CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21567, SE5-015
Submission Date: 09/27/2007
Brand Name: Reyataz®
Generic Name: Atazanavir sulfate
Formulation: 100/150/200/300 mg capsules
Applicant: Bristol-Myers Squibb Company
Reviewer: Jenny H. Zheng, Ph.D.,
Team Leader: Kellie Reynolds, Pharm.D.
OCP Division: DCP IV
OND Division: DAVP

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I. Executive Summary

Atazanavir is a protease inhibitor approved for the treatment of HIV infection in adults in combination with other antiretrovirals. This efficacy supplement was submitted to provide pharmacokinetics, safety and limited efficacy data from Study AI424020 (PACTG Study 1020A) conducted by National Institute of Allergy and Infectious Disease. The data were submitted to support proposed dosing recommendations for Reyataz® capsules to treat pediatric patients 6 years of age and older.

A. Recommendation

The Office of Clinical Pharmacology has reviewed the information submitted to NDA 21-567 (SE5-015). The data provided in this efficacy supplement support the dosing recommendations for treatment naïve HIV-infected pediatric patients at least 6 years of age with body weight 15 kg and above as shown in Table 1, and for treatment-experienced pediatric patients at least 6 years of age with body weight 25 kg and above as shown in Table 2.

Table 1: Dose for treatment naïve pediatric patients (6 to less than 18 years of age) for atazanavir capsules with ritonavir

Body Weight		Atazanavir dose	Ritonavir dose
(kg)	(lbs)	(mg)[a]	(mg)
15 to less than 25	33 to less than 55	150	80[b]
25 to less than 32	55 to less than 70	200	100[c]
32 to less than 39	70 to less than 86	250	100[c]
at least 39	at least 86	300	100[c]

[a] Doses of REYATAZ can be achieved using a combination of commercially available capsule strengths.

[b] Ritonavir liquid.

[c] Ritonavir capsule or liquid.

For treatment naïve patients at least 13 years of age who weigh at least 39 kg who are unable to take ritonavir, the recommended dose is atazanavir 400 mg once daily with food.

Table 2: Dose for treatment experienced pediatric patients (6 to less than 18 years of age) for atazanavir capsules with ritonavir

Body Weight		Atazanavir dose	Ritonavir dose
(kg)	(lbs)	(mg)[a]	(mg)
25 to less than 32	55 to less than 70	200	100[c]
32 to less than 39	70 to less than 86	250	100[c]
at least 39	at least 86	300	100[c]

[a] Doses of REYATAZ can be achieved using a combination of commercially available capsule strengths.

[b] Ritonavir liquid.

[c] Ritonavir capsule or liquid.

There are not enough data to provide dose recommendation for treatment experienced pediatric patients at least 6 years of age with body weight less than 25 kg.

B. Phase IV Commitments:

None.

C. Summary of Clinical Pharmacology Findings

Atazanavir is currently approved in the US for use in HIV+ adults at 400 mg ATV once daily for treatment-naive patients and at 300 mg ATV with 100 mg RTV once daily (ATV/RTV 300/100) for treatment-experienced patients.

This efficacy supplement was submitted to provide pharmacokinetics, safety and limited efficacy data from Study AI424020 (PACTG Study 1020A) conducted by National Institute of Allergy and Infectious Disease. The data were submitted to support proposed dosing recommendations for atazanavir capsules to treat pediatric patients 6 to less than 18 years of age. The study includes 62 subjects for ATV only regimens and 41 subjects for ATV/RTV regimens for the proposed age range in the PK database.

Background: Relevant atazanavir pharmacokinetics in adults

As shown in Table 3, the atazanavir exposures were generally lower in HIV-infected patients than observed in healthy adult volunteers after administration of atazanavir 400 mg once daily and after administration of atazanavir 300 mg with ritonavir 100 mg once daily. The ATV exposures are higher at ATV/RTV 300/100 mg as compared to ATV 400 mg, because ATV is a CYP3A substrate, and RTV is a CYP3A inhibitor which increases ATV concentrations.

Table 3: Steady-State Pharmacokinetics of Atazanavir in Healthy Subjects or HIV-Infected Patients in the Fed State

	400 mg once daily		300 mg with ritonavir 100 mg once daily	
Parameter	**Healthy Subjects (n=14)**	**HIV-Infected Patients (n=13)**	**Healthy Subjects (n=28)**	**HIV-Infected Patients (n=10)**
C_{max} (ng/mL)				
Geometric mean (CV%)	5199 (26)	2298 (71)	6129 (31)	4422 (58)
Mean (SD)	5358 (1371)	3152 (2231)	6450 (2031)	5233 (3033)
T_{max} (h)				
Median	2.5	2.0	2.7	3.0
AUC (ng•h/mL)				
Geometric mean (CV%)	28132 (28)	14874 (91)	57039 (37)	46073 (66)
Mean (SD)	29303 (8263)	22262 (20159)	61435 (22911)	53761 (35294)
T-half (h)				
Mean (SD)	7.9 (2.9)	6.5 (2.6)	18.1 (6.2)[a]	8.6 (2.3)
C_{min} (ng/mL)				
Geometric mean (CV%)	159 (88)	120 (109)	1227 (53)	636 (97)
Mean (SD)	218 (191)	273 (298)[b]	1441 (757)	862 (838)

[a] n=26.
[b] n=12.

Because ATV 400 mg is approved for treatment naïve adult patients, ATV exposures at 400 mg are used as reference when we recommend ATV doses for treatment naïve pediatric patients.

review for the phase II study (AI424089) show that ATV/RTV 300/100 mg regimen has fewer virologic failures and less emergence of PI resistance as compared to ATV 400 mg regimen in treatment naïve patients. Therefore, ATV exposure equivalent to ATV 400 mg in adults was considered as a minimum requirement when we recommend ATV doses for pediatric patients. ATV exposures at ATV/RTV 300/100 mg are used as reference for determining the doses for treatment experienced pediatric patients because it is the approved dose for treatment experienced adult patients. Exposures following ATV/RTV 300/100 mg in adults provide the upper bound for safety.

The pharmacokinetics of ATV are non-linear. At doses less than 400 mg, there is a more than dose proportional increase in the area under the ATV plasma concentration versus time curve (AUC). The pharmacokinetics of ATV are close to dose proportional at doses above 400 mg.

When 100 mg RTV is coadministered with ATV in healthy subjects, ATV exposure is more than dose proportional when dose increases from ATV 200 mg to 300 mg, but dose proportional above 300 mg. At 200 mg RTV, ATV exposure increases approximately dose proportionally with ATV dose between 200 and 400 mg.

Atazanavir pharmacokinetics in pediatric patients

The Pediatric Acquired Immunodeficiency Syndrome (AIDS) Clinical Trials Group (PACTG) 1020-A study (also designated as BMS Study No. AI424020) was a dose-finding study using body surface area (BSA)-based dosing of ATV with and without RTV in different age groups. The study was designed to determine dosing of ATV with and without RTV in pediatric patients based on ATV exposures and safety profiles as compared to adult patients. The study only provides limited efficacy data.

Study AI424020 includes two steps. Step 1 (dose-finding) was conducted in the US and South Africa, and consisted of 2 parts:

Part A: ATV plus 2 NRTIs (excluding abacavir sulfate [ABC, Ziagen®] and tenofovir disoproxil fumarate [TDF, Viread®]).
Part B: ATV/RTV plus 2 NRTIs (excluding ABC and TDF).

All groups began at 310 mg/m^2 of ATV QD; ATV/RTV groups also received RTV 100 mg/m^2 QD (liquid, up to 100 mg QD or 100 mg capsule). All groups escalated or decreased ATV doses based on PK exposure targets (targeted on the exposure in adults who received ATV/RTV 300/100 mg) and safety criteria.

Table 4: Stratification and Regimens Used

ATV without RTV	ATV with RTV	Formulation	Age Ranges
Group 1	Group 5	Powder	Infants 3 months to ≤ 2 years
Group 2	Group 6	Powder	Children > 2 to ≤ 13 years
Group 3	Group 7	Capsules	Children > 2 to ≤ 13 years
Group 4	Group 8	Capsules	Adolescents > 13 to ≤ 21 years

Step 2 is only open to South African subjects who are virologically responding to treatment when the last enrollee into either part of Step 1 (Part A or Part B) has completed 96 weeks of treatment (end of Step 1).

In this efficacy supplement, only data from Step 1 are included. The applicant only seeks the approval for atazanavir capsules in pediatric patients age 6 years and above in this supplement. The applicant requests deferral for pediatric patients at least 3 months to less than 6 years of age, which will be submitted later

ATV only regimen

Study AI424 020 shows ATV alone is not recommended for pediatric patients less than 13 years of age, because Cmax/Cmin ratio is higher for this population than adults. ATV AUC and Cmin following ATV 400 mg are predicted to be in the range of values observed in adult patients at ATV 400 mg, but Cmax is close to or above Adult ATV/RTV 300/100 mg. Thus, it is not possible to recommend an ATV-alone dose in this population that will achieve adequate Cmin, but not a Cmax above the highest adult exposure.

ATV 400 mg can be used for treatment naive pediatric patients aged 13 -18 years, because in this age range, ATV AUC and Cmin at 400 mg are in the range of values observed in adult patients at ATV 400 mg, and Cmax will not be higher than values observed in adult patients at ATV/RTV 300/100 mg. There is slightly lower exposures for patients aged 13-18 years who weigh less than 39 kg (Geometric means: AUC 13.5 ug.h/mL, Cmin 69 ng/mL, Cmax 2011 ng/mL) as compared to those who weigh at least 39 kg (Geometric means: AUC 15.7 ug.h/mL, Cmin 155 ng/mL, Cmax 2501 ng/mL) at ATV 400 mg. Subjects with weight less than 39 kg have a higher Cmax/Cmin ratio (29) as compared to subjects with weight more than 39 kg (16). Only treatment naive pediatric patients aged 13 -18 years with weight at least 39 kg can receive ATV 400 mg QD.

See Individual Study Report Review for details.

ATV/RTV regimen

Study AI424 020 shows that at ATV 205 mg/m^2 + RTV 100 mg/m^2 (up to 100 mg) in pediatric subjects between 6 and 13 years old, ATV exposures are generally within the range observed in adult patients with ATV/RTV 300/100 mg, except for subjects with body weight between 15 to 25 kg. For those subjects, ATV Cmin is higher than observed in adult patients with ATV 400 mg, but is lower than observed in adult patients with ATV/RTV 300/100 mg. Therefore, no dose regimen is recommended in treatment experienced pediatric patients with weight between 15 to 25 kg. Weight-based dose regimens are recommended for treatment naïve patients with weight at least 15 kg, and for treatment experienced patients with weight at least 25 kg. The recommended doses are similar to the 205 mg/m^2 ATV + RTV dose used in this study in patients 6-13 years of age, and are the same as adult dose (ATV/RTV 300/100 mg) in patients 13 years and older. The exposures estimated at ATV/RTV 300/100 mg in pediatric patients with weights above 39 kg are similar to exposures observed in adult patients at ATV/RTV 300/100 mg.

See Individual Study Report Review for details.

II. Question Based Review

A. General Attributes

i. What is the proposed therapeutic indication?

Atazanavir is currently approved for the treatment of HIV-1 infection in adults in combination with other antirectroviral agents. This supplement is seeking the approval for use in pediatric patients at least 6 years of age.

ii. What is the proposed dosage and route of administration?

The data provided in this efficacy supplement support the Applicant's proposed dosing recommendations for treatment naïve pediatric patients at least 6 years of age with body weight 15 kg and above as shown in Table 1 (for simplicity, the Agency combined original proposed two weight groups 15 kg to 20 kg and 20 kg to 25 kg, into one group), and for treatment-experienced pediatric patients at least 6 years of age with body weight 25 kg and above as shown in Table 2. Atazanavir (with or without ritonavir) should be taken orally with food. The approved atazanavir capsules and ritonavir capsule or liquid are used for pediatric patients.

Table 1: Dose for Treatment Naïve Pediatric patients (6 to less than 18 years of age) for Atazanavir Capsules with ritonavir

Body Weight		Atazanavir dose	Ritonavir dose
(kg)	(lbs)	(mg)[a]	(mg)
15 to less than 25	33 to less than 55	150	80[b]
25 to less than 32	55 to less than 70	200	100[c]
32 to less than 39	70 to less than 86	250	100[c]
at least 39	at least 86	300	100[c]

[a] Doses of REYATAZ can be achieved using a combination of commercially available capsule strengths.

[b] Ritonavir liquid.

[c] Ritonavir capsule or liquid.

For treatment naïve patients at least 13 years of age who weigh at least 39 kg who are unable to take ritonavir, the recommended dose is atazanavir 400 mg once daily with food.

Table 2: Dose for treatment-experienced Pediatric patients (6 to less than 18 years of age) for Atazanavir Capsules with ritonavir

Body Weight		Atazanavir dose	ritonavir dose
(kg)	(lbs)	(mg)[a]	(mg)
25 to less than 32	55 to less than 70	200	100[c]
32 to less than 39	70 to less than 86	250	100[c]
at least 39	at least 86	300	100[c]

[a] Doses of REYATAZ can be achieved using a combination of commercially available capsule strengths.

[b] Ritonavir liquid.

[c] Ritonavir capsule or liquid.

There is not enough data to provide dose recommendation for treatment experienced pediatric patients at least 6 years of age with body weight less than 25 kg.

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

For pediatric dosing instructions for HIV drugs, only safety and PK are required. The proposed dose in pediatric patients should provide exposures similar to the exposure observed in adult patients with the approved doses with no new safety concerns. Efficacy is based on data from clinical trials in adults. Limited efficacy data from pediatric subjects in the study are only used as supporting evidence.

In Study AI424-020, the safety data for subjects age 6 to less than 18 years up to 24 weeks were submitted for 63 patients treated with ATV and 41 patients with ATV/RTV. There are no new safety concerns were identified.

B. General Clinical Pharmacology

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

The surrogate efficacy endpoints for HIV-1 infection are plasma HIV viral load and CD4 cell counts. The viral load tends to be more predictive of the progression of HIV infection than CD4 cell counts. The primary efficacy endpoint for Study AI424-020 was the proportion of subjects with a treatment response (HIV RNA < 50 c/mL) through Week 24.

ii. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

The concentrations of atazanavir in human plasma were determined by a validated liquid chromatographic method using MS/MS detection. The DSI inspection of the bioanalytical site identified 6 issues. See DSI review for details. The applicant's

responses for Observations 3, 4 and 6 are acceptable. However, for Questions 1, 2 and 5 regarding the inaccuracy of Quality Control (QC) samples, we do not accept the lower standard of quality control accuracy. Fourteen subjects in Group 4 were affected. The data from these subjects should have been rejected. The PK data excluding these subjects were reanalyzed by the reviewer. The reanalysis does not change the overall conclusions.

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

The concentration-response relationship was not developed for adults and pediatric patients. Phase II studies show there is no dose-response relationship for atazanavir efficacy from dose of 200 mg to 600 mg QD in treatment naïve adult patients. However, only 400 mg was studied for long term efficacy and safety in treatment naïve adult patients in Phase III studies, and is approved for use in treatment naïve adult patients.

The clinical review and microbiology review for the phase II study (AI424089) show that ATV/RTV 300/100 mg regimen has fewer virologic failures and less emergence of PI resistance as compared to ATV 400 mg regimen in treatment naïve patients. For treatment experienced adult patients, only ATV/RTV 300/100 mg was studied in Phase III studies, and is approved for use in treatment experienced adult patients.

The major adverse events related to atazanavir were hyperbilirubinemia and associated jaundice. Bilirubin levels (both total and indirect (unconjugated)) tended to increase as atazanavir exposure increased in adult patients (Study A424011). Indirect bilirubin is not associated with a hepatic toxicity

iv. *Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?*

Adults

The pharmacokinetics of ATV are non-linear in adults. At doses less than 400 mg, there are more than dose proportional increases in the area under the ATV plasma concentration versus time curve (AUC). The pharmacokinetics of ATV are close to dose proportional at doses above 400 mg.

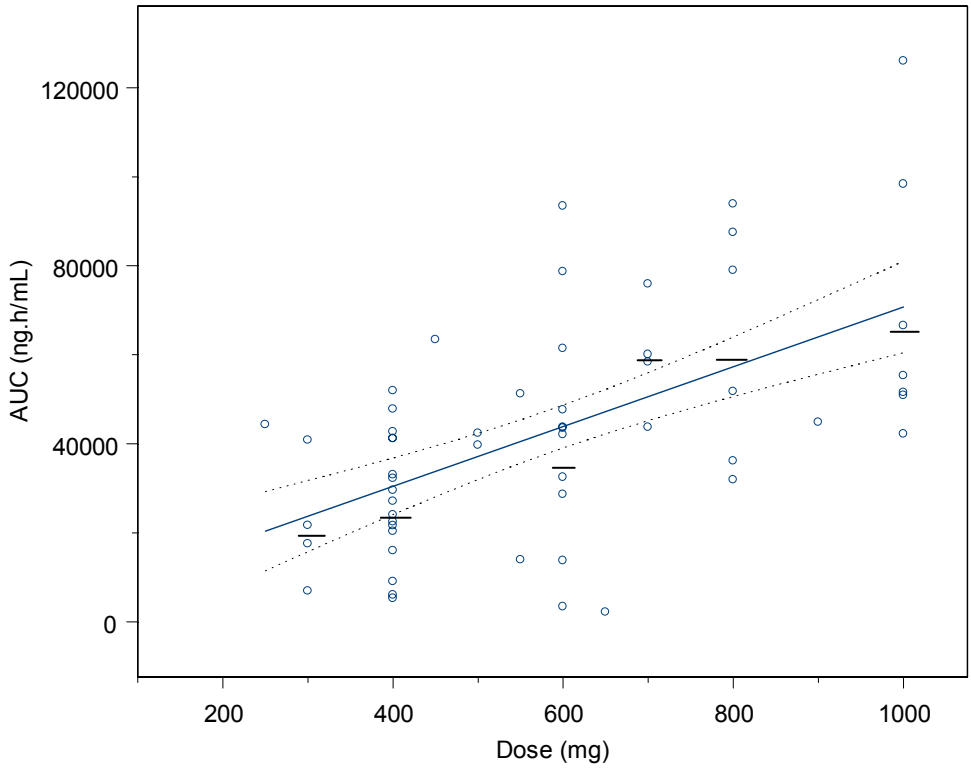
When 100 mg RTV is coadministered with ATV in healthy subjects, ATV exposure increase is more than dose proportional from ATV 200 mg to 300 mg, but dose proportional above 300 mg. At 200 mg RTV, ATV exposure increases approximately dose proportional with ATV dose between 200 and 400 mg.

Pediatrics

For pediatric patients between 6 and 18 years of age, ATV CLss/F is not changed with age when ATV capsules only were administered. Therefore, dose proportionality can be determined by combining ages of 6 to 18 years. In pediatric patients 6- 18 years of age, ATV AUC shows approximately dose-proportional increase (the lines show the geometric means) for ATV capsule only groups (Groups 3 and 4), which is consistent with the adult data (Figure 1). The geometric means show Cmax increase is more than

dose proportional, while Cmin is approximately dose proportional, with higher variability as compared to AUC and Cmax.

Figure 1: ATV AUC vs. Dose for Patients 6 to 18 years in Groups 3 & 4 using all available data



For pediatric patients with ages between 6 and 18 years, ATV CLss/F tends to increase with age when ATV/RTV was administered. Since CLss/F is changed with age, it is not appropriate to access dose proportionality in pediatric patient with ATV/RTV regimens.

v. *Do PK parameters change with time following chronic dosing?*

No. PK parameters do not change with time following chronic dosing in both adults and pediatric patients. The PK parameters are similar between Week 1 and Week 56 in pediatric subjects.

vi. *Are the dose and dosing regimen consistent with the known relationship between dose-concentration-response?*

We assume the exposure-response relationship is the same between adult and pediatric patients. The proposed doses in pediatric patients have similar exposures as compared to adult patients at approved doses.

vii. *How does the PK of atazanavir in healthy volunteers compare to that in patients?*

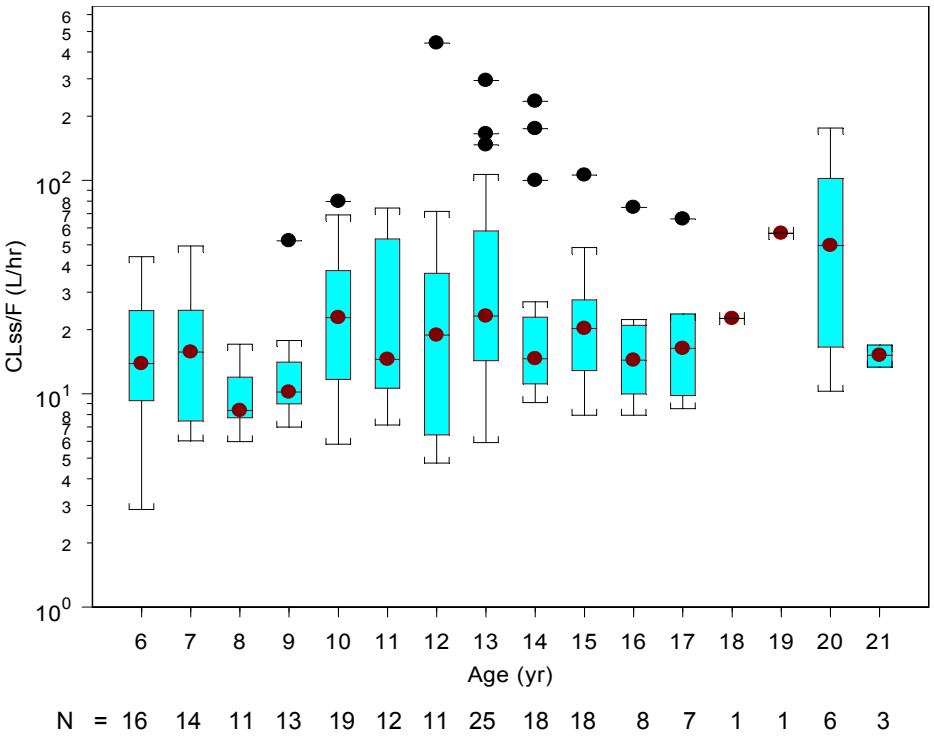
The atazanavir pharmacokinetics were not studied in healthy pediatric subjects. In adults, exposure is higher in healthy volunteers compared to patients.

C. Intrinsic Factors

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

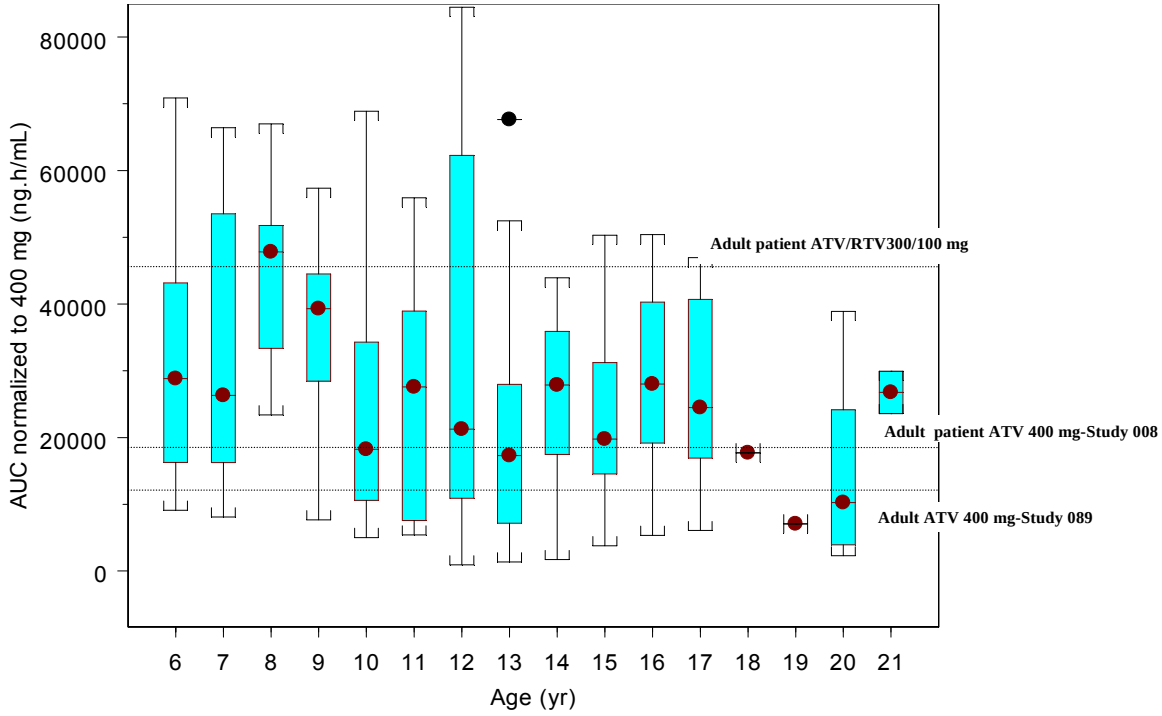
Only age was assessed in the pediatric study. With ATV capsule only regimens, Clss/F does not change with age between 6 to 18 years of age as shown in Figure 2. The median CLss/F is between 22 to 30 L/hr for adults administered 400 mg ATV. The CLss/F in pediatric is slightly less than adults (median: 16 L/hr).

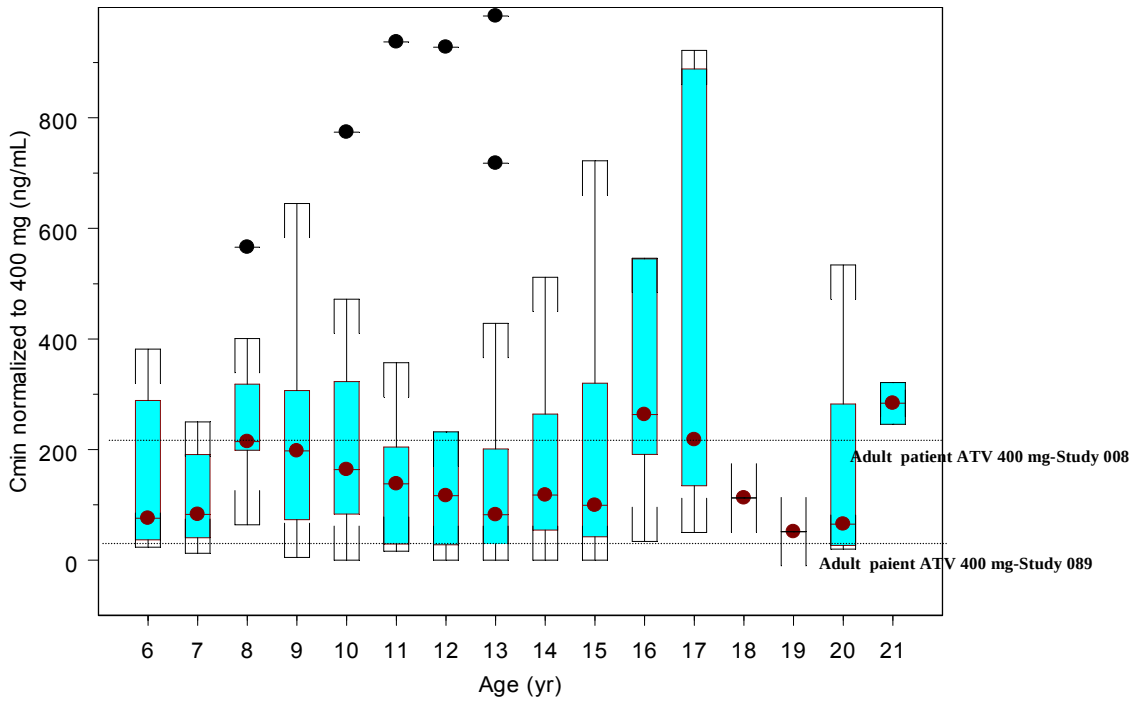
Figure 2: ATV clearance vs age for Groups 3 and 4 (ATV capsule only) using combined all the available Data

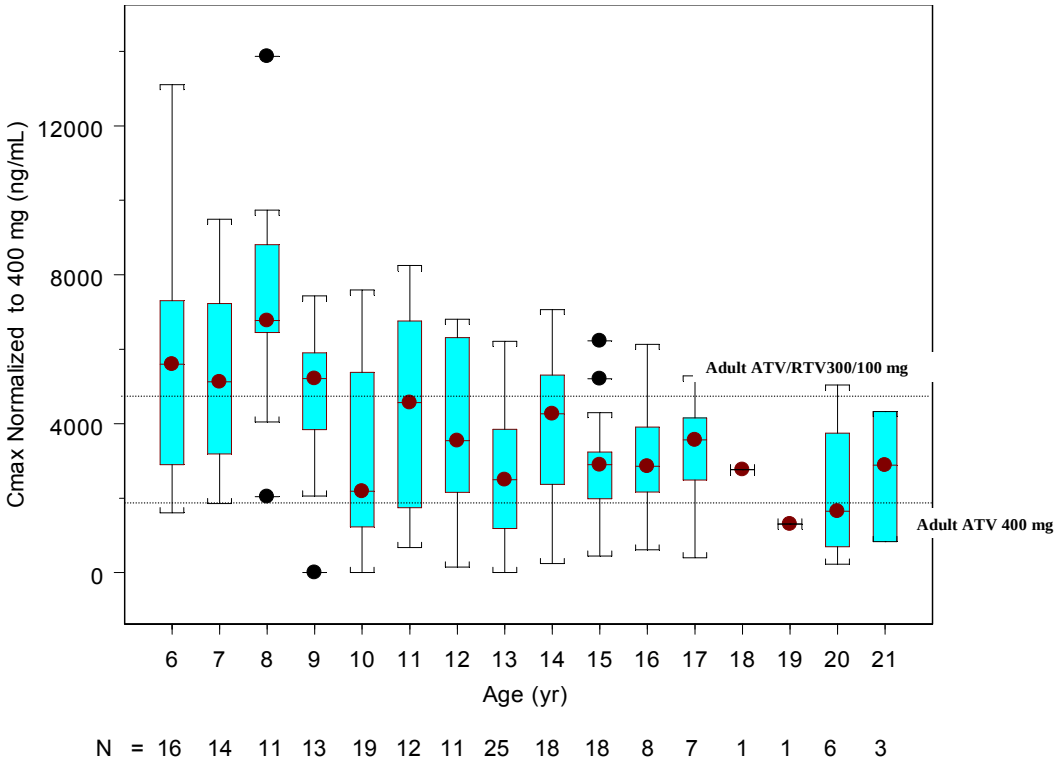


The exposures for Group 3 and 4 are normalized to 400 mg by linear PK to compare the exposures of ATV in pediatric patients who took ATV 400 mg capsules with exposures observed in adult patients who took ATV 400 mg or ATV/RTV 300/100 mg (Figure 3).

Figure 3: Estimated exposures at ATV 400 mg vs. Age using all the available data from Group 3 and Group 4







The data show that ATV alone is not recommended for pediatric patients less than 13 years of age, because Cmax/Cmin ratio is higher for this population. ATV AUC and Cmin at 400 mg are in the range of values observed in adult patients at ATV 400 mg, but Cmax is close to or above Adult ATV/RTV 300/100 mg. Data from 13 subjects who took ATV 400 mg in the study support the conclusion (Table 3).

Table 3: ATV Pharmacokinetics from subjects taking ATV 400 mg in Group 3

Pharmacokinetic Parameter	Group 3 400 mg (observed)[a,b] N=13	400 mg QD in HIV+ Adults Study 008[a] N=13	400 mg QD in HIV+ Adults Study 089[c] N=15	300/100 mg QD in HIV+ Adults Study 074 N=10
AUC(TAU) (µg•h/mL) Geometric Mean (CV%) Median [Range]	 29.1 (22) 32.2 [9.0-51.9]	 14.9 (91) 18.1 [3.0-75.9]	 11.0 (161) 13.1 [0.8-144]	 46.1 (66) 47.7 [23.1-142]
Cmin (ng/mL) Geometric Mean (CV%) Median [Range]	 117 (57) 151 [5-472]	 120 (109) 218 [12.2-890]	 60 (246) 35 [2.5-2935]	 636 (97) 532 [158-3081]
Cmax (ng/mL) Geometric Mean (CV%) Median [Range]	 4752 (17) 5229 [2036-7811]	 2298 (71) 2618 [448-7446]	 1845 (116) 1944 [82-15238]	 4422 (58) 4967 [1694-9950]

[a] n=12 for Cmin; [b] one BLQ Cmin set to 5 ng/mL for summary; [c] one BLQ Cmin set to 2.5 ng/mL for summary

ATV 400 mg can be used for treatment naive pediatric patients aged 13 -18 years, because in this age range, the predicted and observed ATV AUC and Cmin at 400 mg are in the range of values observed in adult patients at ATV 400 mg, and Cmax will not be higher than values observed in adult patients at ATV/RTV 300/100 mg. There is slightly lower exposures for patients aged 13-18 years who weigh less than 39 kg as compared to who weigh at least 39 kg at ATV 400 mg (Table 4). Subjects with weight less than 39 kg have a higher Cmax/Cmin ratio (29) as compared to subjects with weight more than 39 kg (16). **Only treatment naive pediatric patients aged 13 -18 years with weight at least 39 kg can receive ATV 400 mg QD.**

Table 4: ATV pharmacokinetics in Group 4 classified by body weight

Geometric means	Body weight (Group 4)	
	< 39	≥ 39
AUC (ng.h/mL)	13.5	15.7
Cmin (ng/mL)	69	155
Cmax (ng/mL)	2011	2501

For ATV/RTV regimens, Clss/F tends to increase with age as shown in Figure 4. The solid dots in the figure are from the protocol accepted dose of 205 mg/m^2 ATV+RTV, and the empty circles are from the protocol non-accepted dose. In the protocol, doses were accepted based on PK and safety criteria.

Figure 4: ATV clearance vs. age for ATV/RTV regimens

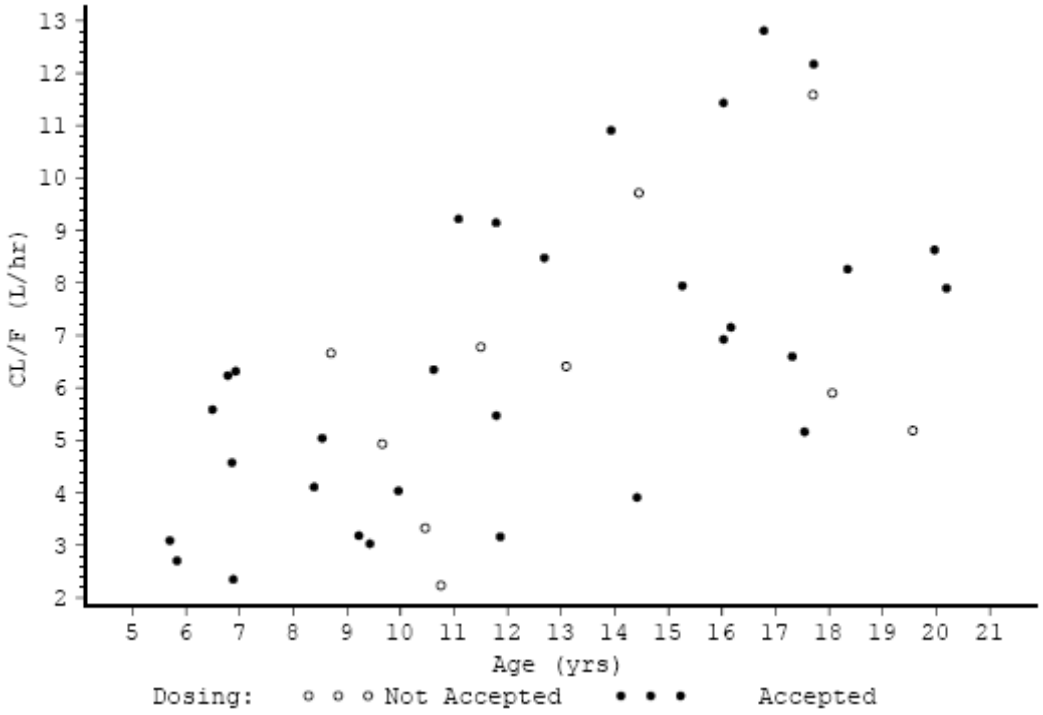
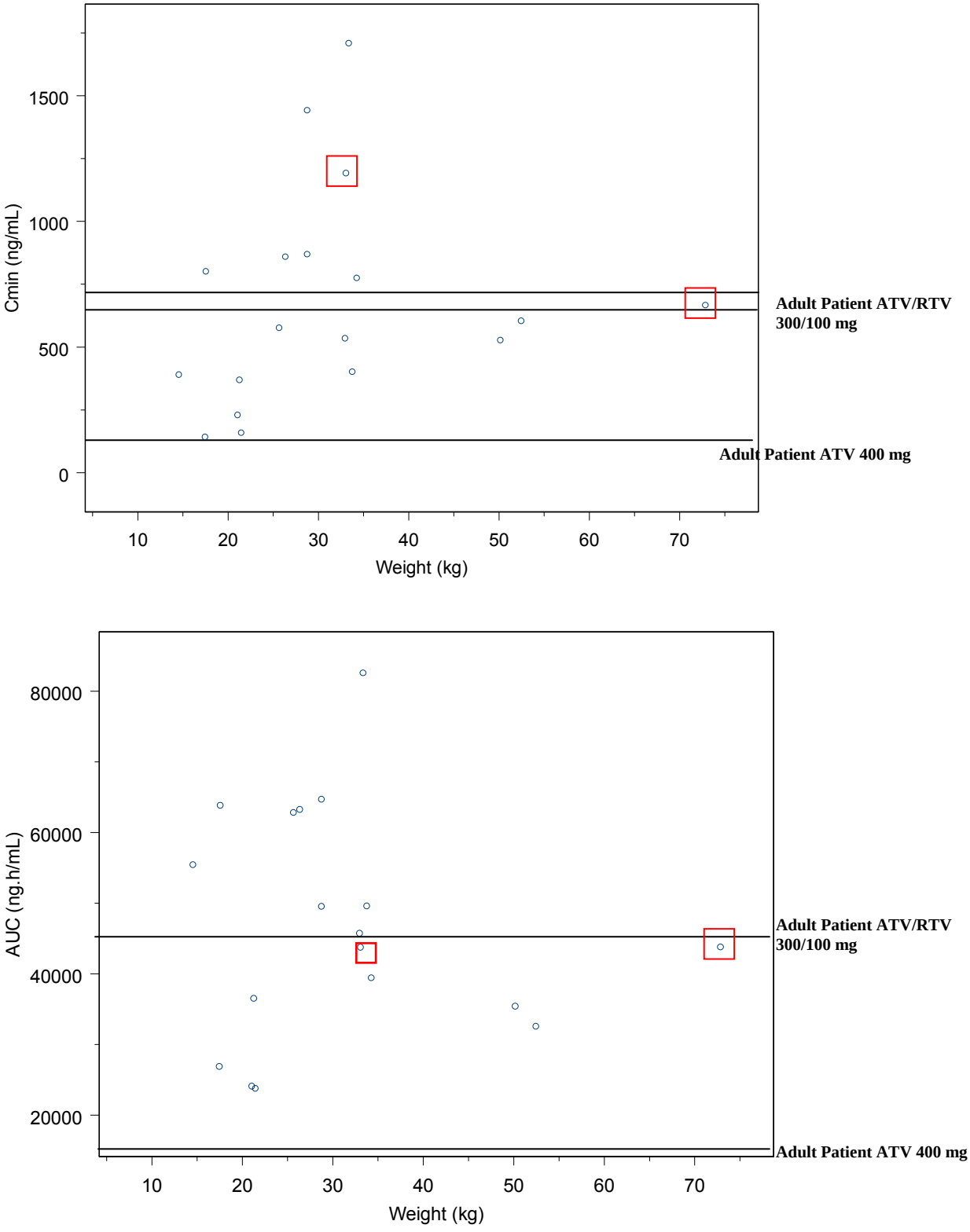
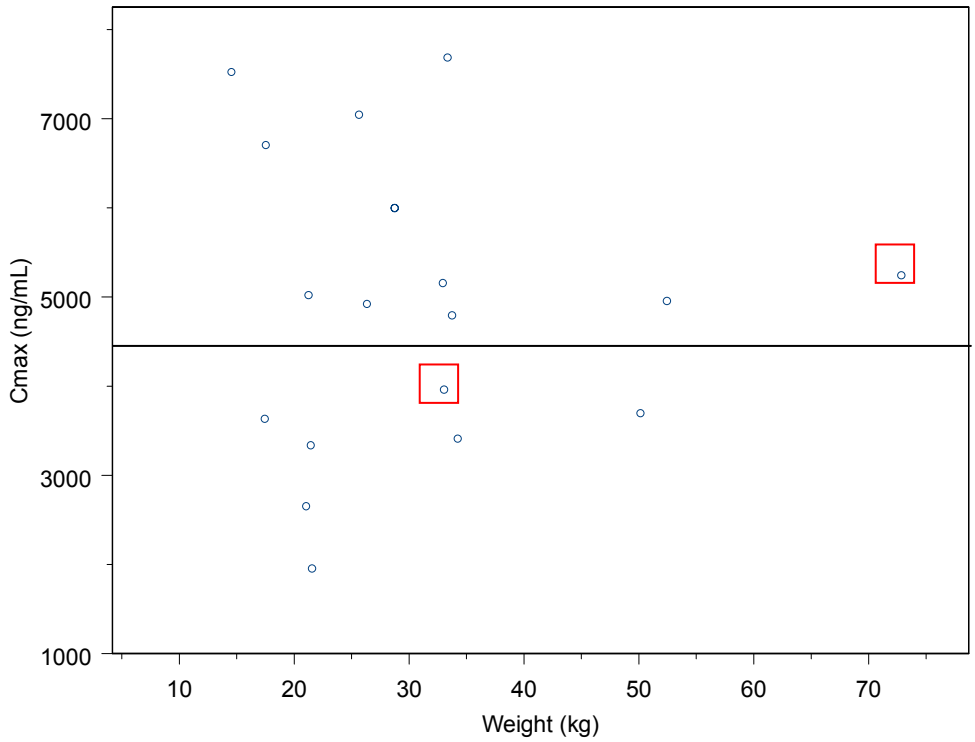


Figure 5 shows the ATV exposures vs. weight for Group 7 at the protocol accepted dose 205 mg/m^2 +RTV using data from dose finding stage (normally at Week 1) (including two subjects who are between 5.5 to 6 years of age and three subjects who weigh more than 39 kg). The data show that ATV Cmin is relatively low for children who weigh less than

25 kg as compared to adult patients who took ATV/RTV 300/100 mg. However, the Cmax is similar to adult patients who took ATV/RTV 300/100 mg. If we increase dose for this group of patients to achieve the Cmin for adults at ATV/RTV 300/100 mg, the ATV Cmax will exceed the Cmax for which we have safety data. Therefore, **we don't have enough data to suggest an ATV/RTV dose for treatment experienced pediatric patients who weigh less than 25 kg.**

Figure 5: ATV exposures vs. weight for Group 7 at accepted dose ATV 205 mg/m^2 +RTV





The applicant proposes the body weight based dosing regimens which are similar to the doses received in Group 7 with ATV dose of 205 mg/m^2 + RTV, as follows.

Table 5: Pediatric Dose (6 to 18 years of age) for Atazanavir Capsules with Ritonavir

Body Weight (kg)	Body Weight (lbs)	Atazanavir dose (mg)[a]	Ritonavir dose (mg)
15 to less than 20	33 to less than 44	150	64
20 to less than 25	44 to less than 55	150	80
25 to less than 32	55 to less than 70	200	100 [b]
32 to less than 39	70 to less than 86	250	100 [b]
at least 39	at least 86	300	100 [b]

[b] Doses of atazanavir can be achieved using a combination of commercially available capsule strengths.
[c] Ritonavir capsule or liquid.

In group 7, most of the subjects who took ATV 205 mg/m^2 and RTV received the proposed dose, except the dose of ritonavir for children with body weight of 15 to <20 kg was about 72 mg. In addition, one subject with weight 33 kg took 200/100 mg instead of 250/100 mg ATV/RTV in the study, and one subject with weight 73 kg took 400/100 mg instead of ATV/RTV 300/100 mg. These two subjects are identified by red squares in Figure 5 (Pages 16 and 17). As indicated previously, **we don't have enough data to suggest a dose for experienced pediatric patients who weigh less than 25 kg.** However, because the Cmin for pediatric subjects who weigh 15 - 25 kg at ATV 205

mg/m^2 +RTV is higher than the Cmin observed for adults ATV 400 mg (recommended dose for treatment naïve adult patients), **the proposed doses** (with change of RTV dose for 15 to 20 kg to 72 mg) **are acceptable for treatment naive patients who weigh 15 - 25 kg.** For simplicity, we combine original proposed two weight groups 15 to 20 kg and 20 to 25 kg, into one group with RTV of 80 mg. The slight increase of RTV in patients with weight of 15 to 20 kg is not expected to change ATV exposures significantly.

In weight group 25 -39 kg, only one subject (out of 8) received less than the proposed dose (200 mg instead of 250 mg in a subject who weighed 33 kg). The proposed dose provides adequate exposure as compared to HIV+ adults with ATV/RTV 300/100 mg QD as shown in the following table. **The proposed dose is acceptable for subjects who weigh 25 - 39 kg.**

Table 6: ATV Pharmacokinets for Subjects age 6 to 13 years who weigh 25- 39 kg

Pharmacokinetic Parameter (for subjects with weight 25-39 kg)	Group 7 (observed) 205 mg/m^2	300/100 mg QD in HIV+ Adults Study 074	300/100 mg QD in HIV+ Adults Study 089
AUC(TAU) (µg•h/mL) n Geometric Mean(CV%) Median [Range]	 8 53.1 (10.6) 49.5 [43.7-82.5]	 10 46.1 (66) 47.7 [23.1-142]	 12 44.2 (34) 43.4 [26.1-83.2]
Cmin (ng/mL) n Geometric Mean (CV%) Median [Range]	 8 784(20.3) 815 [194-1708]	 10 636 (97) 532 [158-3081]	 12 709 (60) 858 [184-2064]
Cmax (ng/mL) n Geometric Mean (CV%) Median [Range]	 8 5193 (12.0) 5032 [1007-7678]	 10 4422 (58) 4967 [1694-9950]	 12 4427 (28) 4757 [2426-6792]

As shown in Figure 5 (Pages 16+17), for the 3 subjects who weigh more than 39 kg in Group 7 (age 6-13), the Cmin, AUC and Cmax are in the range of what have been observed for adult patients with ATV/RTV 300/100 mg, although the mean AUC is slightly lower as compared to AUC observed for adult patients with ATV/RTV 300/100 mg. Therefore, **the proposed dose ATV/RTV 300/100 mg can be used for subjects 6-13 years of age who weigh more than 39 kg.**

For patients 13 to less than 18 years of age, all subjects except 1 (weight 37.5 kg) have weight above 39 kg. Although with 300/100 mg QD, the AUC and Cmax for pediatric subjects with weight above 39 kg are lower than observed for adults with ATV/RTV 300/100 mg, Cmin is higher than observed for adults with ATV/RTV 300/100 mg. Therefore **for pediatric patients with weights above 39 kg, ATV/RTV 300/100 mg can be used.**

The recommended doses are fixed doses in different weight ranges instead of doses per body weight, because only certain doses can be given based on the approved strength of ATV capsules.

Table 7: Summary Statistics for ATV Pharmacokinetic Parameters in Group 8 Observed at 205 mg/m2 and Estimated for ATV/RTV 300/100 mg QD vs ATV/RTV 300/100 mg QD in HIV+ Adults

Pharmacokinetic Parameter	Group 8 205 mg/m^2 (observed) N=10	Group 8 300/100 mg QD (estimated) N=10	300/100 mg QD in HIV+ Adults Study 074 N=10	300/100 mg QD in HIV+ Adults Study 089 N=12
AUC(TAU) (µg•h/mL) Geometric Mean (CV%) [Range]	44.9 (34) [26.2-77.4]	39.7 (59) [24.0-112]	46.1 (66) [23.1-142]	44.2 (34) [26.1-83.2]
Cmin (ng/mL) Geometric Mean (CV%) [Range]	1090 (60) [409-2763]	978 (65) [409-2566]	636 (97) [158-3081]	709 (60) [184-2064]
Cmax (ng/mL) Geometric Mean (CV%) [Range]	3711 (46) [1614-6821]	3279 (59) [1242-8458]	4422 (58) [1694-9950]	4427 (28) [2426-6792]
Doses with RTV (mg) Median [Range]	400 [250-500]	All 300	All 300	All 300

For other intrinsic factors, please see the original NDA review.

D. Extrinsic Factors

Atazanavir is an inhibitor of CYP3A, CYP2C8, and UGT1A1. Coadministration of atazanavir and drugs primarily metabolized by CYP3A, CYP2C8, or UGT1A1 may result in increased plasma concentrations of the other drug that could increase or prolong its therapeutic and adverse effects.

Atazanavir is a CYP3A4 substrate; therefore, drugs that induce CYP3A4 may decrease atazanavir plasma concentrations and reduce atazanavir's therapeutic effect.
The magnitude of CYP3A-mediated drug interactions with coadministered drug may change when atazanavir is coadministered with ritonavir.

Atazanavir solubility decreases as pH increases. Reduced plasma concentrations of atazanavir are expected if proton-pump inhibitors, antacids, buffered medications, or H_2-receptor antagonists are administered with atazanavir.

Please see the original NDA review for details.

E. General Biopharmaceutics

The approved ATV capsules were used in Study AI424-020. Administration of REYATAZ with food enhances bioavailability and reduces pharmacokinetic variability. Therefore atazanavir is administered with food. Please see the original NDA review.

F. Analytical Section

Quantitative Determination of ATV in Human Plasma was conducted by [redacted], using LC/MS/MS methods. DSI has inspected all three sites and identified 6 deficiencies. See DSI review for details. The applicant's responses for Observations 3, 4 and 6 are acceptable. However, for Questions 1, 2 and 5 regarding the inaccuracy of Quality Control (QC) samples, we do not accept the lower standard of quality control accuracy. Also see QBR section B/ii for the impact of these deficiencies.

III. Labeling Recommendations

The dosing recommendation for pediatric patients 6 to less than 18 years of age is added in the label as following:

2.2 Recommended Pediatric Dosage

The recommended dosage of REYATAZ for pediatric patients (6 to less than 18 years of age) is based on body weight and should not exceed the recommended adult dose. REYATAZ Capsules must be taken with food. The data are insufficient to recommend dosing of REYATAZ for any of the following: (1) patients less than 6 years of age, (2) without ritonavir in patients less than 13 years of age, and (3) treatment-experienced pediatric patients with body weight less than 25 kg.

Therapy-Naive Pediatric Patients

The recommended dosage of REYATAZ with ritonavir in treatment-naive patients at least 6 years of age is shown in Table 1.

For treatment-naive patients at least 13 years of age and at least 39 kg, who are unable to tolerate ritonavir, the recommended dose is REYATAZ 400 mg (without ritonavir) once daily with food.

Table 1: Dosage for Treatment-Naive Pediatric Patients (6 to less than 18 years of age) for REYATAZ Capsules with ritonavir

Body Weight (kg)	(lbs)	REYATAZ dose[a,b] (mg)	ritonavir dose[b] (mg)
15 to less than 25	33 to less than 55	150	80[c]
25 to less than 32	55 to less than 70	200	100[d]
32 to less than 39	70 to less than 86	250	100[d]
at least 39	at least 86	300	100[d]

[a] The recommended dosage of REYATAZ can be achieved using a combination of commercially available capsule strengths.

[b] The dosage of REYATAZ and ritonavir was calculated as follows:

15 kg to less than 20 kg: REYATAZ 8.5 mg/kg with ritonavir 4 mg/kg once daily with food.

at least 20 kg: REYATAZ 7 mg/kg with ritonavir 4 mg/kg once daily with food not to exceed REYATAZ 300 mg and ritonavir 100 mg.

[c] Ritonavir liquid.

[d] Ritonavir capsule or liquid.

Therapy-Experienced Pediatric Patients
The recommended dosage of REYATAZ with ritonavir in treatment-experienced patients at least 6 years of age is shown in Table 2.

Table 2: Dosage for Treatment-Experienced Pediatric Patients (6 to less than 18 years of age) for REYATAZ Capsules with ritonavir

Body Weight (kg)	(lbs)	REYATAZ dose[a,b] (mg)	ritonavir dose[b] (mg)
25 to less than 32	55 to less than 70	200	100[c]
32 to less than 39	70 to less than 86	250	100[c]
at least 39	at least 86	300	100[c]

[a] The recommended dosage of REYATAZ can be achieved using a combination of commercially available capsule strengths.
[b] The dosage was calculated as REYATAZ 7 mg/kg with ritonavir 4 mg/kg once daily with food not to exceed REYATAZ 300 mg and ritonavir 100 mg.
[c] Ritonavir capsule or liquid.

Jenny H. Zheng, Ph.D.
Reviewer, Clinical Pharmacology
DCP 4, OCP

Concurrence:

Kellie S. Reynolds, Pharm. D
Deputy director,
DCP 4, OCP

IV. Individual Study Report Reviews

Phase I/II, Open-label, Pharmacokinetic and Safety Study of a Novel Protease Inhibitor (BMS-232632, Atazanavir, ATV, Reyataz™) in Combination Regimens in Antiretroviral Therapy (ART)-Naïve and Experienced HIV-Infected Infants, Children and Adolescents (Study AI424-020)

Objectives:

- To determine the PK profile and dosing schedule of the capsule formulation for ATV and ATV/RTV in combination with 2 nucleoside reverse transcriptase inhibitors (NRTIs) in HIV-infected pediatric subjects
- To determine the PK profile and dosing schedule for the powder formulation of ATV and ATV/RTV in combination with 2 NRTIs in HIV-infected pediatric subjects
- To determine the safety and tolerability of ATV and ATV/RTV in combination with 2 NRTIs in HIV-infected pediatric subjects

Study Design: This was a multicenter, open-label study conducted in the US and South Africa to determine the safety, PK and optimal dose of ATV powder and capsules, administered with or without RTV, in pediatric treatment-naive or treatment-experienced patients aged 91 days to 21 years of age.

Eligible subjects were assigned to treatment groups, stratified by age, ATV formulation, and concomitant administration of RTV as shown in Table 3.1. At the time of initial protocol development only Groups 1 - 4 were implemented. The study was later modified to include regimens of ATV with RTV in Groups 5 - 8.

Table 3.1: Stratification and Regimens Used

ATV without RTV	ATV with RTV	Formulation	Age Ranges
Group 1	Group 5	Powder	Infants 3 months to ≤ 2 years
Group 2	Group 6	Powder	Children > 2 to ≤ 13 years
Group 3	Group 7	Capsules	Children > 2 to ≤ 13 years
Group 4	Group 8	Capsules	Adolescents > 13 to ≤ 21 years

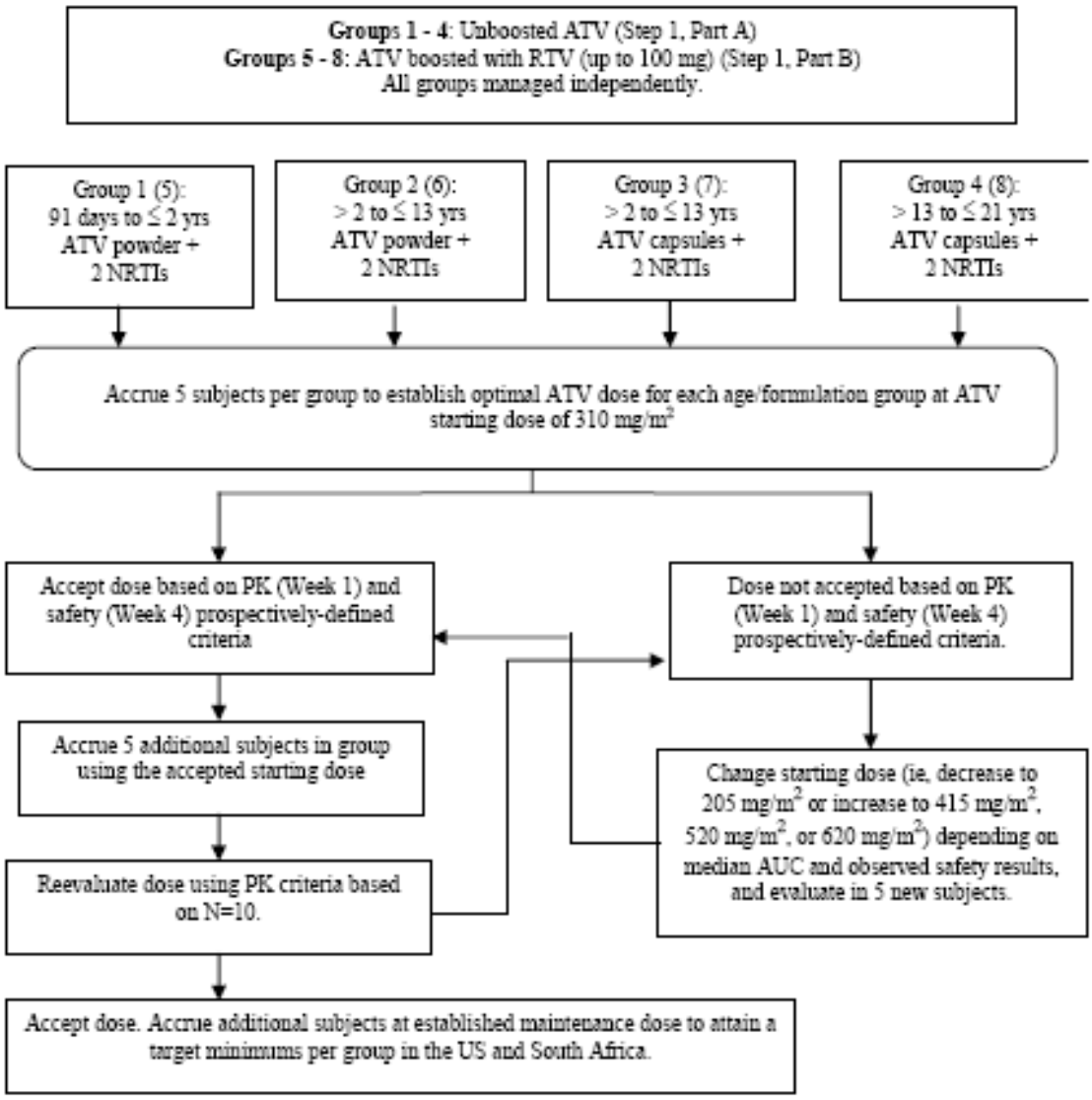
The study includes two steps. Step 1 is a dose-finding step and was conducted in the US and South Africa, and consisted of 2 parts:

Part A: ATV plus 2 NRTIs (excluding abacavir sulfate [ABC, Ziagen®] and tenofovir disoproxil fumarate [TDF, Viread®]).

Part B: ATV/RTV plus 2 NRTIs (excluding ABC and TDF).

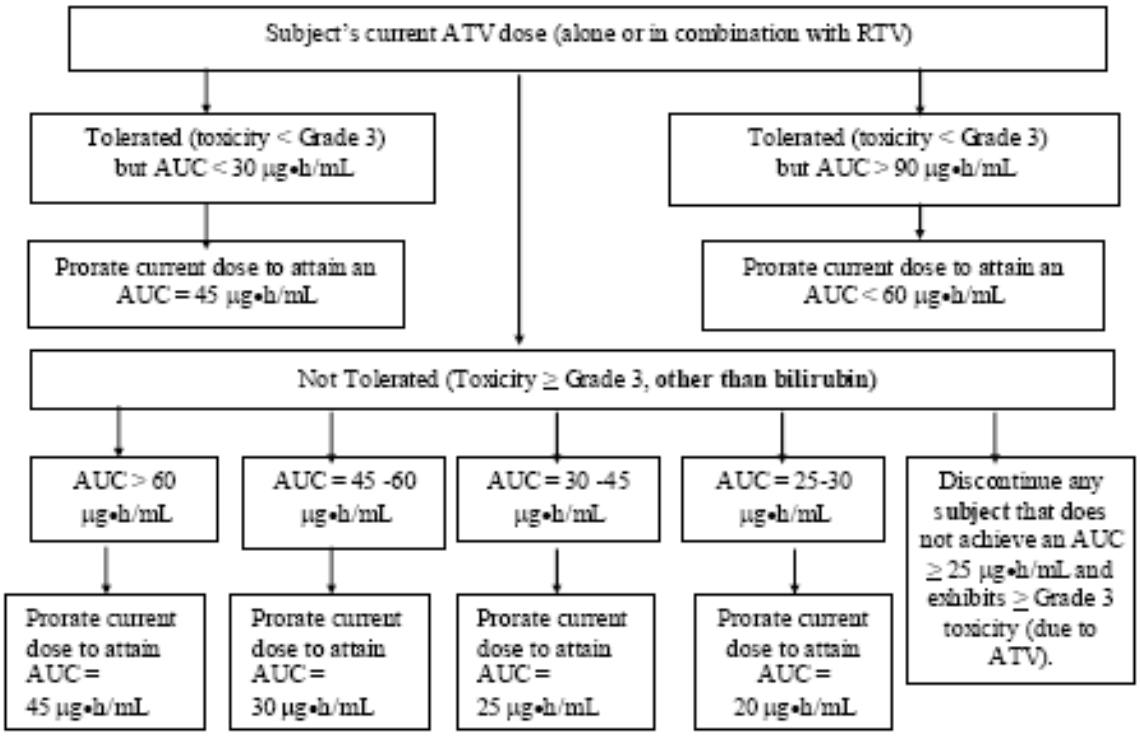
All groups began at 310 mg/m^2 of ATV QD; the boosted groups also received RTV 100 mg/m^2 QD (liquid, up to 100 mg QD or 100 mg capsule). All groups escalated or decreased ATV doses based on PK exposure targets (Week 1) and safety criteria (Week 4) as shown in Figure 3.1. The Group target AUC is 45 ug.h/mL. For Part A, the group dose was accepted if ATV at this dose was tolerated, 0 out of 5 subject had AUC value below 15 ug.h/mL, 4 of the 5 subjects had AUC levels at least 30 ug.h/mL, and at least 4 of the 5 subjects had trough (Cmin) concentration of at least 60 ng/mL. For Part B, the group dose was accepted if ATV at this dose was tolerated, 0 out of 10 subjects had Cmin < 60 ng/mL, at least 2 out of 10 subjects had Cmin < 120 ng/mL.

Figure 3.1: Study Diagram - Step 1 (AI424020)



Based on the tolerability of the study medication regimen and the ATV AUC at Week 1 and Week 56, adjustment of the ATV dose for individual subjects was to occur as shown in Figure 3.4.2.1.

Figure 3.4.2.1: Adjustment of ATV Doses in Individual Subjects



Subjects automatically had dose increases based on an increase in body weight of ≥ 25%.

Step 2 is open to South African subjects who are virologically responding to treatment when the last enrollee into either part of Step 1 (Part A or Part B) has completed 96 weeks of treatment (end of Step 1).

Formulation: The following table shows the formulation used for atazanavir and ritonavir.

Atazanavir and Ritonavir Batch Numbers

Dose Formulation	Vendor (Batch) Numbers
Atazanavir	
oral dispersible powder (50 mg/1.5 g)	N00042, N00071, N00073, N00075, 3G72678, 3G726890, 4B82323, 4C81263, 4C81266, 4H73290, 6K12957
50-mg capsule	N00060, 6A19152, 6A19151, 5C03146
100-mg capsule	C99178, N01086, 4H750568, 6C14392, 6H16423
200-mg capsule	C99331, 3631-MED70, 3631-5K3103A, 6G3102A, 3631-5E3117B
Ritonavir	
oral solution (80 mg/mL)	10512AW21, 11558AW21, 13584AW21, 14628AW21, 15652AW21, 17707AW21, 18723AW21, 19752AW21, 20774AW21, 21802AW21, 25865AW21, 26880AW21, 27901AW21, 31972AW21, 34016AW21, 36041AW21, 37074AW21, 39098AW21, 41131AW21, 43193AW21, 45220AW21, 47259AW21, 49285AW21
100-mg capsule	097772E21, 155622E21, 155882E21, 166242E21, 201772E21, 213692E21, 317082E22, 380102E21, 441462E21,

Pharmacokinetic Measurements:
Pharmacokinetic samples were taken at 0, 1, 2, 3, 4, 6, 8, 12 hours on Day 7 and Week 56 and the following day at 24 hours post-dosing. For patients requiring dose adjustments, repeat 24-hour intensive PK were performed two weeks after initiation of new dose. Dose adjustments after Week 56, if needed, were for individuals only. No group-dose adjustments were done based on Week 56 PK data. Random PK samples were taken at Week 12, 24, 36, 72 and 96 and every 24 weeks after Week 96 until the end of the study for population PK analysis. The random concentrations obtained at Weeks 12, 24, and 36 were also used for assessment of possible non-adherence.

Bioanalytical Methods:
Quantitative determination of ATV in human plasma was conducted by f , using LC/MS/MS methods. A cross validation was performed by .
The following table summarizes the *in vivo* analytical methods used to determine plasma concentrations of ATV. All samples were analyzed during the period within which their analytes were stable. Please see the attached DSI inspection. The applicant's responses for Observations 3, 4 and 6 are acceptable. However, for Questions 1, 2 and 5, we do not accept the lower standard of quality control accuracy. Twelve subjects in Group 3 and 14 subjects in Group 4 were affected. The data from these subjects should have been rejected.

Analytical Methods

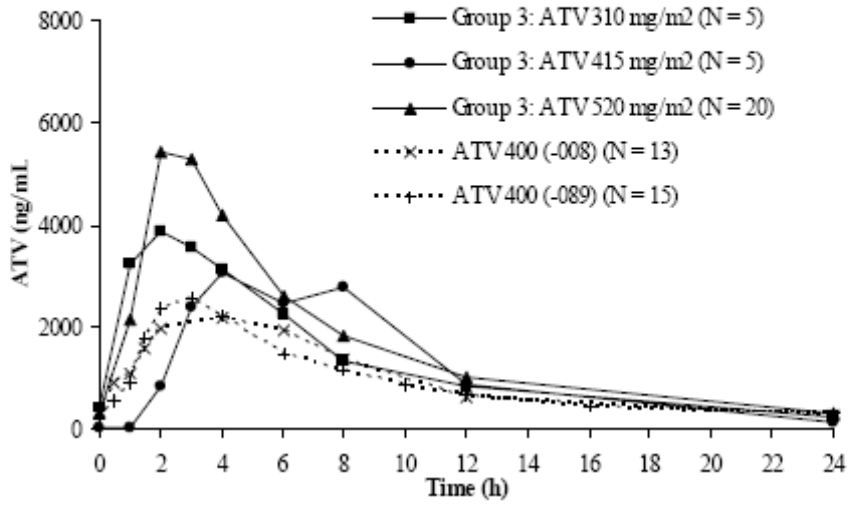
Analyte	Linear Range (ng/mL)	Between Run Precision (%CV)	Between Run Bias (% Deviation)	QC samples (ng/mL)	Stability
ATV	5 – 5000 $R^2 \geq 0.9903$	NA	NA	15, 2500, 4000 and 8000	• Stable in human EDTA plasma at -70°C for at least 2 years. • Stable at room temp. for at least 24 hours • Stable following 3 freeze/thaw cycles
ATV ( )	1– 1000 $R^2 \geq 0.9720$	NA	NA	3, 400, 800 and 8000	• NA
ATV ( )	20 – 20000 R^2 (mean± SD) =0.9992 ± 0.0007	≤ 14.1	-2.0 to -4.5	75, 750 and 7500	• Stable in human EDTA plasma at -70°C for at least 2 years.

Results: For the purpose of the submission, only data from ATV capsules (Groups 3, 4, 7 and 8) are reviewed. The data were designated as confirmatory and non-confirmatory. The PK data associated with visits used for dose finding were designed as "confirmatory". The PK data associated with all visits other than those used for dose finding were designated "non-confirmatory". The visit associated with dose finding was normally Week 1 or 2 weeks after initiation of a new dose, however, not every subject with Week 1 data was included in dose finding. The reasons for the exclusion of certain subjects were often, if not exclusively, dosing errors or non-adherence. PACTG attempted to reschedule this PK visit and the PK data of some subjects at a later visit were included in the confirmatory data. However, a number of subjects continued to have adherence problems and were discontinued or withdrew consent prior to the acquisition of valid PK data. PK data from visits following the visit from which confirmatory data were obtained were designated non-confirmatory and were normally obtained in Week 56.

ATV (capsule) only

The mean ATV concentration-time profiles from Group 3 (ATV capsule for age 2 to 13, but no subjects were younger than 6 years old in Group 3) are presented in Figure 9.1.1C. Only confirmatory data were included.

Figure 9.1.1C: Mean Plasma Concentration Time Profiles for Atazanavir in Group 3 vs Historical Data for ATV 400 QD in ARV-naive HIV+ Adults



Summary statistics for PK parameters from three cohorts within Group 3 (confirmatory data) are presented with historical exposures in HIV-infected adult subjects in Table 9.1.1C.

Table 9.1.1C: Summary Statistics for ATV Pharmacokinetic Parameters in Group 3 (ATV capsules, > 2yr to 13yr) vs ATV 400 QD in ARV-naive HIV+ Adults

Pharmacokinetic Parameter	Dosing Cohort			400 mg QD in HIV+ Adults[a]	400 mg QD in HIV+ Adults[b]
	310 mg/m^2	415 mg/m^2	520 mg/m^2		
	N = 5	N = 5	N = 20	N = 13	N = 15
AUC(TAU) (µg•h/mL) - Geometric Mean (CV%)	31.0 (33)	29.0 (44)	33.9 (51)	14.9 (91)	11.0 (161)
Median	33.1	32.2	41.1	18.1	13.1
[Range]	[17.5-44.3]	[13.9-47.8]	[6.9-93.4]	[3.0-75.9]	[0.8-144]
Cmax (ng/mL) - Geometric Mean (CV%)	4193 (38)	3853 (40)	5752 (41)	2298 (71)	1845 (116)
Median	5229	3841	6463	2618	1944
[Range]	[1530-5934]	[1995-6605]	[1206-12003]	[448-7446]	[82-15238]
Cmin (ng/mL) - Geometric Mean (CV%)	240 (50)	85 (71)	168 (124)	120 (109)	60 (246)
Median	238	165	173	218	35
[Range]	[148-472]	[5.0-272][c]	[18-1392]	[12.2-890]	[2.5-2935]
Doses (mg) Median	300	400	475[d]		
[Range]	[250-400]	[400-550]	[300-800]	All 400	All 400

[a] AI424008, n=12 for Cmin

[b] AI424089, one BLQ Cmin set to 2.5 ng/mL for summary

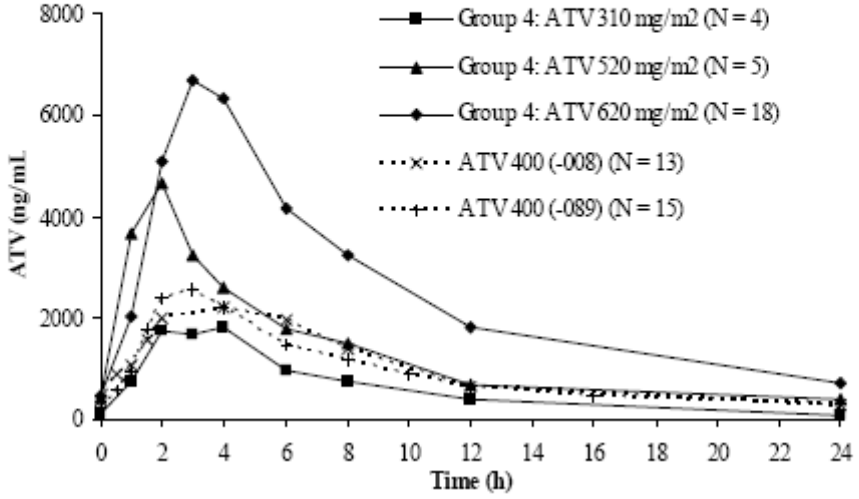
[c] BLQ reported as 5 ng/mL

[d] 11 of 20 subjects received doses > 400 mg

Subjects in the first 2 dosing cohorts for Group 3 had ATV exposures that did not meet the PK criteria set forth in the protocol. While largely comparable to or higher than ATV exposures previously observed in ARV-naive adults receiving ATV 400 mg QD, exposures from these two dosing cohorts were too low to satisfy the PK criteria in the protocol which were set to target on both treatment naive and treatment experienced patients. The 310 mg/m^2 and 415 mg/m^2 dosing cohorts did not meet protocol-specified criteria due to two subjects with AUC values below 30 µg•h/mL in each cohort. In addition, one subject in the 415 mg/m^2 dosing cohort had a Cmin value that was below the lower limit of quantification (reported as 5 ng/mL). In general, the AUC and Cmax at 520 mg/m^2 were 1.5 to 2.5-fold greater than those previously observed in adults receiving ATV 400 mg QD; however, Cmin values were comparable to adults receiving ATV 400 mg QD despite considerably higher doses on a mg/m^2 basis. In order to achieve these exposures, doses of ATV without RTV were as high as 800 mg QD.

The mean ATV concentration-time profiles from Group 4 (confirmatory data) are presented in Figure 9.1.1D.

Figure 9.1.1D: **Mean Plasma Concentration Time Profiles for Atazanavir in Group 4 vs Historical Data for ATV 400 QD in ARV-naive HIV+ Adults**



Summary statistics for PK parameters (confirmatory data) from the dosing cohorts within Group 4 (age 13-18) are presented with historical exposures in HIV-infected adult subjects in Table 9.1.1D.

Table 9.1.1D: Summary Statistics for ATV Pharmacokinetic Parameters in Group 4 (ATV capsules, > 13yr to 18 yr) vs ATV 400 QD in ARV-naive HIV+ Adults

Pharmacokinetic Parameter	Dosing Cohort			400 mg QD in HIV+ Adults[a]	400 mg QD in HIV+ Adults[b]
	310 mg/m^2	520 mg/m^2	620 mg/m^2		
	N = 4[c]	N = 5	N = 18[d]	N = 13	N = 15
AUC(TAU) (µg•h/mL) - Geometric Mean (CV%)	11.2 (69)	22.1 (85)	51.0 (46)	14.9 (91)	11.0 (161)
Median	13.2	28.6	53.5	18.1	13.1
[Range]	[5.3-24.0]	[3.4-75.9]	[2.2-125.9]	[3.0-75.9]	[0.8-144]
Cmax (ng/mL) - Geometric Mean (CV%)	1297 (94)	3258 (77)	6540 (46)	2298 (71)	1845 (116)
Median	1626	4981	7063	2618	1944
[Range]	[400-4393]	[398-10731]	[299-15569]	[448-7446]	[82-15238]
Cmin (ng/mL) - Geometric Mean (CV%)	65.2 (59)	145 (112)	405 (114)	120 (109)	60 (246)
Median	63.5	194	530	218	35
[Range]	[34-135]	[20-955]	[23-3395]	[12.2-890]	[2.5-2935]
Doses (mg) Median		600[e]	800[e]		
[Range]	All 400	[550-700]	[600-1000]	All 400	All 400

Source: Supplemental Table S.8.2.1A

[a] AI424008, n=12 for Cmin

[b] AI424089, one BLQ Cmin set to 2.5 ng/mL for summary

[c] One subject > 18 years of age excluded, see Appendix 8.2.1J for n = 5

[d] Two subjects >18 years of age excluded, see Appendix 8.2.1J for n = 20

[e] All subjects received doses > 400 mg QD

Subjects in the first 2 target dosing cohorts for Group 4 had ATV exposures that did not meet the PK criteria set forth in the protocol. Based on mean data, the exposures observed in subjects receiving 310 mg/m^2 were at lower end of those previously observed in ARV-naive adults receiving ATV 400 mg, although the individual values were within the range observed for adults. The exposures observed in subjects receiving 520 mg/m^2 were comparable to or higher than those previously observed in ARV-naive adults receiving ATV 400 mg. The 310 mg/m^2 and 520 mg/m^2 dosing cohorts did not meet protocol-specified criteria due to two subjects with AUC values below 15 µg•h/mL in each cohort. In general, the exposures at 620 mg/m^2 were 1.5 to 2.5-fold greater than exposures observed in adults receiving ATV 400 mg QD. The median ATV dose without RTV in this cohort was 800 mg and doses were as high as 1000 mg.

The ATV AUC values from the protocol-accepted doses in Groups 3 and 4 were more comparable to those following ATV/RTV 300/100 mg QD in HIV+ adults, but Cmax is higher and Cmin is lower than those following ATV/RTV 300/100 mg QD in HIV+ adults, as shown in Table 9.1.1E.

Table 9.1.1E: Summary Statistics for ATV Pharmacokinetic Parameters in Protocol-Accepted Doses for Group 3 and 4 vs ATV/RTV 300/100 in HIV+ Adults

Pharmacokinetic Parameter	Dosing Cohort		300/100 mg QD in ARV-experienced HIV+ Adults[b]	300/100 mg QD in ARV-naive HIV+ Adults[c]
	Group 3 520 mg/m^2 N = 20	Group 4 620 mg/m^2 N = 18[a]	N = 10	N = 12
AUC(TAU) (μg•h/mL) - Geometric Mean (CV%)	33.9 (51)	51.0 (46)	46.1 (66)	44.2 (34)
Median	41.1	53.5	47.7	43.4
[Range]	[6.9-93.4]	[2.2-125.9]	[23.1-142]	[26.1-83.2]
Cmax (ng/mL) - Geometric Mean (CV%)	5752 (41)	6540 (46)	4422 (58)	4427 (28)
Median	6463	7063	4967	4757
[Range]	[1206-12003]	[299-15569]	[1694-9950]	[2426-6792]
Cmin (ng/mL) - Geometric Mean (CV%)	168 (124)	405 (114)	636 (97)	709 (60)
Median	173	530	532	858
[Range]	[18-1392]	[23-3395]	[158-3081]	[184-2064]
Doses (mg)				
Median	475	800		
[Range]	[300-800]	[600-1000]	All 300	All 300

[a] AI424074

[b] AI424089

[c] Two subjects > 18 years of age excluded

Source: Supplemental Table S.8.2.1A

In order to determine if ATV PK is changed significantly after 1 year, ATV PK at Week 56 was accessed. There were 12 subjects in Group 3 and 4 subjects in Group 4 with valid PK data that were taking capsule doses within 25% of the recommended doses per m^2 for those age groups at Week 56 on study. The PK data from these subjects (non-confirmatory data) are summarized in Table 9.1.2.

Table 9.1.2: Summary Statistics for Pharmacokinetic Parameters for Subjects within 25% of Accepted Doses of ATV without RTV at Week 56 in Groups 3 and 4 vs ATV 400 QD in HIV+ Adults

Pharmacokinetic Parameter	Group 3 520 mg/m^2 N = 12	Group 4 620 mg/m^2 N = 4	400 mg QD in HIV+ Adults[a] N = 13	400 mg QD in HIV+ Adults[b] N = 15
AUC(TAU) (μg•h/mL) - Geometric Mean (CV%)	35.2 (69)	38.9 (52)	14.9 (91)	11.0 (161)
Median	43.5	44.2	18.1	13.1
[Range]	[7.7-103.3]	[16.5-71.8]	[3.0-75.9]	[0.8-144]
Cmax (ng/mL) - Geometric Mean (CV%)	5278 (55)	5133 (46)	2298 (71)	1845 (116)
Median	6407	5535	2618	1944
[Range]	[1827-12169]	[3022-8295]	[448-7446]	[82-15238]
Cmin (ng/mL) - Geometric Mean (CV%)	322 (219)	316 (46)	120 (109)	60 (246)
Median	233	368	218	35
[Range]	[0-7652][c]	[139-528]	[12.2-890]	[2.5-2935]
Doses (mg) Median	525	850		
[Range]	[400-600]	[800-1000]	All 400	All 400

[a] AI424008, n=12 for Cmin

[b] AI424089, one BLQ Cmin set to 2.5 ng/mL for summary

[c] One BLQ reported as zero

The PK at Week 56 in Groups 3 and 4 are comparable to their respective dose finding cohorts, except mean ATV Cmin for 520 mg/m^2 in Group 3 is higher at Week 56 as compared to Week 1. However, there is a high variability in Cmin values on both Weeks 1 and 56.

Because the non-confirmatory data were normally collected after 1 year after confirmatory data were collected (Week 56), the subject's age and weight and sometimes doses were changed. In addition, intrasubject variability is generally as big as intersubject variability, so we combined the confirmatory and non-confirmatory data in some analyses.

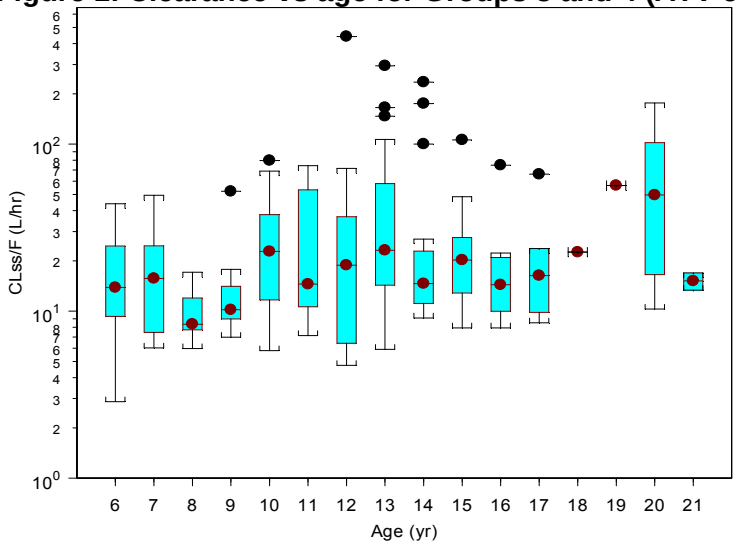
Figure 1 includes all the available data from Groups 3 and 4 (confirmatory +non-confirmatory) to determine the trend of ATV clearance change with age. Figure 1 is box plots that describe median (lines inside the box with dots), the lower quartile (Q1, bottom of the box), the upper quartile (Q3, top of the box), the range of the data excluding outlier (top and bottom lines), and outliers (dots). N is number of data points and not the number of subjects. The data show that CLss/F does not change with age. The median CLss/F is between 22 to 30 L/hr for adults administered with 400 mg ATV. The data show that there is no clear trend of CLss/F with age if excluding patients above 18 years old (62 subjects, there are 5 subjects only have non-confirmatory data). The CLss/F in pediatric is slightly less than adults (median: 16 L/hr).

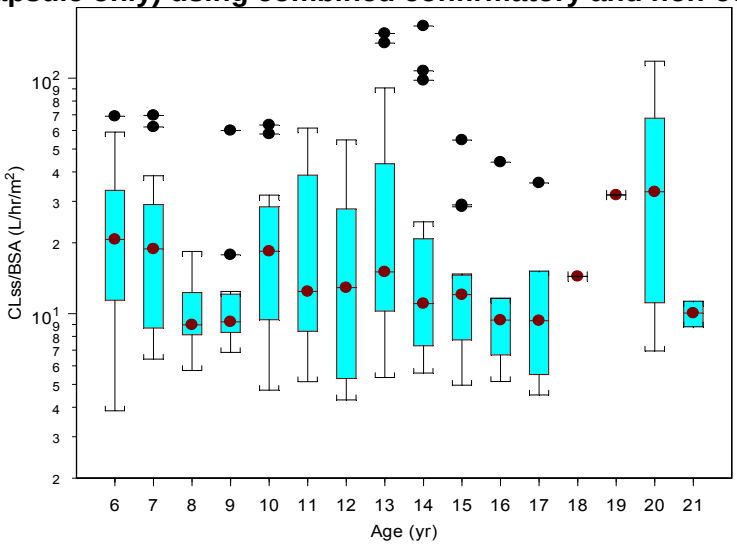
AUC vs. dose for patients between 13 and 18 years of age is plotted assuming no effect of weight and age (Figure 2). The data show more than dose proportional increase of

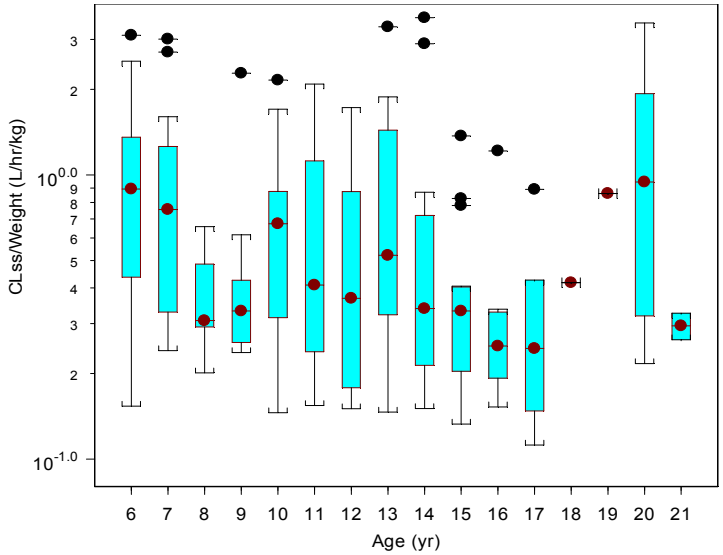
AUC for subjects between 13 and 18 years of age, while the AUC for subjects between 6 and 13 is less than dose proportional increase (Table 9.1.1C). If we use group 3 and group 4 data (age 6 - 18, confirmatory), AUC shows approximately dose-proportional increase (the lines show the geometric means, Figure 3), which is consistent with the adult data. The geometric means show Cmax are more than dose proportional increase, while Cmin is approximately dose proportional, with higher variability as compared to AUC and Cmax.

For simplicity, the exposures for Group 3 and 4 are normalized to 400 mg by linear PK to compare the exposures of pediatric subjects who took ATV 400 mg capsules with observed in adults subjects who took ATV 400 mg or ATV/RTV 300/100 mg (confirmatory +non-confirmatory, n: number of data points, Figure 4). There are 13 subjects in Group 3 and 4 subjects in Group 4 were actually taking 400 mg ATV.

Figure 1: Clearance vs age for Groups 3 and 4 (ATV capsule only) using combined confirmatory and non-confirmatory Data







N = 16 14 11 13 19 12 11 25 18 18 8 7 1 1 6 3

Figure 2: AUC vs. Dose for Patients 13 to 18 years in Group 4 using confirmatory data

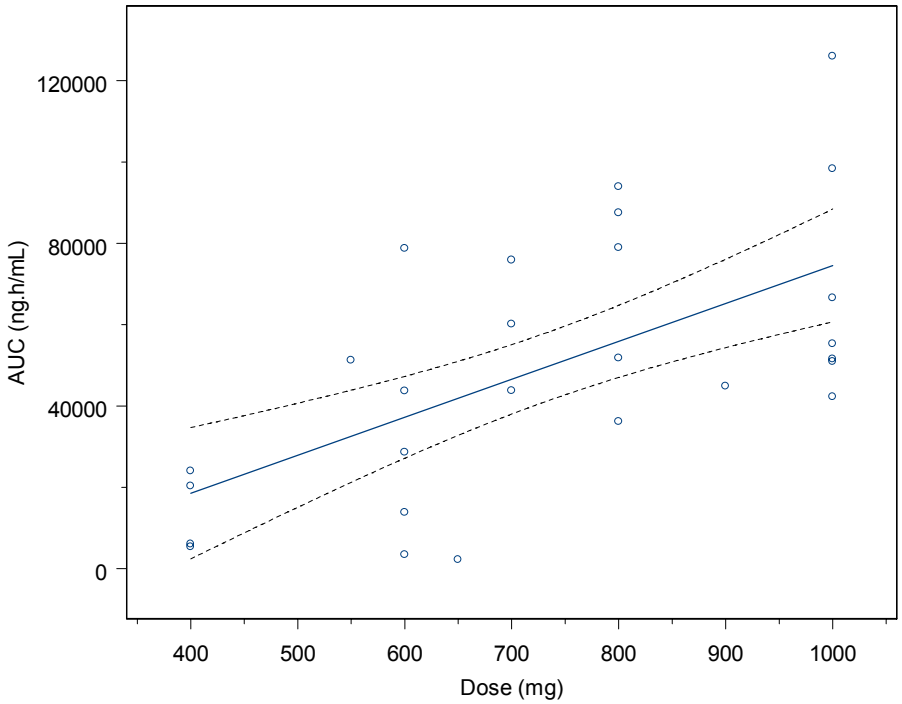


Figure 3: AUC vs. Dose for Patients 6 to 18 years in Groups 3 & 4 using confirmatory data

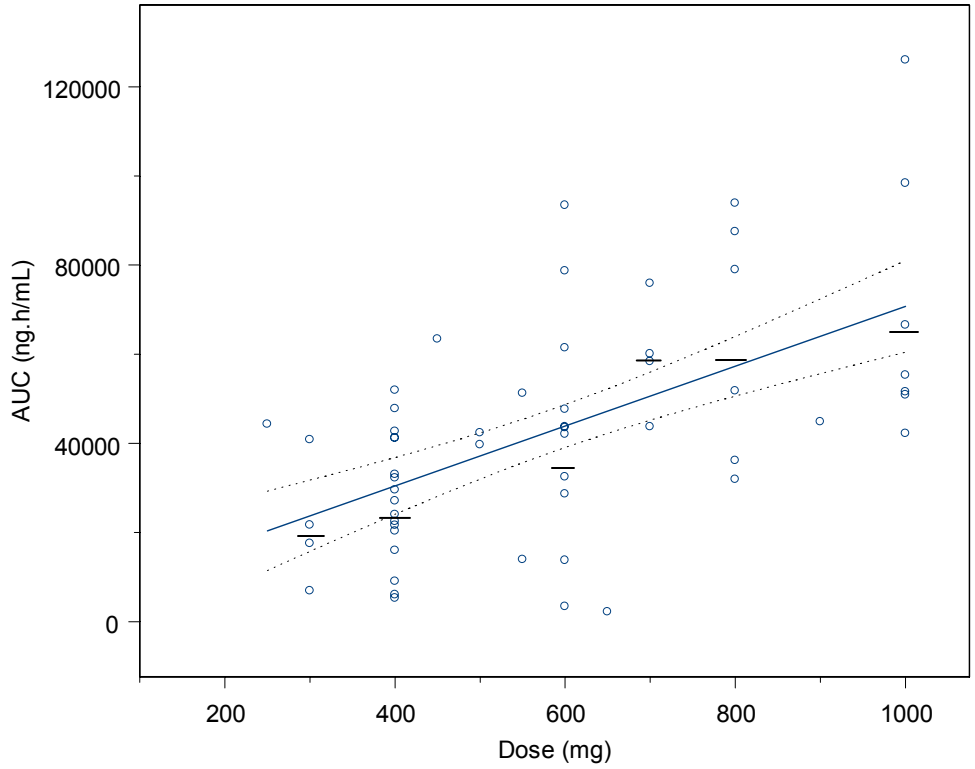
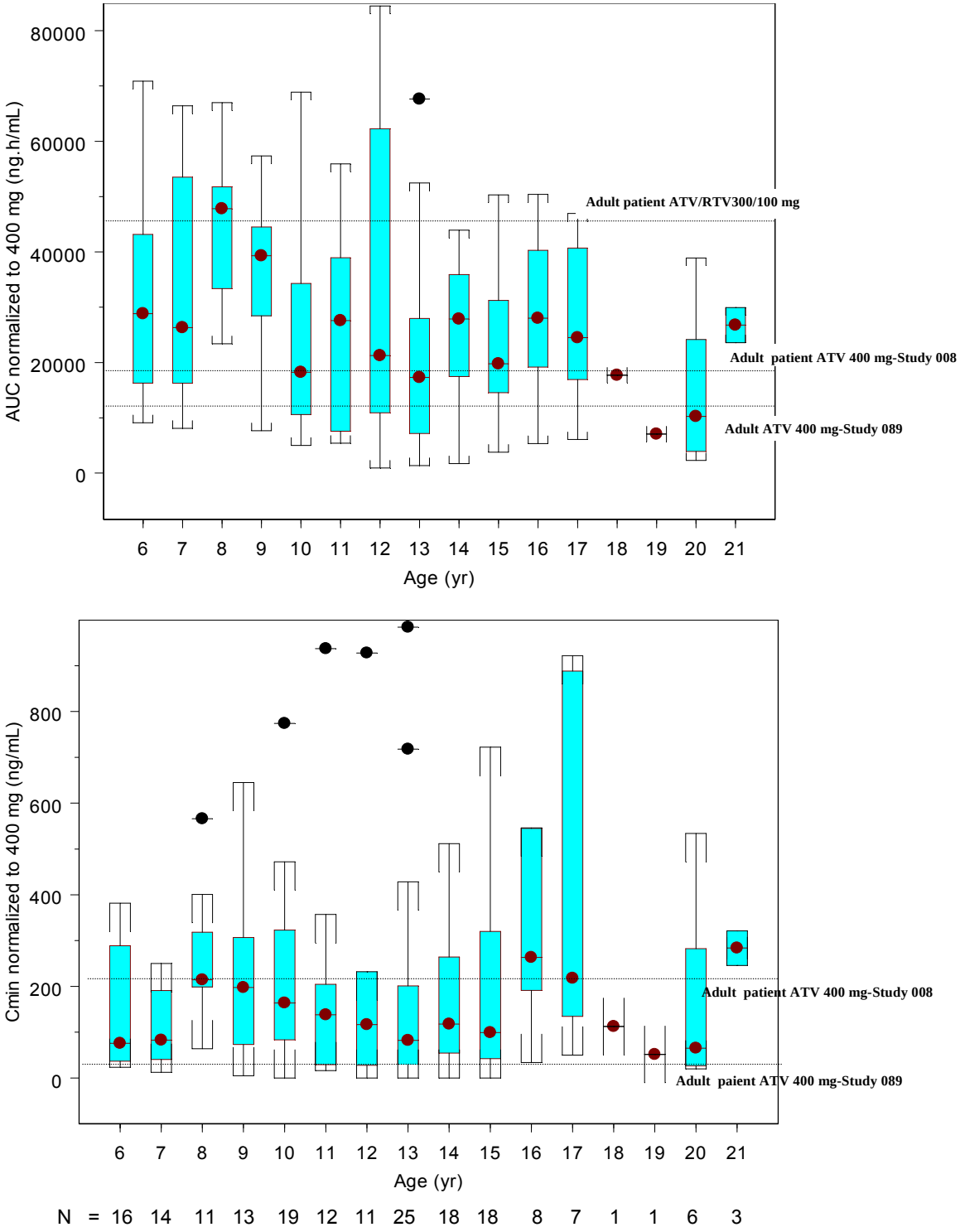
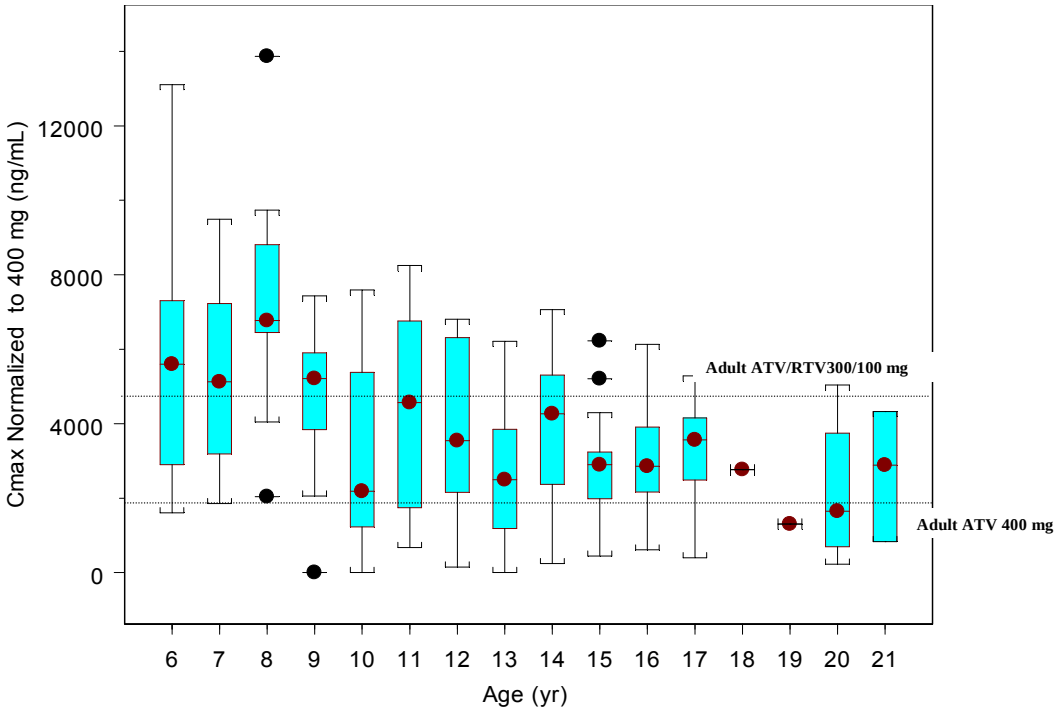


Figure 4: Estimated exposures at ATV 400 mg vs. Age using combined confirmatory and non-confirmatory data





The data show that ATV alone is not recommended for pediatric patients less than 13 years of age, because Cmax/Cmin ratio is higher for this population than for adults. ATV AUC and Cmin at 400 mg are in the range of values observed in adult patients at ATV 400 mg, but Cmax is close to or above adult ATV/RTV 300/100 mg. Data from 13 subjects who took ATV 400 mg in the study support the conclusion (Table 1).

Table 1: ATV Pharmacokinetics from subjects taking ATV 400 mg in Group 3

Pharmacokinetic Parameter	Group 3 400 mg (observed)[a,b] N=13	400 mg QD in HIV+ Adults Study 008[a] N=13	400 mg QD in HIV+ Adults Study 089[c] N=15	300/100 mg QD in HIV+ Adults Study 074 N=10
AUC(TAU) (µg•h/mL) Geometric Mean (CV%) Median [Range]	 29.1 (22) 32.2 [9.0-51.9]	 14.9 (91) 18.1 [3.0-75.9]	 11.0 (161) 13.1 [0.8-144]	 46.1 (66) 47.7 [23.1-142]
Cmin (ng/mL) Geometric Mean (CV%) Median [Range]	 117 (57) 151 [5-472]	 120 (109) 218 [12.2-890]	 60 (246) 35 [2.5-2935]	 636 (97) 532 [158-3081]
Cmax (ng/mL) Geometric Mean (CV%) Median [Range]	 4752 (17) 5229 [2036-7811]	 2298 (71) 2618 [448-7446]	 1845 (116) 1944 [82-15238]	 4422 (58) 4967 [1694-9950]

[a] n=12 for Cmin; [b] one BLQ Cmin set to 5 ng/mL for summary; [c] one BLQ Cmin set to 2.5 ng/mL for summary

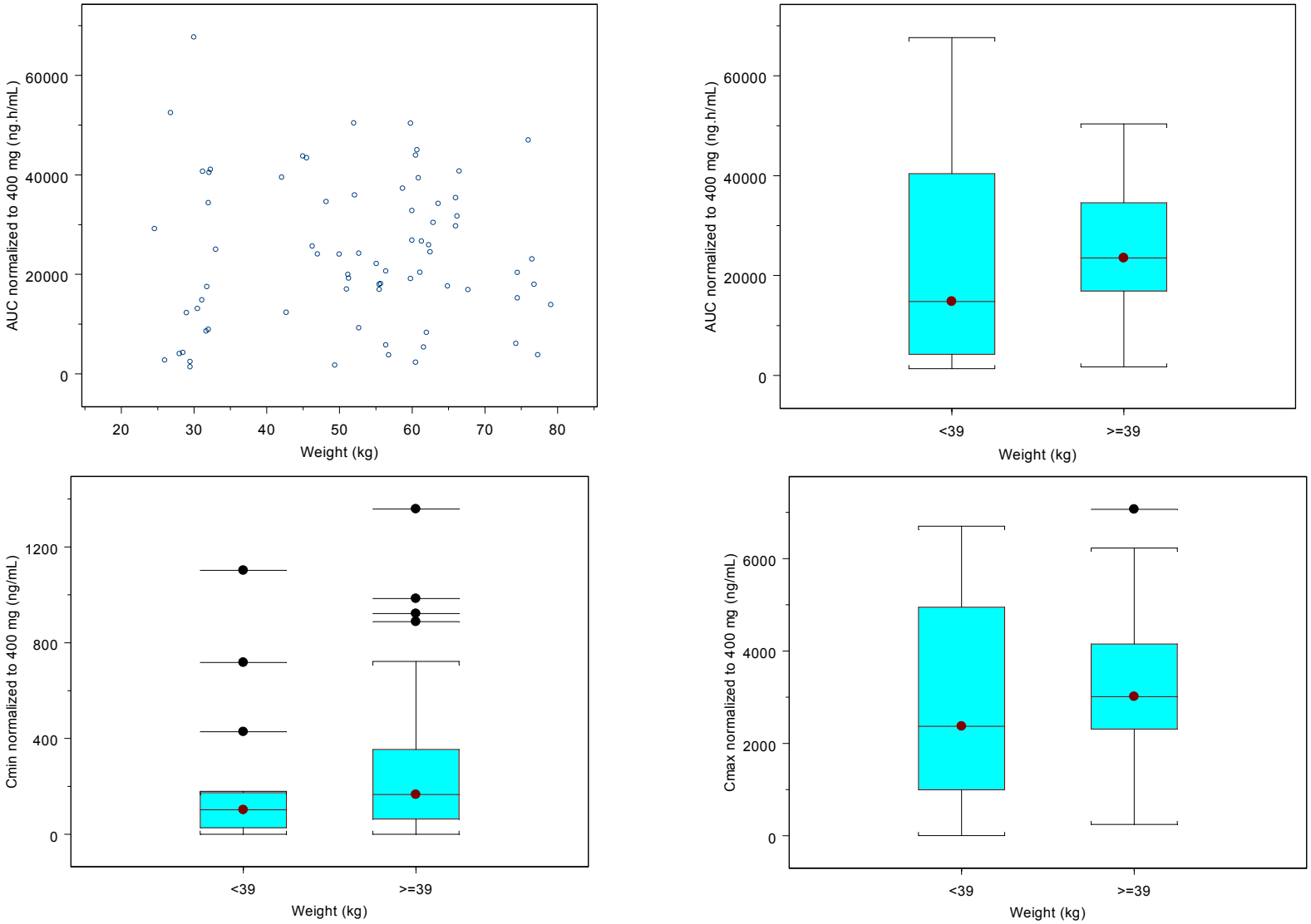
ATV 400 mg can be used for treatment naive pediatric patients aged 13 -18 years, because in this age range, ATV AUC and Cmin at 400 mg are in the range of values observed in adult patients at ATV 400 mg, and Cmax will not be higher than values

observed in adult patients at ATV/RTV 300/100 mg. The data from 4 adolescents who received ATV 400 mg (Table 9.1.1D, Page 30) also support this conclusion. As shown in Table 2 and Figure 5 there is slightly lower exposures for patients aged 13-18 years who weigh less than 39 kg as compared to who weigh at least 39 kg at ATV 400 mg. Subjects with weight less than 39 kg have a higher Cmax/Cmin ratio (29) as compared to subjects with weight more than 39 kg (16). Only treatment naive pediatric patients aged 13 -18 years with weight at least 39 kg should receive ATV 400 mg QD.

Table 4: ATV pharmacokinetics in Group 4 classified by body weight

Geometric means	Body weight (Group 4)	
	< 39	≥ 39
AUC (ng.h/mL)	13.5	15.7
Cmin (ng/mL)	69	155
Cmax (ng/mL)	2011	2501

Figure 5: Estimated ATV exposures at ATV 400 mg vs. weight using combined confirmatory and non-confirmatorty data

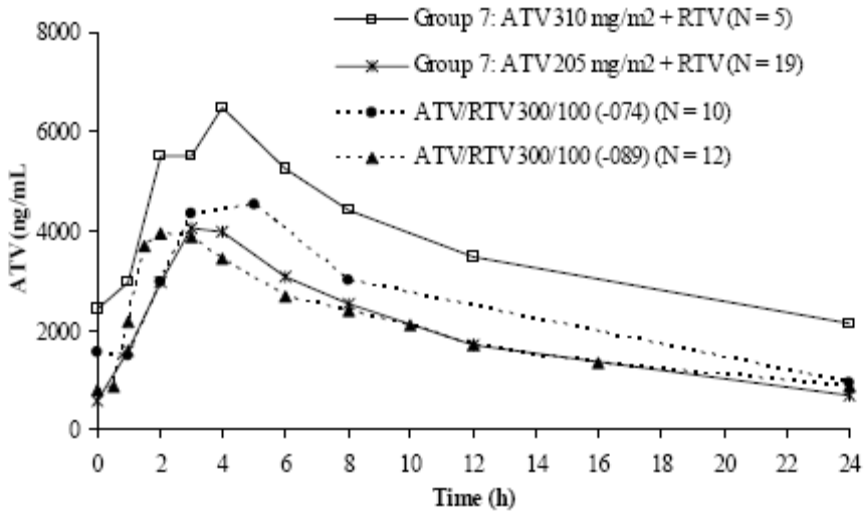


In the late stage of the review cycle (3/07/2008), the results from DSI inspection of clinical PK and bioanalytical sites became available (see attachment). The inspection indicated that in 37 runs, including 26 subjects from Group 3 and Group 4, the concentrations may not be accurate due to the inaccuracy of the quality control data. The data from subjects aged 13 -18 years with weight at least 39 kg were reanalyzed excluding those people, the geometric mean of AUC, Cmin and Cmax are 23.0 ug.h/mL, 177 ng/mL and 2846 ng/mL, respectively, for ATV normalized to 400 mg. The new analyses show that ATV AUC and Cmin are still within the range of observed in adult patients at ATV 400 mg, and Cmax will not be higher than observed in adult patients at ATV/RTV 300/100 mg. Therefore, our recommendation for treatment naïve patients age 13-18 years is not changed.

ATV (capsule)/RTV

The mean ATV concentration-time profiles from Group 7 (confirmatory data) are presented in Figure 9.2.1C.

Figure 9.2.1C: Mean Plasma Concentration-Time Profiles for Atazanavir in Group 7 vs. Historical Data for ATV/RTV 300/100 QD in ARV-naive (-089) and ARV-experienced (-074) HIV+ Adults



Summary statistics for PK parameters from both cohorts within Group 7 (confirmatory data) are presented with ATV/RTV 300/100 QD historical exposures in HIV-infected adult subjects in Table 9.2.1C.

Table 9.2.1C: Summary Statistics for ATV Pharmacokinetic Parameters in Group 7 (ATV capsule + RTV, 2yr to 13 yr) vs ATV/RTV 300/100 QD in ARV-naive and ARV-experienced HIV+ Adults

Pharmacokinetic Parameter	Dosing Cohort		300/100 mg QD in HIV+ Adults[a]	300/100 mg QD in HIV+ Adults[b]
	310 mg/m^2	205 mg/m^2		
	N = 5	N = 19	N = 10	N = 12
AUC(TAU) (µg•h/mL) - Geometric Mean (CV%)	84.6 (40)	44.2 (35)	46.1 (66)	44.2 (34)
Median	73.8	44.7	47.7	43.4
[Range]	[60.0-134.2]	[23.8-82.5]	[23.1-142]	[26.1-83.2]
Cmax (ng/mL) - Geometric Mean (CV%)	7403 (24)	4648 (33)	4422 (58)	4427 (28)
Median	7174	4949	4967	4757
[Range]	[5026-9613]	[1948-7678]	[1694-9950]	[2426-6792]
Cmin (ng/mL) - Geometric Mean (CV%)	1933 (49)	555 (63)	636 (97)	709 (60)
Median	2071	589	532	858
[Range]	[1079-3423]	[141-1708]	[158-3081]	[184-2064]
Doses with RTV[c] (mg) Median	400	200[d]		
[Range]	[300-500]	[150-400]	All 300	All 300

Source: Supplemental Table S.8.2.1A

[a] AI424074

[b] AI424089

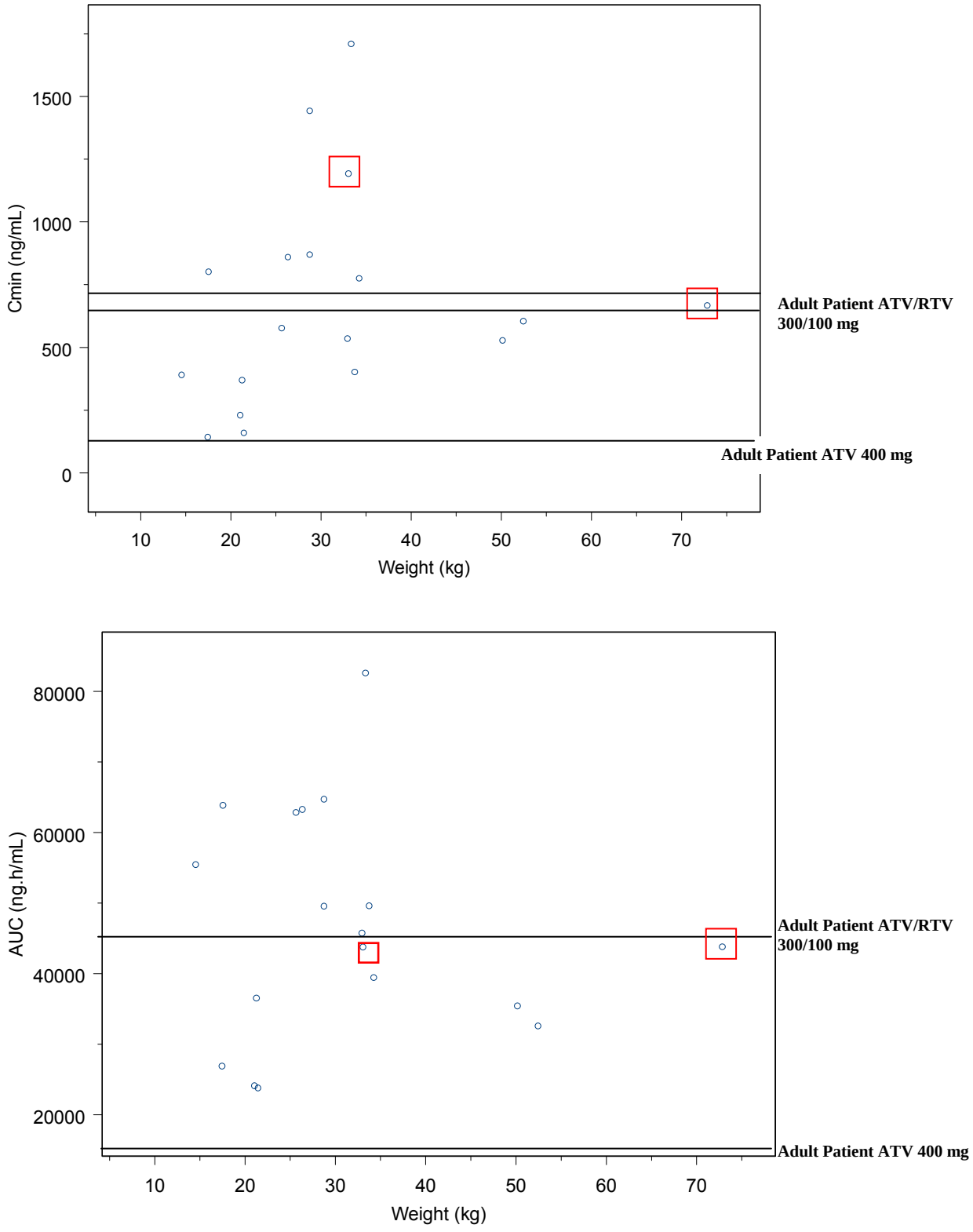
[c] RTV dose was 100 mg/m^2 up to a maximum of 100 mg

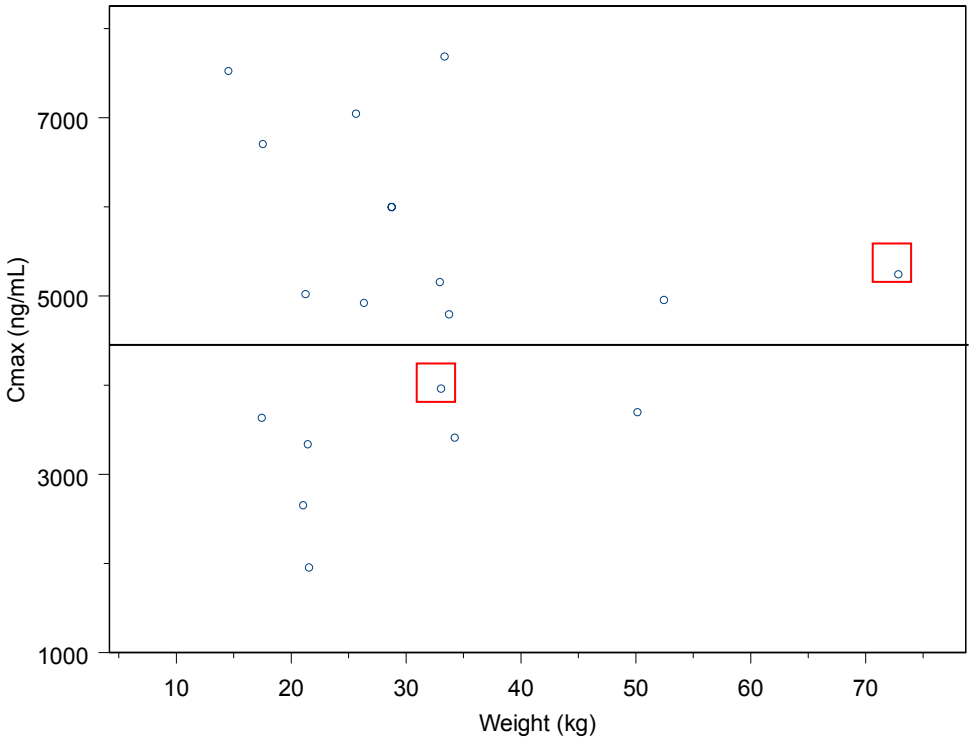
[d] 1 of 19 subjects received a dose > 300 mg ATV with RTV

The PK from the first 5 subjects in the initial dosing cohort of 310 mg/m^2 for Group 7 did not meet the PK criteria set forth in the protocol because AUC were higher than allowed per protocol targets (median AUC > 60 µg•h/mL). ATV exposures at 310 mg/m^2 with RTV in this group are notably higher than those observed in adults receiving ATV 300 mg with RTV 100 mg QD. The target dose for this Group was reduced to 205 mg/m^2 and this dose met the protocol-specified PK criteria. In general, the ATV exposures at 205 mg/m^2 with RTV 100 mg/m^2 (up to a maximum of 100 mg) are comparable to those observed in HIV+ adults receiving ATV 300 mg QD with 100 mg RTV QD. Only one of 19 subjects in the 205 mg/m^2 dosing cohort in Group 7 received an ATV dose above 300 mg with RTV. That subject was approximately 12 years of age and had a BSA of 1.86 m^2.

Figure 6 shows the ATV exposures vs. weight for Group 7 at the protocol accepted dose 205 mg/m^2 + RTV using confirmatory data (including two subjects who are between 5.5 to 6 years of age and three subjects who are more than 39 kg). The data show that ATV Cmin for children who weigh less than 25 kg is relatively low as compared to Cmin in adult patients who received ATV/RTV 300/100 mg. However, the Cmax is similar to observed in adult patients who took ATV/RTV 300/100 mg. If we increase dose for this group of patients to achieve the Cmin observed in adults who receive 300/100 mg, the ATV Cmax will be higher than the observed Cmax for ATV/RTV 300/100 mg in adult patients. Therefore, **we don't have enough data to suggest an ATV/RTV dose for experienced pediatric patients who weigh less than 25 kg.**

Figure 6: ATV exposures vs. weight for Group 7 at accepted dose 205 mg/m^2 using confirmatory data





Adult Patient ATV/RTV 300/100 mg

The applicant proposes the body weight based dosing regimens which are similar to the doses received in Group 7 with ATV dose of 205 mg/m^2 + RTV, as follows.

Table 2.2.4B: Dosing Table for Atazanavir Capsules with Ritonavir

Body Weight (kg)	Body Weight (lbs)	Approximate Corresponding BSA (m^2)	Dose of Atazanavir (mg)[a]	Dose of Ritonavir (mg)
15 to < 20	33 to < 44	0.65-0.75	150	64
20 to < 25	44 to < 55	0.76-0.88	150	80
25 to < 32	55 to < 70	0.89-1.09	200	100[b]
32 to <39	70 to < 86	1.1-1.34	250	100[b]
≥ 39	≥ 86	≥ 1.35	300	100[b]

[a] Doses of REYATAZ can be achieved using a combination of commercially available dose strengths

[b] capsule or liquid

In group 7, most of the subjects who took ATV 205 mg/m^2 and RTV received the proposed dose, except the dose of ritonavir for children with body weight of 15 to <20 kg was about 72 mg. In addition, one subject with weight 33 kg took 200/100 mg instead of 250/100 mg ATV/RTV in the study, and one subject with weight 73 kg took 400/100 mg instead of ATV/RTV 300/100 mg. These two subjects are identified by red squares in Figure 6. As

indicated previously, **we don't have enough data to suggest a dose for experienced pediatric patients who weigh less than 25 kg.** However, because the Cmin for pediatric subjects who weigh 15 - 25 kg at ATV 205 mg/m^2 +RTV is higher than the Cmin observed for adults ATV 400 mg (recommended dose for treatment naïve adult patients), **the proposed doses** (with change of RTV dose for 15 to 20 kg to 72 mg) **are acceptable for treatment naive patients who weigh 15 - 25 kg.** For simplicity, we combine original proposed two weight groups 15 to 20 kg and 20 to 25 kg, into one group with RTV of 80 mg. The slight increase of RTV in patients with weight of 15 to 20 kg is not expected to change ATV exposures significantly.

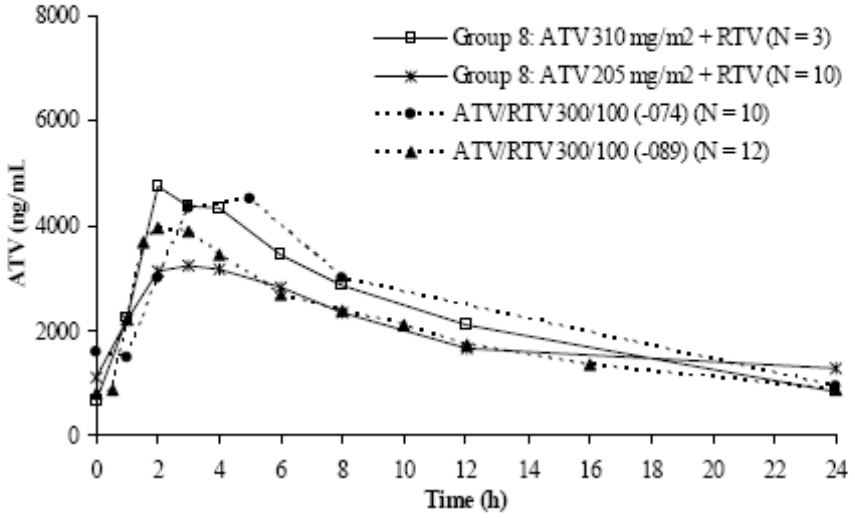
In weight group 25 -39 kg, only one subject (out of 8) received less than the proposed dose (200 mg instead of 250 mg in a subject who weighed 33 kg). The proposed dose provides adequate exposure as compared to HIV+ adults with ATV/RTV 300/100 mg QD as shown in the following table. **The proposed dose is acceptable for subjects who weigh 25 - 39 kg.**

Pharmacokinetic Parameter (for subjects with weight 25-39 kg)	Group 7 (observed) 205 mg/m^2	300/100 mg QD in HIV+ Adults Study 074	300/100 mg QD in HIV+ Adults Study 089
AUC(TAU) (µg•h/mL) n Geometric Mean(CV%) Median [Range]	 8 53.1 (10.6) 49.5 [43.7-82.5]	 10 46.1 (66) 47.7 [23.1-142]	 12 44.2 (34) 43.4 [26.1-83.2]
Cmin (ng/mL) n Geometric Mean CV%) Median [Range]	 8 784(20.3) 815 [194-1708]	 10 636 (97) 532 [158-3081]	 12 709 (60) 858 [184-2064]
Cmax (ng/mL) n Geometric Mean CV%) Median [Range]	 8 5193 (12.0) 5032 [1007-7678]	 10 4422 (58) 4967 [1694-9950]	 12 4427 (28) 4757 [2426-6792]

As shown in Figure 6, for the 3 subjects age 6-13 who weigh more than 39 kg in Group 7, the Cmin, AUC and Cmax are in the range of what have been observed for adult patients with ATV/RTV 300/100 mg, but mean AUC is relatively low as compared to AUC observed for adult patients with ATV/RTV 300/100 mg.

The mean ATV concentration-time profiles from Group 8 (confirmatory data) are presented in Figure 9.2.1D.

Figure 9.2.1D: Mean Plasma Concentration-Time Profiles for Atazanavir in Group 8 vs. Historical Data for ATV/RTV 300/100 QD in ARV-naive (-089) and ARV-experienced (-074) HIV+ Adults



Summary statistics for PK parameters from dosing cohorts within Group 8 (confirmatory data) are presented with ATV/RTV 300/100 mg QD historical exposures in HIV-infected adult subjects in Table 9.2.1D.

Table 9.2.1D: Summary Statistics for ATV Pharmacokinetic Parameters in Group 8 (ATV capsule + RTV, 13yr to 21yr) vs ATV/RTV 300/100 QD in ARV-naive and ARV-experienced HIV+ Adults

Pharmacokinetic Parameter	Dosing Cohort		300/100 mg QD in HIV+ Adults[a]	300/100 mg QD in HIV+ Adults[b]
	310 mg/m^2 N = 3[c]	205 mg/m^2 N = 10[d]	N = 10	N = 12
AUC(TAU) (µg•h/mL) - Geometric Mean (CV%)	55.0 (11)	44.9 (34)	46.1 (66)	44.2 (34)
Median	51.8	41.2	47.7	43.4
[Range]	[51.5-62.4]	[26.2-77.4]	[23.1-142]	[26.1-83.2]
Cmax (ng/mL) - Geometric Mean (CV%)	5566 (32)	3711 (46)	4422 (58)	4427 (28)
Median	4725	4257	4967	4757
[Range]	[4662-7829]	[1614-6821]	[1694-9950]	[2426-6792]
Cmin (ng/mL) - Geometric Mean (CV%)	791 (36)	1090 (60)	636 (97)	709 (60)
Median	721	1015	532	858
[Range]	[595-1152]	[409-2763]	[158-3081]	[184-2064]
Doses with RTV[e] (mg) Median	500	400[f]		
[Range]	[400-600]	[250-500]	All 300	All 300

[a] AI424074

[b] AI424089

[c] Two subjects >18 years of age excluded, see Appendix 8.2.1J for N = 5

[d] Four subjects > 18 years of age excluded, see Appendix 8.2.1J for N = 14

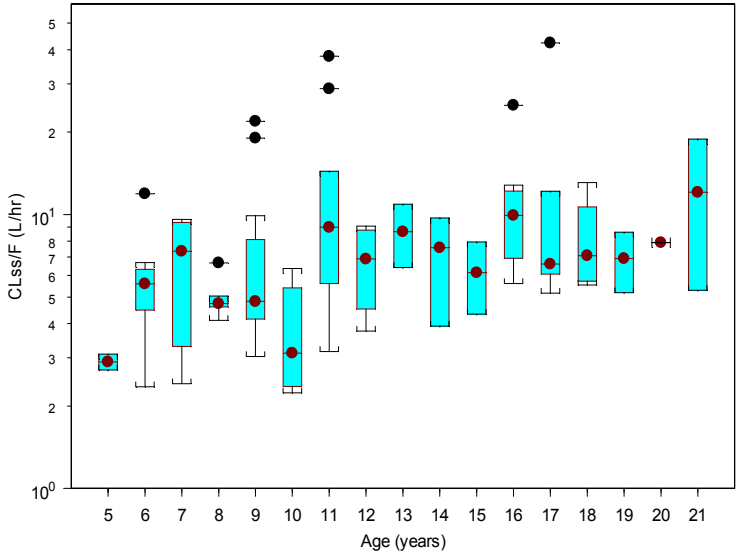
[e] RTV dose was 100 mg/m^2 up to a maximum of 100 mg

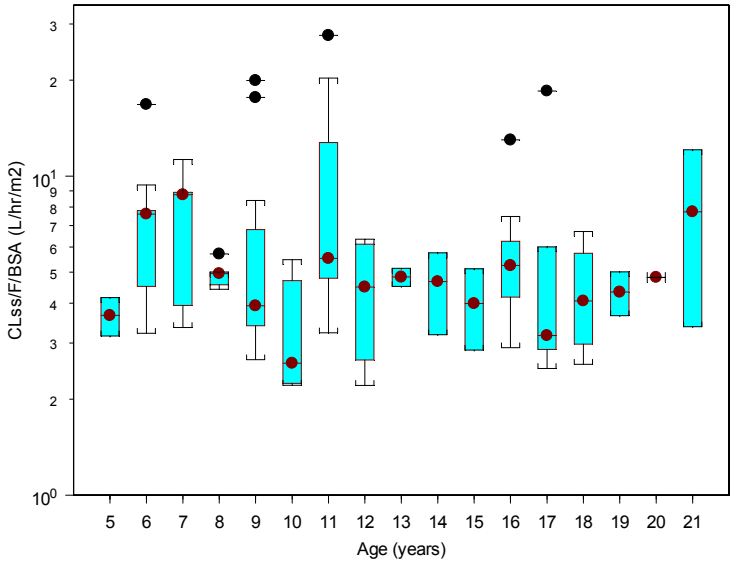
[f] 6 of 10 subjects received doses > 300 mg ATV with RTV

Similar to Group 7, the PK from the first 5 subjects in the initial dosing cohort of 310 mg/m^2 in Group 8 did not meet the PK criteria set forth in the protocol because AUC were higher than allowed per protocol targets (median AUC> 60 µg•h/mL, including 2 subjects > 18 years of age (the data are not included in Table 9.2.1D)). The target dose for Group 8 was reduced to 205 mg/m^2 and this dose met the protocol-specified PK criteria. In general, the ATV exposures at 205 mg/m^2 with RTV 100 mg/m^2 (up to a maximum of 100 mg) are comparable to those observed in adults receiving ATV 300 mg QD with 100 mg RTV QD. However, it should be noted that 6 of 10 subjects received a dose in excess of the currently recommended ATV adult dose of 300 mg with RTV 100 mg in ARV-experienced subjects and some subjects in this group had a BSA ≥ 2 m^2.

To determine the trend of ATV clearance change with age in the presence of RTV, analyses including all the data from Groups 7 and 8 (confirmatory +non-confirmatory, Figure 7) and confirmatory data from Groups 7 and 8 (Figure 8) are performed.

Figure 7: Clearance vs age for Groups 7 and 8 (ATV capsule/RTV) using combined confirmatory and non-confirmatory Data





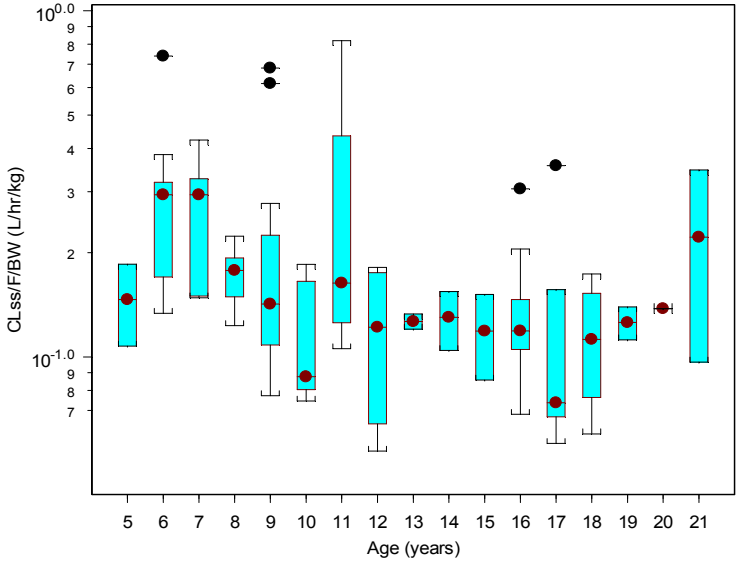
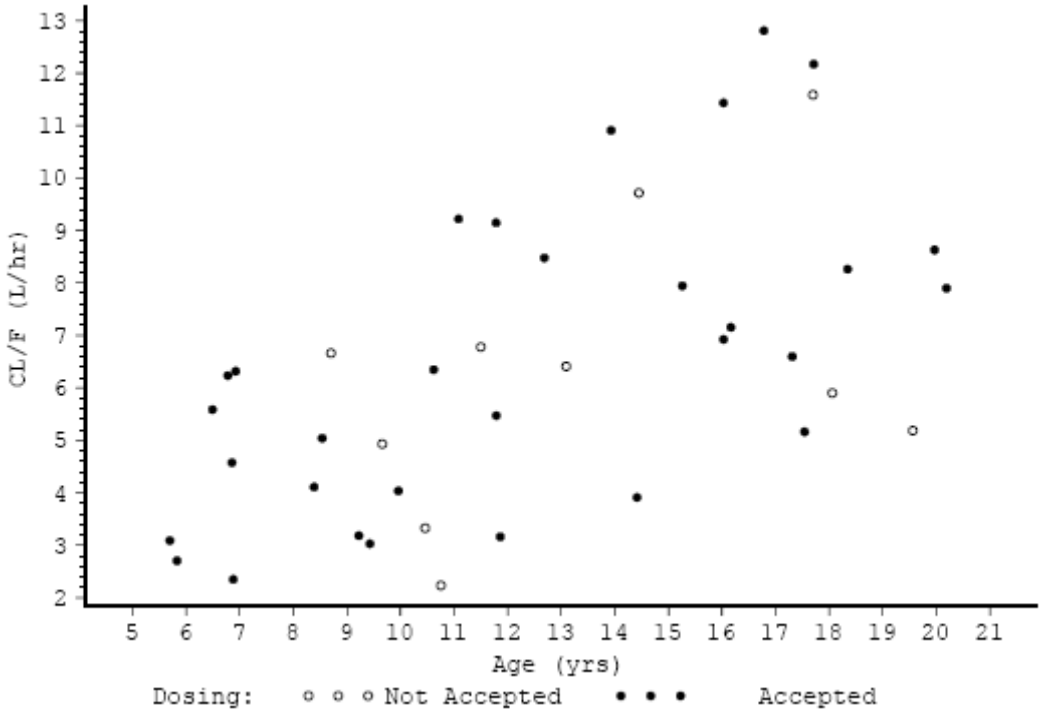


Figure 8: ATV clearance vs. age for ATV/RTV regimens (confirmatory data)



The data show that there is a slight trend of increasing CL/F as age increase, but there is notable variability (especially for children younger than 13 years old) and considerable overlap among different ages. When CL/F is corrected for body weight, there is a slight trend toward lower clearance with increasing age. CL/F corrected for BSA is more constant across the age range.

The reviewer tried to determine dose proportionality for ATV in presence of RTV using data from Groups 7 and 8. However, because clearance slightly increases with age and different levels of RTV were administered, the dose proportionality for ATV in presence of RTV can not be determined in children. Therefore, the dose proportionality data from adult healthy subjects are used in ATV exposure estimation at ATV/RTV 300/100 mg. In adult healthy subjects who took RTV 100 mg with ATV, ATV exposures increase more than dose proportionally at doses below 300 mg (linearity factor 1.67), and are proximately dose proportional above 300 mg.

For subjects 13 to less than 18 years old, all subjects except 1 (weight 37.5 kg) have weight above 39 kg. Although with 300/100 mg QD, the AUC and Cmax for pediatric subjects with weight above 39 kg are lower than observed for adults with ATV/RTV 300/100 mg, Cmin is higher than observed for adults with ATV/RTV 300/100 mg. Therefore for pediatric patients with weights above 39 kg, ATV/RTV 300/100 mg can be used. Because the results for pediatric subjects 6 -13 years of age at least 39 kg are similar to the values for subjects 13 to less than 18 years of age, the dose recommendation for weights above 39 kg are appropriate for the ages between 6 and less than 18 years old.

Table 2.2.4A: Summary Statistics for ATV Pharmacokinetic Parameters in Group 8 Observed at 205 mg/m^2 and Estimated for ATV/RTV 300/100 mg QD vs ATV/RTV 300/100 mg QD in HIV+ Adults

Pharmacokinetic Parameter	Observed	Estimated	300/100 mg QD in HIV+ Adults	300/100 mg QD in HIV+ Adults
	Group 8 205 mg/m^2	Group 8 300/100 mg QD		
	N = 10	N = 10	N = 10	N = 12
AUC(TAU) (µg•h/mL) - Geometric Mean (CV%) [Range]	44.9 (34) [26.2-77.4]	39.7 (59) [24.0-112]	46.1 (66) 47.7 [23.1-142]	44.2 (34) 43.4 [26.1-83.2]
Cmax (ng/mL) - Geometric Mean (CV%) [Range]	3711 (46) [1614-6821]	3279 (59) [1242-8458]	4422 (58) 4967 [1694-9950]	4427 (28) 4757 [2426-6792]
Cmin (ng/mL) - Geometric Mean (CV%) [Range]	1090 (60) [409-2763]	978 (65) [409-2566]	636 (97) 532 [158-3081]	709 (60) 858 [184-2064]
Doses with RTV (mg) Median [Range]	400 [250-500]	All 300	All 300	All 300

* Adult data are from Studies AI424074 and Study AI424089

Conclusion:

- The recommended dosage of atazanavir for pediatric patients (6 to less than 18 years of age) is based on body weight and should not exceed the recommended adult dose.
- Atazanavir Capsules must be taken with food.
- The data are insufficient to recommend dosing of atazanavir for any of the following: (1) patients less than 6 years of age, (2) without ritonavir in patients less than 13 years of age, and (3) treatment-experienced pediatric patients with body weight less than 25 kg.
- *Therapy-Naive Pediatric Patients:*
    - The recommended dosage of atazanavir with ritonavir in treatment-naive patients at least 6 years of age is shown in Table 1.
    - For treatment-naive patients at least 13 years of age and at least 39 kg, who are unable to tolerate ritonavir, the recommended dose is atazanavir 400 mg (without ritonavir) once daily with food.

Table 1: Dosage for Treatment-Naive Pediatric Patients (6 to less than 18 years of age) for REYATAZ Capsules with ritonavir

Body Weight (kg)	(lbs)	atazanavir dose[a,b] (mg)	ritonavir dose (mg)
15 to less than 25	33 to less than 55	150	80[b]
25 to less than 32	55 to less than 70	200	100[b]
32 to less than 39	70 to less than 86	250	100[b]
at least 39	at least 86	300	100[b]

[a] The recommended dosage of REYATAZ can be achieved using a combination of commercially available capsule strengths.
[b] Ritonavir liquid.
[c] Ritonavir capsule or liquid.

- *Therapy-Experienced Pediatric Patients:*
    - The recommended dosage of REYATAZ with ritonavir in treatment-experienced patients at least 6 years of age is shown in Table 2.

Table 2: Dosage for Treatment-Experienced Pediatric Patients (6 to less than 18 years of age) for REYATAZ Capsules with ritonavir

Body Weight (kg)	(lbs)	atazanavir dose[a,b] (mg)	ritonavir dose (mg)
25 to less than 32	55 to less than 70	200	100[b]
32 to less than 39	70 to less than 86	250	100[b]
at least 39	at least 86	300	100[b]

[a] The recommended dosage of atazanavir can be achieved using a combination of commercially available capsule strengths.
[b] Ritonavir capsule or liquid.

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Mark Seaton
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