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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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^2 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^2 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^2 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^2 BID dosing were similar to historical data in older children after 250 to 350 mg/m^2 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^2 BID dose compared to the 350 mg/m^2 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		Children > 2 yrs			Adults	
	350 mg/m^2 (N = 14)	450 mg/m^2 (N = 27)	250 mg/m^2 (N = 7)	300 mg/m^2 (N = 9)	350 mg/m^2 (N = 11)	400 mg/m^2 (N = 10)	400 mg (N = 13)	600 mg (N = 10)
$C_{max,ss}$ (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)
$C_{trough,ss}$ (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)	--	--	--	--	9.5 ± 3.7 (8.7)	8.8 ± 3.2 (8.6)
CL/F (L/h/m^2)	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)

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^2 was used to calculate the normalized values of CL/F (L/h/m^2)

In Study PACTG 366, ritonavir exposures in children ≤ 2 years of ago were lower than in older children receiving 350 mg/m^2 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.

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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^2 BID dosing were similar to historical data in older children after 250 to 350 mg/m^2 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^2 BID dose compared to the 350 mg/m^2 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		Children > 2 yrs				Adults	
	350 mg/m^2 (N = 14)	450 mg/m^2 (N = 27)	250 mg/m^2 (N = 7)	300 mg/m^2 (N = 9)	350 mg/m^2 (N = 11)	400 mg/m^2 (N = 10)	400 mg (N = 13)	600 mg (N = 10)
$C_{max,ss}$ (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)
$C_{trough,ss}$ (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)	--	--	--	--	9.5 ± 3.7 (8.7)	8.8 ± 3.2 (8.6)
CL/F (L/h/m^2)	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)

Data for infants and children (1 month – 2 yrs.) are from the current study using Week 4 values.
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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^2 was used to calculate the normalized values of CL/F (L/h/m^2)

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

Table 2. Mean + SD (Median) Pharmacokinetic Parameters of Ritonavir Following 350 mg/m^2 BID Dosing

Age/Weight Group	C0 (μg/mL)	C8 (μg/mL)	C_{max} (μg/mL)	T_{max} (h)	AUC_{0-8} (μg•h/mL)	$AUC_{0-\tau}$ (μg•h/mL)	CL/F (L/h/m^2)	CL/F (L/h)
A (n = 9)	0.6 ± 0.7 (0.4)	2.7 ± 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 ± 11‡(49)	7.3±2.8‡ (7.0)	10 ± 3.6‡ (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.

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^2 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^2 twice-daily in PACTG Study 345. Across dose groups, ritonavir steady-state oral clearance (CL/F/ m^2) 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^2 twice-daily in pediatric patients > 2 years were comparable to those obtained in adults receiving 600 mg (approximately 330 mg/m^2) twice-daily. The following observations were seen regarding ritonavir concentrations after administration with 350 or 450 mg/m^2 twice daily in children < 2 years of age. Higher ritonavir exposures were not evident with 450 mg/m^2 twice-daily compared to the 350 mg/m^2 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^2 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^2 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^2 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^2.

Cohort II: RTV dose was 450 mg/m^2 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

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^2
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 / 3 F	3B / 2W	0.444	154	347
	SD	2.2	10.0		1H	0.080	29	14
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
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		/ 1U	0.057	16	20
			TOTAL:	9M / 5F	9B / 3W 1H / 1U			

Gender Codes:	1 = male; 2 = female		
Race Codes:	1 = White, non-Hispanic;	2 = Black, non-Hispanic;	
	3 = Hispanic / Latino;	4 = Asian, Pacific Islander;	
	5 = American Indian / Inuit;	6 = Unknown	

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

	PID	Weight	Height	Gender	Race	BSAcalc	Initial Dose	Dose mg/m^2
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			0.10	43	30
Group II	400393*	6.3	61.0	1	1	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	5B / 2W / 1H	0.32	129	406
	SD	1.2	3.5			0.04	13	32
	* Dose of 420 mg/m2 prior to protocol amendment.							
	** PK parameters estimated from week 1 data.							
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	0.256	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 & height are Wk4 data; BSAcalc based on Wk4 weight and height			TOTAL:	10M / 17F	19B / 6H / 2W			

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 [redacted] (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		Children > 2 yrs				Adults	
	350 mg/m^2 (N = 14)	450 mg/m^2 (N = 27)	250 mg/m^2 (N = 7)	300 mg/m^2 (N = 9)	350 mg/m^2 (N = 11)	400 mg/m^2 (N = 10)	400 mg (N = 13)	600 mg (N = 10)
$C_{max,ss}$ (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)
$C_{trough,ss}$ (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)	--	--	--	--	9.5 ± 3.7 (8.7)	8.8 ± 3.2 (8.6)
CL/F (L/h/m^2)	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)

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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^2 was used to calculate the normalized values of CL/F (L/h/m^2)

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

	Group I				Group II				Group III				All Groups			
	Predose		2-h Postdose		Predose		2-h Postdose		Predose		2-h Postdose		Predose		2-h Postdose	
	Median		Median		Median		Median		Median		Median		Median		Median	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
	Week 8															
Cohort I	1679 (n=6)		8084 (n=6)		863 (n=2)		3207 (n=2)		306 (n=6)		4057 (n=6)		857 (n=14)		5726 (n=14)	
	853	4139	895	18678	79	1647	580	5835	188	1329	562	11147	79	4139	562	18678
Cohort II	188 (n=4)		4658 (n=4)		399 (n=7)		4405 (n=8)		773 (n=10)		7099 (n=9)		587 (n=21)		4986 (n=21)	
	45	1921	2512	7157	0	1034	0	12111	98	5383	873	18465	0	5383	0	18465
	Week 12															
Cohort I	1749 (n=5)		6528 (n=6)		3553 (n=2)		14713 (n=2)		584 (n=5)		4526 (n=6)		1582 (n=12)		5484 (n=14)	
	1092	3783	2437	16164	2944	4161	5039	24387	118	1829	2726	15314	118	4161	2437	24387
Cohort II	723 (n=7)		5326 (n=6)		769 (n=7)		8394 (n=7)		959 (n=11)		8572 (n=11)		769 (n=25)		8225 (n=24)	
	66	3143	2281	25159	0	8020	3241	16845	517	4360	414	15645	0	8020	414	25159
	Week 16															
Cohort I	830 (n=6)		8881 (n=6)		628 (n=2)		4800 (n=2)		615 (n=4)		6745 (n=4)		668 (n=12)		8737 (n=12)	
	0	2398	88	12599	0	1255	367	9234	111	843	3288	9786	0	2398	88	12599
Cohort II	782 (n=7)		8487 (n=7)		867 (n=6)		10840 (n=6)		1424 (n=12)		13392 (n=11)		1160 (n=25)		11418 (n=24)	
	229	11757	772	14490	14	2419	2669	13635	73	6440	10350	24362	14	11757	772	24362
	Average Week 8, 12, and 16[a]															
Cohort I	1481 (n=17)		7876 (n=18)		1681 (n=6)		7574 (n=6)		491 (n=15)		5138 (n=16)		986 (n=38)		6507 (n=40)	
	700	3181	2310	12795	1008	2354	1995	13152	204	980	2529	11598	204	3181	1995	13152
Cohort II	740 (n=18)		6450 (n=17)		588 (n=20)		8158 (n=21)		1632 (n=33)		12171 (n=31)		740 (n=71)		8158 (n=69)	
	210	7450	1526	13973	5	3751	639	11355	534	3078	5863	13626	5	7450	639	13973

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

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

Group I (n=13)	Cohort	BSAcalc	Weight	CL/F (L/hr)	CL/F (L/hr/m2)	V/F (L/hr)	V/F (L/hr/m2)	T 1/2	Cmax	AUC (mg*hr/L)
										(b) (4)
mean		0.45	9.63	2.90	6.09	8.97	19.87	3.18	10999	68.38
SD		0.08	2.44	2.11	3.78	3.65	8.81	2.17	10214	67.34
Median		0.44	8.70	2.33	4.42	8.68	17.84	2.46	6422	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	289.69

Group II (n=10)	Cohort	BSAcalc	Weight	CL/F (L/hr)	CL/F (L/hr/m2)	V/F (L/hr)	V/F (L/hr/m2)	T 1/2	Cmax	AUC (mg*hr/L)
										(b) (4)
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	32.71
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	3.31	7.01	19.72	0.93	126	17.67
max		0.41	8.00	6.34	23.97	8.84	32.25	4.27	17351	124.44

Group III (n=18)	Cohort	BSAcalc	Weight	CL/F (L/hr)	CL/F (L/hr/m2)	V/F (L/hr)	V/F (L/hr/m2)	T 1/2	Cmax	AUC (mg*hr/L)
										(b) (4)
mean		0.32	5.76	3.35	10.32	8.94	28.34	2.82	7674	53.19
SD		0.03	0.98	1.89	5.70	2.38	8.37	2.48	4947	46.27
Median		0.33	5.95	2.93	8.96	8.78	26.25	2.24	6542	36.10
min		0.24	3.60	0.31	1.29	5.12	21.56	0.96	2926	15.22
max		0.37	7.20	6.07	18.77	17.71	59.57	11.56	18706	208.40

ALL GROUPS (n=41)		BSAcalc	Weight	CL/F (L/hr)	CL/F (L/hr/m2)	V/F (L/hr)	V/F (L/hr/m2)	T 1/2	Cmax	AUC (mg*hr/L)
mean		0.37	7.10	3.11	8.69	8.79	24.75	2.85	8856.56	64.76
SD		0.09	2.36	1.85	5.47	2.57	8.32	2.11	7169.08	52.70
Median		0.34	6.60	2.68	7.78	8.72	24.78	2.20	6829.00	50.03
min		0.24	3.60	0.31	1.29	5.12	12.37	0.91	126.00	15.22
max		0.63	14.60	7.47	23.97	20.49	59.57	11.56	31654.00	289.69

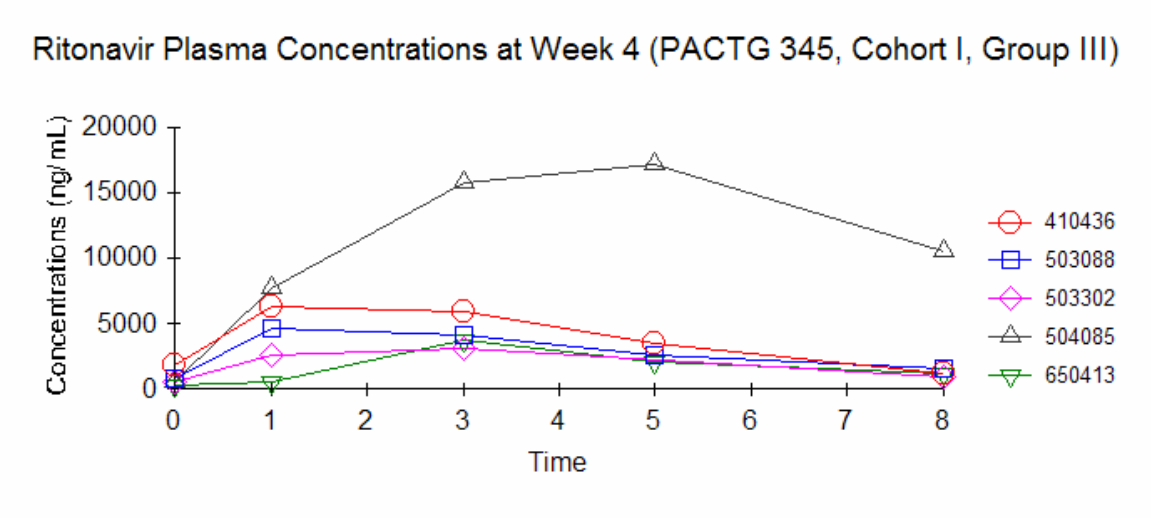
SAFETY RESULTS: No new safety concerns compared to adults and old children. See Medical Officer's review for more detailed information.

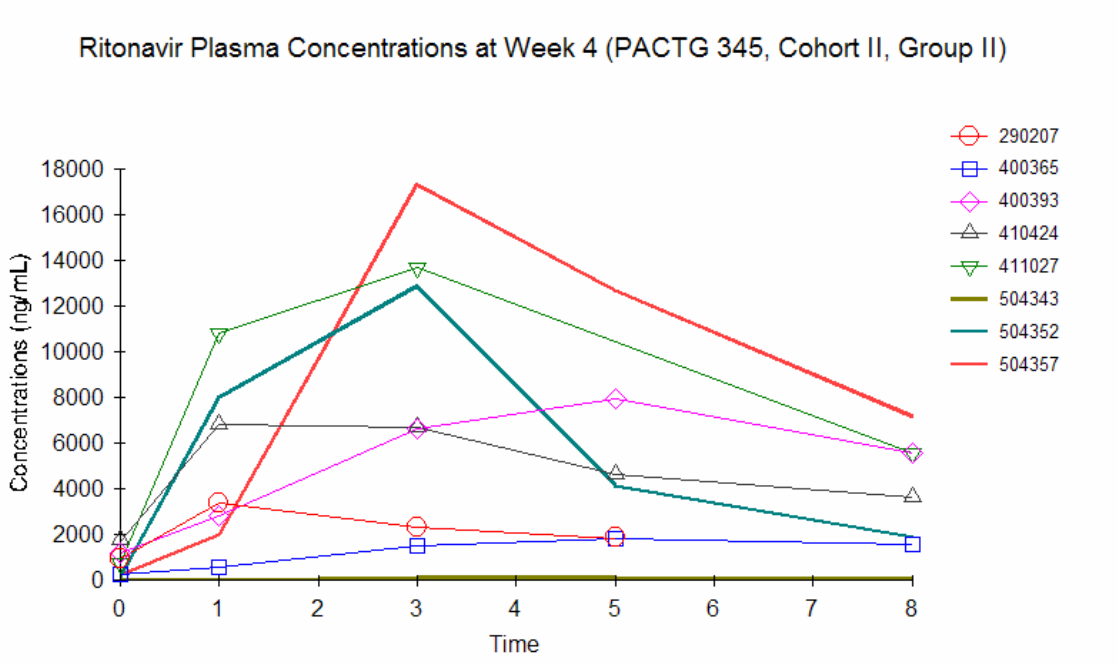
CONCLUSIONS AND DISCUSSION: In Study PACTG 345, ritonavir exposures in infants and children < 2 years of age after 350 or 450 mg/m^2 BID dosing were similar to historical data in older children after 250 to 350 mg/m^2 BID dosing, with the exception that steady-state trough concentrations were lower in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

Note: One study center, the [redacted] (b) (4) 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 II, Group II)
Concentrations (ng/mL)
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
0
1
2
3
4
5
6
7
8
Time
290207
400365
400393
410424
411027
504343
504352
504357

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^2 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 (b) (4)

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^2 BID Dosing

Age/Weight Group	C0 (μg/mL)	C8 (μg/mL)	C_{max} (μg/mL)	T_{max} (h)	AUC_{0-8} (μg•h/mL)	$AUC_{0-\tau}$ (μg•h/mL)	CL/F (L/h/m^2)	CL/F (L/h)
A (n = 9)	0.6 ± 0.7 (0.4)	2.7 ± 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 ± 11‡(49)	7.3±2.8‡ (7.0)	10 ± 3.6‡ (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.

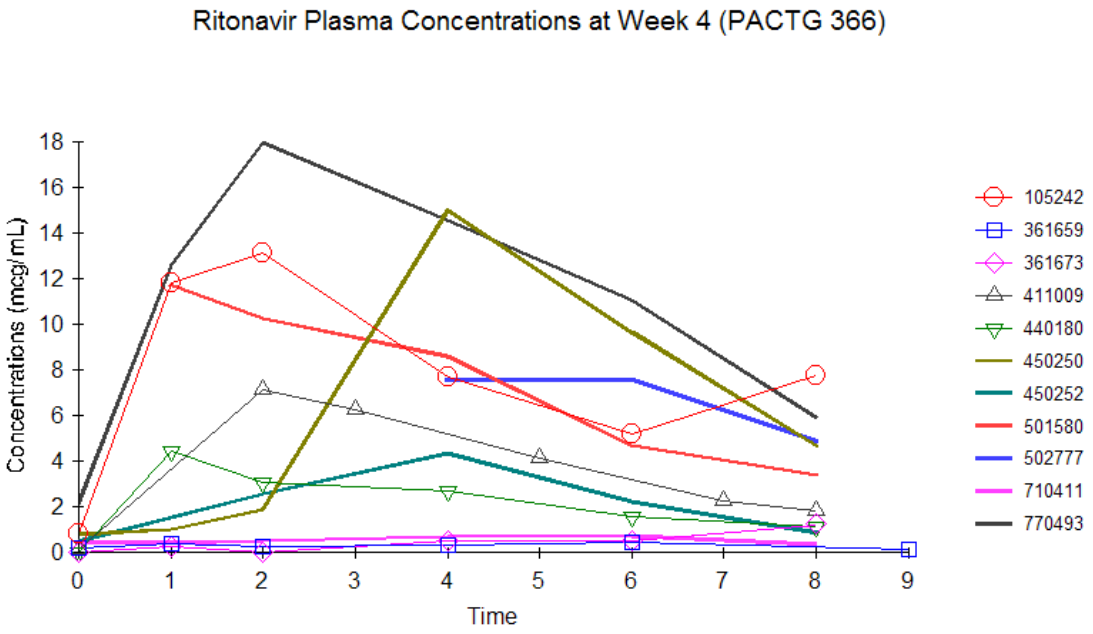
CONCLUSIONS AND DISCUSSION: In Study PACTG 366, ritonavir exposures in children ≤ 2 years of ago were lower than in older children receiving 350 mg/m^2 BID dose, and also were lower than those observed in the PACTG 345 study.

Note: One study center, the (b) (4) 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)
Concentrations (mcg/mL)
Time
0
2
4
6
8
10
12
14
16
18
0
1
2
3
4
5
6
7
8
9
105242
361659
361673
411009
440180
450250
450252
501580
502777
710411
770493

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/s/

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Kellie Reynolds
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