of the study.

Two plasma concentration-time graphs below and PK analysis supported the above conclusion.



Ritonavir Plasma Concentrations at Week 4 (PACTG 345, Cohort I, Group III)



Ritonavir Plasma Concentrations at Week 4 (PACTG 345, Cohort II, Group II)

#### PACTG 366

**TITLE**: A phase I/II master protocol of novel antiretroviral combination therapies in antiretroviral experienced children with rapidly progressing or advanced HIV disease (RAD)

RAD-1: A phase I/II antiretroviral management algorithm for pediatric subjects of four-drug combination therapies based on prior antiretroviral experience

#### Pharmacokinetic Report

(Only pharmacokinetic data of subjects less than two years old of age have been reviewed)

**OBJECTIVES**: The primary objective of this study was to determine the steady-state pharmacokinetics of ritonavir, nevirapine and nelfinavir when used in combination with respect to age and treatment group.

**SUBJECTS AND STUDY DESIGN**: Patients were placed into one of four groups based on prior antiretroviral experience.

Group 1:	No prior PI and no prior NNRTI therapy 2 NRTIs + Nevirapine + Nelfinavir or Ritonavir
Group 2	Prior PI and no prior NNRTI therapy NRTIs + Nevirapine + Nelfinavir + Ritonavir
Group 3	No prior PI and prior NNRTI therapy 2 NRTIs + Nelfinavir + Ritonavir
Group 4	Prior PI and prior NNRTI therapy 2 NRTIs + Nelfinavir + Ritonavir

All treatment groups received ritonavir 350 mg/m<sup>2</sup> BID.

There were 9 subjects of age >6 months to 2 years.

**INVESTIGATOR AND STUDY LOCATION: Multicenter** 

**FORMULATION**: Ritonavir (RTV) 80 mg/mL liquid and 100 mg capsules

**SAMPLE COLLECTION**: Blood samples for the determination of ritonavir were collected at Week 4 at pre-dose, 1, 2, 4, 6 and 8 hrs post-dose

ASSAY: Plasma concentrations of ritonavir were determined using a validated HPLC assay

The lower limit of quantification of ritonavir was 100 ng/mL.

**PHARMACOKINETIC DATA ANALYSIS**: The pharmacokinetic parameter values of ritonavir were estimated using non-compartmental methods. Summary statistics of pharmacokinetic parameters such as means and standard deviations for Cmax, Tmax and AUC were provided.

#### PHARMACOKINETIC RESULTS:

#### Table 1. Mean + SD (Median) Pharmacokinetic Parameters of Ritonavir Following 350 mg/m<sup>2</sup> BID Dosing

Age/Weight Group	C0 (µg/mL)	C8 (µg/mL)	C <sub>max</sub> (µg/mL)	T <sub>max</sub> (h)	AUC <sub>0-8</sub> (μg•h/mL)	AUC <sub>0-τ</sub> (μg•h/mL)	CL/F (L/h/m <sup>2</sup> )	CL/F (L/h)
A (n = 9)	0.6 ± 0.7 (0.4)	$2.7 \pm 2.8$ (1.2)	7.2 ± 6.6 (4.4)	3.9 ± 2.5 (4.0)	34 ± 33 (20)	40 ± 39 (22)	31±37 (11)	14 ± 18 (4.7)
B (n = 12)	7.5 ± 6.9 (6.5)	7.7 ± 5.4 (6.5)	14 ± 6.1 (14)	2.7 ± 1.8 (2.1)	87 ± 41 (79)	111 ± 63 (98)	3.9±2.1 (3.4)	3.0 ± 1.4 (2.7)
C (n = 10)	2.4 ± 1.8 (2.5)	4.1 ± 1.8 (3.7)	6.9 ± 2.2 (6.7)	4.5 ± 2.9 (5.5)	32 ± 14 (36)	$48 \pm 11^{\ddagger}(49)$	7.3±2.8 <sup>‡</sup> (7.0)	$10 \pm 3.6^{\ddagger}(11)$

‡ n=9.

Age/Weight Group A: 6 months ≤ age ≤ 2 yrs. Group B: age 2 yrs. and weight ≤ 30 kg. Group C: age 2 yrs. and weight > 30 kg.

SAFETY RESULTS: See Medical Officer's review.

**CONCLUSIONS AND DISCUSSION**: In Study PACTG 366, ritonavir exposures in children  $\leq 2$  years of ago were lower than in older children receiving 350 mg/m<sup>2</sup> BID dose, and also were lower than those observed in the PACTG 345 study.

**Note:** One study center, the <sup>(b) (4)</sup> was found noncompliant with ethical standards in several clinical trials including PACTG 366. One subject of age >6 months to 2 years with pharmacokinetic data was enrolled at the Columbia site (ID 411009).

After reviewing the pharmacokinetic data, we concluded that excluding this subject from the study has little impact on the overall pharmacokinetic conclusions of the study.

The plasma concentration-time graph below and PK analysis supported the above conclusion.

Pending on the DSI's inspection results (bioanalytical assay results), Study 366 may need to be excluded from the review. However, it will have no impact on the overall conclusions of this review.



Ritonavir Plasma Concentrations at Week 4 (PACTG 366)

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/s/ Derek Zhang 10/6/2005 11:40:03 AM BIOPHARMACEUTICS

Kellie Reynolds 10/6/2005 11:44:17 AM BIOPHARMACEUTICS