OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	21567, S026
Submission Date	Dec 17, 2010
Brand Name	Reyataz
Generic Name	Atazanavir sulfate
Sponsor	Bristol-Myers Squibb Company
Submission Type	Pediatric supplement for dose modification
Formulation	100/150/200/300 mg capsule
Indication	With ritonavir for the treatment of HIV-1 infection
Intended Population	Pediatric subjects 6 to < 18 years of age
OCP Division	Division of Clinical Pharmacology IV
OND Division	DAVP
OCP & PM Reviewer	Jiang Liu, Ph.D.
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1 EXECUTIVE SUMMARY

Atazanavir (ATV) is a protease inhibitor approved for the treatment of HIV infection in adult and pediatric subjects 6 years of age and above. The pediatric approval was based on Study AI424020 (ongoing) conducted by the National Institute of Allergy and Infectious Disease (NIAID). In the current submission, the sponsor proposes to refine the dosing recommendations for pediatric ATV capsules in combination with ritonavir (RTV) based on the updated data from Study AI424020 and the population PK modeling and simulation (Table 1). The sponsor is proposing to

1. extend the use of ATV/RTV in treatment experienced subjects weighing 15 to 25 kg
2. simplify the current 250 mg dose that requires 2 different capsule strengths, 100-mg and 150-mg capsules, in the 32 to 40 kg weight group with a single capsule strength.

Table 1: Comparison between the approved and proposed pediatric ATV/RTV doses

Body Weight (kg)	ATV dose (mg)			RTV dose (mg)		
	current	proposed	change (%)	current	proposed	change (%)
15 - 20	150	150	0 (0)	80	100	+20 (25%)
20 - 25	150	200	+50 (33%)	100	100	0 (0)
25 - 32	200	200	0 (0)	100	100	0 (0)
32 - 40	250	200	-50 (20%)	100	100	0 (0)
> 40	300	300	0 (0)	100	100	0 (0)

Based on the newly available data and population PK analysis:

1. The exposures (C24, Cmax and AUC) at the proposed doses were reasonably similar to that of adults and pediatrics weighing >40 kg.

2. The exposures (Cmax) at the alternate doses in 15-20 Kg patients (200/100 mg of ATV/RTV) were slightly higher than that of adults and pediatrics weighing > 40 kg.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology has reviewed the information submitted to NDA 21-567 (SE5-026). The revised ATV/RTV doses as shown in Table 1 are acceptable.

1.2 PHASE IV COMMITMENTS

None.

2 SUMMARY OF CLINICAL PHARMACOLOGY

The revised pediatric ATV/RTV dosing recommendations were mainly based on the comparison of ATV pharmacokinetics between HIV-positive pediatric subjects and adults. The exposures in adults after 400 mg of ATV once daily for treatment-naive subjects (Study 008) and 300/100 mg of ATV/RTV once daily (ATV/RTV 300/100) for treatment-experienced subjects (Study 074, 089, and 137) were used as a reference for this comparison (Table 2).

Table 2: Steady-state PK of ATV in HIV-infected adults (once daily)

Geometric Mean (CV%) [Range]	ATV 400 mg		ATV/RTV 300/100 mg		
	AI424-008	AI424-089	AI424-074	AI424-089	AI424-137
	N=13	N=15	N=10	N=12	N=11
C_{trough} (ng/mL)	120 (109) [12.2-890]	60 (246) [2.5-2935]	636 (97) [158-3081]	709 (60) [184-2064]	613 (79)
C_{max} (ng/mL)	2289 (71) [448-7446]	1845 (116) [82-15238]	4422 (58) [1694-9950]	4427 (28) [2426-6792]	4549 (39)
AUC(Tau) (ug*h/mL)	14.9 (91) [3.0-75.9]	11.0 (161) [0.8-144]	46.1 (66) [23.1-142]	44.2 (34) [26.1-83.2]	42.6 (50)

The updated data from Study AI424020 included 42 subjects with the ATV capsule administered with RTV (4 subject in the 15 to < 20 kg and 7 subjects in the 20 to <25 kg weight groups). ATV dosing was based on body surface area (the starting dose of ATV was 310 mg/m^2 initially chosen based on the ATV 600 mg QD PK data in HIV-infected adults). The ATV dose could have been adjusted according to the tolerability of the study medication regimen and the ATV AUC from the scheduled 24-hour PK profile at Weeks 1 and 56. All subjects had intensive 24-hour PK sampling at Week 1, and again at Week 56, for those who continued on study. Intensive 24-hour PK sampling was also performed 2 weeks after a new dose of ATV had been initiated. Blood samples for determination of plasma ATV and RTV concentrations were collected before study drug administration and at 1, 2, 3, 4, 6, 8, 12, and 24 hours after study drug administration. These observed data were normalized to the proposed doses and were compared to that of adults and other pediatric subjects. In addition to the proposed doses, a higher dose (200/100 mg ATV/RTV) was evaluated (through simulations) in pediatric subjects weighing 15-20 kg. As shown in Figure 1:

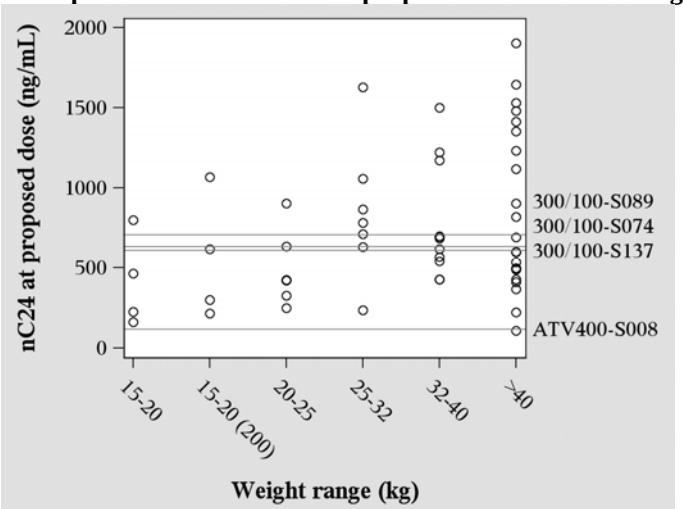
1. Observed C_{trough}, C_{max}, AUC normalized to the proposed 200/100 mg ATV/RTV dose for subjects weighing 32-40 kg were comparable to that of treatment-experienced adults (ATV/RTV 300/100) and other pediatric subjects weighing 25 to 32 kg or >40 kg at the approved doses
2. Observed C_{max}, AUC normalized to the proposed 150/100 mg for 15-20 kg subjects and 200/100 mg for 20-25 kg subjects were comparable to that of treatment-experienced adults and other pediatric subjects at the approved doses
3. Observed C_{trough} values normalized to the proposed 150/100 mg for 15-20 kg subjects and 200/100 mg for 20-25 kg subjects were slightly lower (especially for the 15-20 kg

group) than that of treatment-experienced adults and other pediatric subjects at the approved doses.

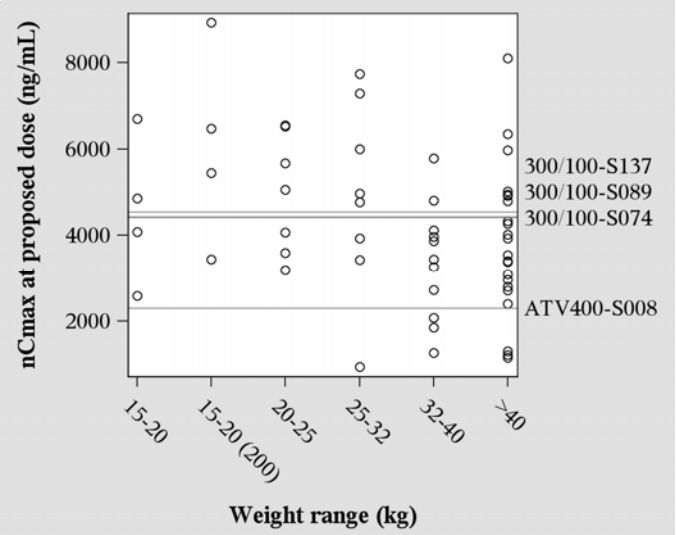
4. Observed C_{trough} values normalized to the 200/100 mg ATV/RTV dose for subjects weighing 15-20 kg were comparable to that of treatment-experienced adults and other pediatric patients at the approved doses. However, the C_{max} and AUC at the 200/100 mg ATV/RTV dose for pediatric subjects weighing 15-20 kg were higher than that of adults and other pediatric subjects.

Figure 1. Comparison of observed ATV exposure normalized to the proposed dose for each weight group

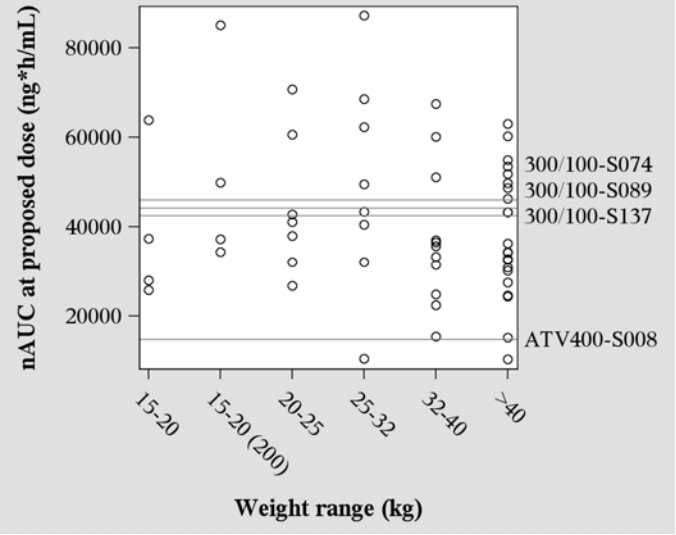
A. C_{trough}



B. C_{max}



C. AUC



*15-20(200) represents the 15-20 kg group normalized to the 200/100 mg ATV/RTV dose

In addition to the observed data, the sponsor also conducted simulations based on population PK model. The simulation results were generally consistent with the observed data described above. As shown in Table 3.

1. Predicted geometric mean C_{trough} at the proposed 150/100 mg for 15-20 kg subjects and 200/100 mg for 20-40 kg subjects were 76% and 85% of the mean C_{trough} in adult subjects. For each weight group, there were more than 75% of subjects with predicted C_{trough} within 10^{th} and 90^{th} percentile of C_{trough} in adult subjects.
2. Predicted geometric mean C_{max} at the proposed 150/100 mg for 15-20 kg subjects and 200/100 mg for 20-40 kg subjects were 126% and 119% of the adult mean. And for each weight group, there were more than 75% of subjects with predicted C_{max} within 10^{th} and 90^{th} percentile of C_{max} in adult subjects.
3. Predicted geometric mean AUC at the proposed 150/100 mg for 15-20 kg subjects and 200/100 mg for 20-40 kg subjects were within 80-125% of adult geometric mean. And for each weight group, there were more than 75% of subjects with predicted AUC within 10^{th} and 90^{th} percentile of AUC in adult subjects.
4. Predicted geometric means of C_{max} and AUC at the 200/100 mg dose for subjects weighing 15-20 kg was 70% and 40% higher compared to those of adult subjects.

The 150/100 mg ATV/RTV dose was likely to balance the efficacy by attaining adequate exposures and safety issues about the potential hyperbilirubinemia for subjects weighing 15-20 kg. These dosing recommendations allow subjects to achieve ATV geometric mean of C_{trough} > 500 ng/mL (75% of the adult geometric mean), and can be recommended for both treatment-naive and -experienced pediatric subjects. The proposed dosing recommendation for the 20 to < 40 kg weight group was also reasonable and, therefore, two different capsule strengths can be avoided.

Table 3: Summary of simulated ATV Exposure Measures (capsule doses)

		C24		Cmax		AUC	
BWT (kg)	ATV/RTV Dose (mg)	GM [ng/mL] (%CV)	PER (%)	GM [ng/mL] (%CV)	PER (%)	GM [ng*h/mL] (%CV)	PER (%)
15 - <20	150/100	504 (99.5%)	76.8	5213 (78.7%)	81.4	42902 (77.0%)	82
15 - <20	200/100	674 (99.6%)	78.1	6985 (78.4%)	74.4	57376 (76.9%)	77.4
20 - <25	200/100	615 (98.6%)	78.2	5887 (79.2%)	78.7	49699 (77.0%)	80.7
25 - <30	200/100	575 (99.4%)	77.5	5170 (80.2%)	80.6	44578 (77.9%)	81.4
30 - <35	200/100	545 (98.3%)	78.6	4643 (80.7%)	82.1	40770 (77.9%)	82.0
35 - <40	200/100	519 (98.0%)	77.6	4233 (81.5%)	82.1	37701 (78.4%)	81.2
Adult	300/100	661 (95.2%)	80	4153 (85.9%)	80	40615 (80.6%)	80

PER is the percentage of subjects attaining exposures within 10th and 90th percentile of the adult exposures.

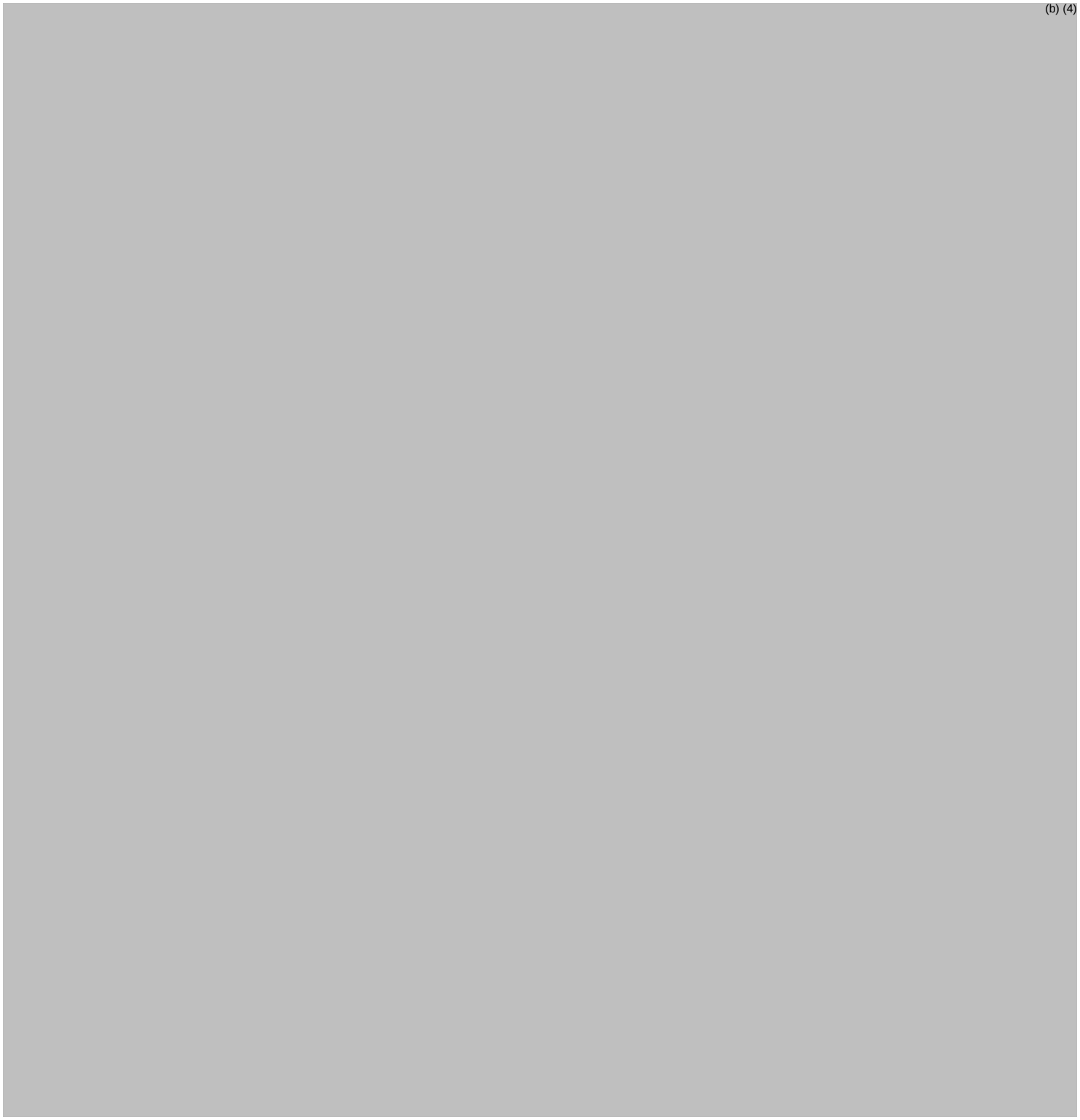
3 QUESTION BASED REVIEW

A Question Based Review (QBR) section was not necessary because the key elements have been addressed previously (see Dr. Jenny Zheng's ClinPharm review). The rationale for the labeling change is included in the Summary of Clinical Pharmacology Findings section.

4 DETAILED LABELING RECOMMENDATIONS

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font. At the time of this review, labeling negotiation is ongoing.

(b) (4)


(b) (4)

5 POPULATION PK STUDY REPORT REVIEW

Population PK modeling

The sponsor conducted population pharmacokinetic analyses and model-based simulation to support pediatric dosing recommendation. The dataset used for the population PK analyses was from four clinical studies in 227 HIV-infected adults (n=60) and pediatric subjects (n=167) (Table 4).

Table 4: Summary of Clinical Studies used in the Population Pharmacokinetic Analysis

Study	Study Population	Study Design	Study Drug Dosage Regimens	#of Patients	Nominal PK Assessments
AI424008	Adult HIV Patients	Phase 2/3 active-controlled, 3-arm parallel group	400 mg QD ATV, or 600 mg QD ATV (not incl.), or 1250 mg BID NFV (not incl.)	13	0, 0.5, 1, 1.5, 2, 4, 6, 8, 12, and 24 hours on Day 29
AI424089	Adult HIV Patients	Phase 4 open label, 2-arm parallel group	400 mg QD ATV, or 300 mg QD ATV+ 100 mg QD RTV	27	0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours on Day 29
AI424137	Adult HIV Patients	Phase 1 open label, two-cohort sequential design	300 mg QD ATV + 100 mg QD RTV (2nd cohort only)	11	0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, and 24 hours on Day 10
AI424020	Pediatric HIV Patients	Phase 1/2 open label, titration design	100 – 1200 mg QD ATV, or 50 - 600 mg QD ATV + 26 - 100 mg QD RTV	176[a]	0, 1, 2, 3, 4, 6, 8, 12, and 24 hours on Weeks 1 and 56 plus two weeks after a dose adjustment

[a] 9 subjects in the pediatric study AI424020 were above 18 yrs of age

Source: sponsor's modeling and simulation report, Page 26

The structural model describing steady-state ATV concentration-time profiles was determined to be a trough concentration prior to the initial dose-delinked 1-compartment model with first-order absorption, in which the pre-dose concentration (C_0) was estimated as a separate term in the model.

$$C(t) = C_{0k}e^{-k_e t} + \frac{F_{rel}Dk_a}{V(k_a - k_e)}\left(e^{-k_e t} - e^{-k_a t}\right)$$

The population PK model parameters are summarized in Table 5. The following covariate effects were included in the final model: an age effect on ka (the first-order absorption rate), body weight effects on V/F (apparent volume of distribution) and CL/F (apparent clearance), RTV comedication effects on CL/F and Frel (relative bioavailability), and a formulation effect on Frel.

Table 5: Base, Full and Final Model Parameter Estimates

Parameter	Estimate ± SE		
	Base Model (basemodel70nc)	Full Model (fullmodel6nc)	Final Model (finalmodel4nc)
OFV	942.920	657.859	671.037
ΔOFV	0	285.061	271.883
k_a (θ_1)(1/hr)	2.00 ± 0.31	1.90 ± 0.37	2.04 ± 0.31
AGE (θ_9)	-0.838 ± 0.144	-0.500 ± 0.270	-0.822 ± 0.139
BWT (θ_{10})	0	0.155 ± 0.318	0
FORM_Powder (θ_{11})	0	2.40 ± 1.69	0
k_e (θ_2)(1/hr)	0.107 ± 0.003	0.129 ± 0.010	0.130 ± 0.006
V/F (θ_3) (L)	107 ± 8	260 ± 33	266 ± 25
AGE (θ_{12})	0	0	0
BWT (θ_{13})	0	0.753 ± 0.110	0.706 ± 0.082
SEX_Female (θ_{14})	0	0	0
CL/F ($\theta_2\theta_3$) (L/hr)	11.4	33.5	34.6
RACE_Black (θ_{15})	0	0.00787 ± 0.06410	0
RACE_Other (θ_{16})	0	0.0803 ± 0.0845	0
REGN_Africa (θ_{17})	0	0.115 ± 0.0743	0.145 ± 0.045
REGN_Europe (θ_{18})	0	0.145 ± 0.121	0
AGE (θ_{19})	0	0.0246 ± 0.0721	0
BWT (θ_{20})	0	0.603 ±0.112	0.600 ± 0.083
SEX_Female (θ_{21})	0	-0.113 ± 0.035	-0.115 ± 0.035
COMD_w/RTV (θ_{22})	0	-0.411 ± 0.027	-0.409 ± 0.026
ART_Experienced (θ_{23})	0	-0.0429 ± 0.0526	0
t_{lag} (θ_4) (hr)	0.913 ± 0.002	0.913 ± 0.002	0.913 ± 0.002
C_0 (ng/mL)			
ATV (θ_5)	200 ± 24	158 ± 17	158 ± 17

Parameter	Estimate ± SE		
ATV + RTV (θ_6)	611 ± 62	671 ± 61	672 ± 61
F_{rel}	1	1	1
RACE_Black (θ_{24})	0	-0.0471 ± 0.1320	0
RACE_Other (θ_{25})	0	-0.136 ± 0.158	0
REGN_Africa (θ_{26})	0	0.00972 ± 0.13200	0
REGN_Europe (θ_{27})	0	0.323 ± 0.132	0
FORM_Powder (θ_{28})	0	-0.385 ± 0.109	-0.355 ± 0.100
COMD_w/RTV (θ_{29})	0	1.26 ± 0.24	1.32 ± 0.24
σ (%CV)			
ATV (θ_7)	55.0	55.3	55.2
ATV + RTV (θ_8)	34.8	35.2	35.3
IIV (%CV)			
$\omega - k_a$	175	170	173
$\omega - k_e$	30.8	14.1	14.6
$\omega - V/F$	72.6	42.3	42.5
IOV (%CV)			
$\omega - k_a$	0	0	0
$\omega - k_e$	23.5	22.4	22.2
$\omega - F_{rel1}$	92.2	88.8	88.8
$\omega - F_{rel2}$	64.7	59.7	59.4
$\omega - C_0$	119	118	118

note: covariate reference (SEX: male, RACE: white, REGN: North America, COMD: ATV alone, FORM: Capsule, ART: naïve, AGE: 18 yrs, BWT: 70 kg)

Source: sponsor's modeling and simulation report, Page 71

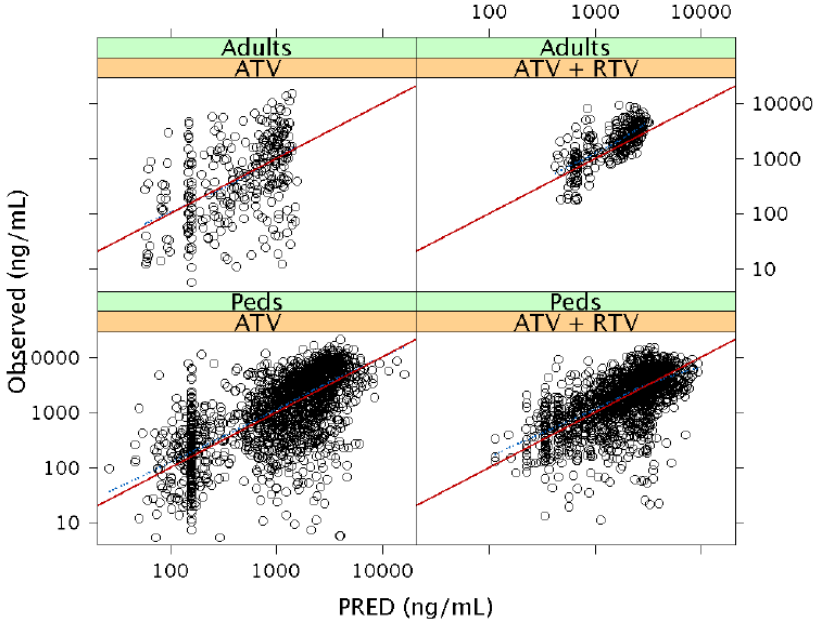
Model-based simulation

Model-based simulation was conducted to evaluate an extensive set of capsule weight-based dosing scenarios for pediatric subjects weighing 15 to 70 kg. The final population PK model was used to simulate steady-state ATV concentration-time curves for 10,000 hypothetical subjects for each dosing scenario. The geometric means of the noncompartmental parameters were calculated across the 10,000 simulated subjects and compared against the adult ATV exposure (

Table 3).

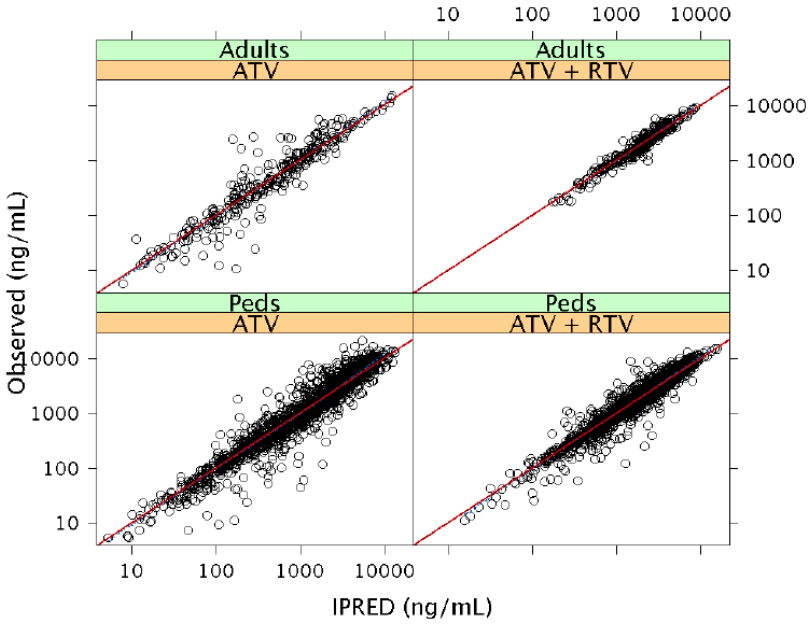
Reviewer's Comments:
The diagnostic analyses suggest that the final population PK model is able to reasonably characterize ATV PK profile in the studied population (Figure 2 and Figure 3). The predictive performance analyses suggest that the final population PK model provides acceptable predictive performance of the central tendency and variability of the key ATV exposure parameters, C_{24}, C_{max} and AUC (Figure 4). Therefore, the simulation results based on the final population PK model are reasonable.

Figure 2: Goodness of fit - observed vs. population prediction (final model)



Source: sponsor's modeling and simulation report, Page 260

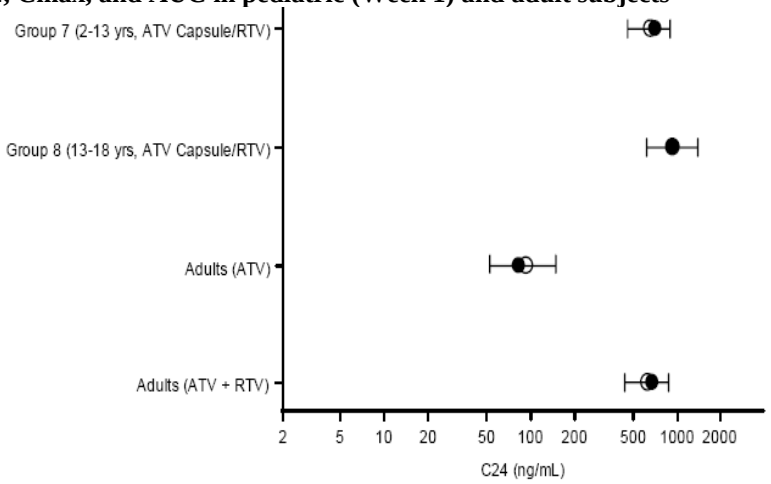
Figure 3: Goodness of fit - observed vs. individual prediction (final model)



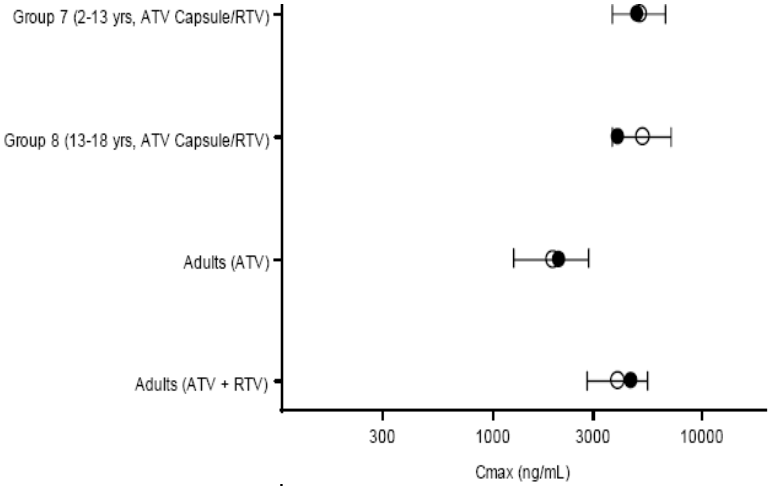
Source: sponsor's modeling and simulation report, Page 261

Figure 4. Comparison of the Observed (•) and Predictive distribution (median with 5th-95th percentile range bars) of the geometric mean C24, Cmax, and AUC in pediatric (Week 1) and adult subjects

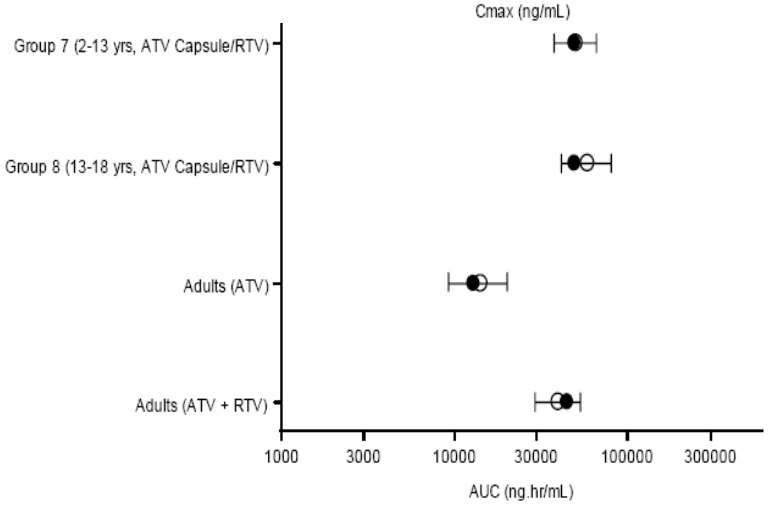
A. C24



B. Cmax



C. AUC



Source: sponsor's modeling and simulation report, Page 83-88. The posterior predictive check (PPC) was performed using the final population PK model to simulate 1000 datasets.

6 LISTING OF ANALYSES DATA SETS, CODES AND OUTPUT FILES

Study Number	Name	Link to EDR
AI424020	pkdata3.xpt	\\Cdsesub1\evsprod\NDA021567\0078\m5\datasets\ai424020\analysis\
AI424020	concdata.xpt	\\Cdsesub1\evsprod\NDA021567\0078\m5\datasets\ai424020\analysis\

7 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
PK_data.sas	Accessing ATV exposure	\Atazanavir_NDA021567_JL\PPK Analyses
finalmodel4nc.sas	Model-based simulation based on the final PK model	\Atazanavir_NDA021567_JL\PPK Analyses
sim10000.lst	Simulation output	\Atazanavir_NDA021567_JL\PPK Analyses
finalmodel4nc_proposedqddoses_atvrtv.dat	Predicted exposures of different doses	\Atazanavir_NDA021567_JL\PPK Analyses

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/s/

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09/12/2011

PRAVIN R JADHAV
09/12/2011