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Atazanavir and Atazanavir/Ritonavir Pharmacokinetics in HIV-Infected Infants, Children, and Adolescents

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Abstract

Objective—To describe the pharmacokinetics of atazanavir (ATV) and ritonavir-boosted ATV/r in children ages 91 days to 21 years.

Design—Phase I/II, open label, multicenter study of once daily ATV and ATV/r as part of combination antiretroviral treatment in HIV-infected treatment experienced and naïve children.

Setting—Sites in the United States and South Africa.

Subjects—195 children enrolled; 172 had evaluable ATV pharmacokinetics on day seven.

Intervention—Children were entered in age, dose and formulation (powder or capsule) cohorts. Intensive pharmacokinetic sampling occurred seven days after starting ATV. ATV doses were increased or decreased if the 24-hour area under the concentration time curves (AUC_{0-24hr}) were <30 or >90 mcg*hr/mL, respectively.

Main outcomes—Cohorts satisfied protocol-defined pharmacokinetic criteria if the median ATV $AUC_{0-24hr} \leq 60$ mcg*hr/mL, and AUC_{0-24hr} and ATV concentrations 24 hours post-dose (C24) were >30 mcg*hr/mL and ≥ 60 ng/mL, respectively, in $\geq 80\%$ of children, with no individual $AUC_{0-24hr} < 15$ mcg*hr/mL.

Results—Unboosted ATV capsules satisfied pharmacokinetic criteria at a dose of 520 mg/m² for those >2 to ≤ 13 years and 620 mg/m² for those >13 to ≤ 21 years. ATV/r capsules satisfied criteria at a dose of 205 mg/m² for those >2 to ≤ 21 years. ATV/r powder satisfied criteria at a

dose of 310 mg/m² for those >2 to ≤ 13 years, but pharmacokinetics in those ≤ 2 years were highly variable.

Conclusions—Body surface area-determined doses of ATV capsules and ATV/r powder and capsules provide ATV exposures in children >2 years that approximate values in adults receiving ATV/r.

Keywords

atazanavir; pharmacokinetics; children; pediatrics; protease inhibitor; HIV

Introduction

In 2009, 2.5 million children world-wide were estimated to be living with human immunodeficiency virus (HIV) infection, 90% of whom reside in Africa.[1] While HIV-related deaths in children and the incidence of mother to child transmission of HIV have declined globally, rates are still unacceptably high in some resource-limited countries.[2, 3] Additionally, many children infected with HIV at birth in high-resource countries have aged into adolescence and adulthood. Many of these children and young adults are highly treatment-experienced and developing long-term toxicities associated with current antiretroviral drugs and are therefore in need of new treatment options.[4] Unfortunately, not all of the antiretroviral agents deemed safe and efficacious in HIV-infected adults are approved for use in children or available in pediatric formulations. Thus, additional antiretroviral options and formulations are needed for use in children.

Atazanavir (ATV), an azapeptide HIV protease inhibitor, is administered once daily as part of combination antiretroviral therapy. The Food and Drug Administration-approved dosing in adults is 300mg ATV once daily when administered with ritonavir as a pharmacokinetic enhancer, and 400mg ATV once daily in the absence of ritonavir. ATV and ATV boosted with ritonavir (ATV/r) /r have demonstrated excellent virologic efficacy with favorable tolerability in several pivotal clinical trials in adults.[5–8] Relative to other protease inhibitors, ATV causes fewer perturbations in lipids and less gastrointestinal intolerance. The most common toxicity of ATV is asymptomatic accumulation of indirect bilirubin due to inhibition of uridine glucuronosyl transferase 1A1, which results in cosmetic effects (e.g., jaundice, scleral icterus) in 5–9% of adult patients.

ATV is primarily metabolized by cytochrome P450 (CYP450) 3A and also inhibits this hepatic enzyme. ATV concentrations are increased with food, and thus the drug should be administered with a meal. ATV absorption is pH-dependent and concomitant administration of gastric acid modifiers should be avoided.

International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) P1020A was a Phase I/II open-label study to evaluate the safety and pharmacokinetics, and determine the appropriate doses of ATV and ATV/r as part of combination antiretroviral therapy in antiretroviral treatment-naïve and experienced HIV-infected infants, children, and adolescents from the United States and South Africa. Two formulations of ATV, capsules and a dispersible orange-vanilla flavored powder, were evaluated. This manuscript presents the pharmacokinetic findings of the study.

Methods

Patients

HIV-infected treatment naïve and treatment experienced children 91 days to 21 years of age with plasma HIV-1 RNA levels > 5,000 copies/mL were eligible to receive ATV or ATV/r plus two nucleoside reverse transcriptase inhibitors (NRTIs) (excluding abacavir and tenofovir disoproxil fumarate). Baseline genotypic resistance testing was performed on all ARV experienced subjects and genotypic susceptibility to the NRTIs in their regimen confirmed. Subjects previously treated with more than one HIV protease inhibitor had a baseline viral phenotypic assay performed; those with less than 10-fold loss of sensitivity to ATV remained eligible. Subjects who were pregnant or breastfeeding, had hepatitis, any clinical or laboratory event at baseline greater than grade 2 per the 1994 Division of AIDS (DAIDS) Table for Grading the Severity of Pediatric (> 3 months) Adverse Experiences[9], cardiac abnormalities, or had received intravenous pentamidine for prophylaxis or treatment of *Pneumocystis jiroveci* within 3 months of study entry were ineligible. Female participants of reproductive potential were required to use at least two forms of contraception and males engaging in sexual intercourse that could result in pregnancy were required to use condoms. Subjects receiving systemic cytotoxic chemotherapy, acetaminophen exceeding seven days, anabolic steroids, megestrol acetate, interleukins, interferons, thalidomide, verapamil, intravenous pentamidine, and growth hormone were excluded. Consumption of grapefruit juice was prohibited.

Study Design

IMPAACT P1020A was a Phase I/II, open label, multicenter study of ATV and ATV/r as part of combination antiretroviral treatment of HIV-infected infants, children, and adolescents. Subjects from the United States and South Africa were enrolled. Unboosted ATV and ATV/r were evaluated in several age and formulation groups. These groups are shown in Table 1. Group assignment was based on age and the formulation and dose being evaluated at the time of enrollment. The study was originally designed to evaluate doses in at least eight groups, but a ninth group was added to define better the pharmacokinetics and safety of ATV/r in infants ages 3–6 months (group 5A, table 1).

All subjects underwent 24 hour intensive pharmacokinetic sampling seven days after starting treatment with ATV or ATV/r, after 56 weeks of treatment, and 14 days after any pharmacokinetic-guided dose adjustment. For these intensive pharmacokinetic visits, subjects were admitted approximately 24 hours after their previous ATV dose. A light (non-standardized) meal was consumed. A pre-dose sample was obtained 15–30 minutes following the meal. Within 30 minutes of the pre-dose sample, clinic personnel observed study drug(s) administration. Whole blood for quantification of ATV (and ritonavir in those subjects taking ritonavir) in plasma was obtained at 1, 2, 3, 4, 6, 8, and 12 hours post-dose and the following day at 24-hours post-dose.

Study Drug(s)

Atazanavir—ATV was supplied as 50mg, 100mg, and 200mg capsules and powder containing 50mg of ATV in a 2.5 mL scoop. The ATV powder also contained sucrose, aspartame, and an orange vanilla flavor. The powder could be mixed with apple sauce, milk, yogurt, water, or formula within three hours of dosing. There were limited (unpublished) data on ATV powder bioavailability relative to the capsules in seven adults at the time of study initiation.

Ritonavir—Commercially available ritonavir liquid and capsules were used. Subjects with a body surface area less than 0.66 m² took ritonavir liquid and those weighing at least 0.66

m² could take the liquid or capsule formulation. The orange 80 mg/mL liquid could be mixed with chocolate milk, pudding, custards or nutritional supplements within an hour of dosing.

Bioanalyses

Blood for determination of ATV and ritonavir was processed by centrifugation with the plasma stored (−70°C) within 30 minutes of collection. ATV and ritonavir plasma concentrations were determined using a simultaneous, validated HPLC-UV method. Briefly, after addition of internal standard, a liquid-liquid extraction procedure with t-butylmethylether at basic pH was used to prepare the samples. The chromatographic separation of the compounds and the internal standard was accomplished on a Waters YMC HPLC, 100 × 4.6 mm, reversed-phase octyl column with a 3 micron particle size (Waters Corp., Milford MA). The mobile phase consisted of 54.7% 20 mM acetate buffer / 45.3% acetonitrile, pH 4.9 with an isocratic flow rate of 1 mL/min. Detection and quantification of the drugs was at 212 nm. The assay was linear over the range of 20–20,000 ng/mL with a minimum limit of quantification (LOQ) of 20 ng/mL using 0.2 mL of human plasma. The standard curves generated had coefficients of determination (r²) greater than 0.9988. Precision and accuracy were measured in quality controls at 75, 750, and 7500 ng/mL and all accuracies were within 15% of the nominal concentration with percent relative standard deviation of less than 10%.

Pharmacokinetic Targets

In adults, the geometric mean (CV%) ATV AUC_{0–24hr} and concentration 24 hours post-dose (C24) are 14,874 (91) ng*hr/mL and 120 (109) ng/mL, respectively following a 400mg unboosted ATV dose and 46,073 (66) ng*hr/mL and 636 (97) ng/mL, respectively following a 300mg ATV dose with 100mg of ritonavir.[10] For this study, the cohort AUC_{0–24hr} target was 45,000 ng*hr/mL and 15,000 ng*hr/mL was considered the minimum acceptable AUC_{0–24hr}. Due to the faster elimination half-lives observed in young children relative to adults taking protease inhibitors, an AUC_{0–24hr} of 15,000 ng*hr/mL was expected to correspond to a C24 of 60 ng/mL (the in vitro protein-binding adjusted 95% inhibitory concentration[11]).

Cohort—Allometric scaling indicated an ATV dose of 310 mg/m² should provide average exposures of 45,000 ng*hr/mL for a cohort. Thus, all groups were started at this dose. To establish an acceptable ATV or ATV/r dose for a given age range, 10 patients had to meet the *a priori* protocol-defined safety and pharmacokinetic criteria. The pharmacokinetic cohort dose acceptance criteria were: ATV AUC_{0–24hr} ≥ 30,000 ng*hr/mL and C24 ≥ 60 ng/mL in at least 80% of patients, no AUC_{0–24hr} < 15,000 ng*hr/mL, and median AUC_{0–24hr} ≤ 60,000 ng*hr/mL. Safety criteria were (1) no life threatening toxicities, (2) one or fewer patients with grade 3 or 4 toxicities (not including bilirubin) attributable to study treatment, and (3) two or fewer patients with total bilirubin values greater than 5.1 times the upper limit of normal. Cohort dose finding proceeded with the initial enrollment of five subjects in a cohort. If pharmacokinetic and safety criteria were not met, the cohort ATV starting dose was modified, either increased to 415, 520 then 620 mg/m² or decreased to 205 mg/m², and five new subjects were enrolled. If pharmacokinetic and safety criteria were met, five additional patients were enrolled at that dose, and pharmacokinetics re-evaluated on the first 10 study subjects treated at this dose.

Individual—Each subject's AUC_{0–24hr} was determined and reported within two weeks of an intensive pharmacokinetic visit. Subjects with AUC_{0–24hr} < 30,000 ng*hr/mL had their ATV dose increased, and those with AUC_{0–24hr} > 90,000 ng*hr/mL underwent ATV dose decreases. Doses were adjusted to target an individual AUC_{0–24hr} of 45,000 ng*hr/mL (the

cohort AUC_{0-24hr} target), but no doses were increased by an amount greater than 250mg at one time in any individual subject. Doses were decreased in the event of a grade 3 or higher toxicity per the DAIDS tables and/or total bilirubin values greater than or equal to 5.1 times the upper limit of normal. Subjects with total bilirubin values greater than 10 times the upper limit of normal were discontinued from study. Repeat 24-hour pharmacokinetic studies were performed 14 days after these dose adjustments to confirm exposures. Subjects with a $\geq 25\%$ increase in weight also underwent dose increases.

Pharmacokinetic Assessments

Pharmacokinetics were determined by non-compartmental analysis and AUC_{0-24hr} calculated by the linear trapezoidal method. Maximum concentration (C_{max}) and C_{24} were determined visually, except in the instance when the patient re-dosed the study medication prior to the 24 hour blood draw or the 24 hour level was not obtained, in which case the C_{24} was calculated from the elimination rate (k_e) and the last measured concentration. Apparent oral clearance (CL/F) was calculated as ATV dose divided by AUC_{0-24hr} .

Statistical Methods

Descriptive statistics were used to summarize demographic and pharmacokinetic data in the individual dosing cohorts. Univariate correlations between age, BSA, and weight versus ATV AUC_{0-24hr} at day seven in the dosing cohorts that satisfied the protocol-defined pharmacokinetic criteria were evaluated using the Pearson correlation coefficient. The following statistical tests were used to evaluate whether the mean ATV AUC_{0-24hr} in the dosing cohorts, which satisfied the protocol-defined pharmacokinetic criteria varied by gender, formulation, country, ritonavir-boosting (Univariate t-test); or race (ANOVA-F Test). P-values less than 0.05 were considered significant. SAS version 9 (Cary, NC) was used for data analyses.

Results

Subjects

One hundred ninety five HIV-infected infants, children and adolescents enrolled and 172 (51% female) had evaluable pharmacokinetic data at day seven. Of the 23 participants without evaluable pharmacokinetic data: 10, had problems with adherence; four, had dosing errors; sample integrity was compromised for three patients during shipment from South Africa; two subjects were not sampled at day seven; one, did not consent; one, inadvertently enrolled; one, had problems with intravenous access; and one, discontinued due to nausea and vomiting prior to day seven. Sixty two percent of participants received ATV capsules and 38% received ATV powder. Seventy eight participants (45%) were naïve to antiretroviral treatment. The median (range) age, weight, and body surface area at the day seven intensive pharmacokinetic visit were 8.7 years (0.3–21.3), 26.6 kg (4.3–121.9), and 0.98 m^2 (0.27–2.32), respectively. One hundred ten (64%) and 62 (36%) participants were from the United States and South Africa, respectively. Sixty five percent were black, 23% were white, and 29% of participants were of Hispanic ethnicity regardless of race. The median (range) HIV viral load, CD4 count, and CD4 percentage at entry were 4.7 log_{10} copies/mL (3.3–6.5), 459 cells/mm³ (0–3060), and 19% (0–46), respectively.

Pharmacokinetics

Five dosing cohorts (two unboosted and three ritonavir-boosted) satisfied the protocol-defined safety and pharmacokinetic criteria (Table 2). Two ritonavir-boosted dosing cohorts, Groups 5 and 5A, which enrolled children 3 months–2 years, did not satisfy the protocol-defined pharmacokinetic criteria. There was considerable intersubject variability in systemic

exposures in this age group, such that a dose escalation to 415 mg/m² may have resulted in ATV exposures in some children of greater than 90,000 ng*hr/mL. Thus, a further dose increase in Groups 5 and 5A was not attempted; however, the parameters for these groups are included in Table 2 and in statistical determinations of predictors of ATV exposures.

The dosing cohorts that failed to meet the protocol-defined pharmacokinetic criteria are shown in Table 3.

Predictors of Day Seven ATV AUC_{0–24hr}—Dosing cohorts that satisfied protocol-defined pharmacokinetic criteria were used to examine predictors of ATV exposures. Age ($r=0.15$, $p=0.10$), BSA ($r=0.14$, $p=0.12$), and weight ($r=0.12$, $p=0.18$) were not significantly correlated with ATV AUC_{0–24hr}. Day seven mean ATV AUC_{0–24hr} was significantly ($p=0.04$) lower in South African children relative to children in the United States. The mean ($\pm$ SD) ATV AUC_{0–24hr} was 53,432 ng*hr/mL (23,372) in United States children vs. 44,313 ng*hr/mL (25,383) in South African children. Table 4 shows ATV pharmacokinetics by country for the individual dosing cohorts. Race ($p=0.10$), gender ($p=0.53$), formulation ($p=0.77$), and ritonavir-boosting ($p=0.81$) were not significantly correlated with ATV AUC_{0–24hr}.

Discussion

In this study of ATV pharmacokinetics administered without or with ritonavir, we identified doses for infants, children and adolescents that met protocol-defined pharmacokinetic criteria. An unboosted ATV dose (capsule formulation) of 520 mg/m² met the study pharmacokinetic criteria for children > 2 to $\leq$ 13 years and a dose of 620 mg/m² met the criteria for adolescents > 13 to $\leq$ 21 years. A ritonavir-boosted ATV dose (powder formulation) of 310 mg/m² met the criteria for children > 2 to $\leq$ 13 years and a dose (capsule formulation) of 205 mg/m² met the criteria for ages > 2 to $\leq$ 21 years. A ritonavir-boosted ATV dose of 310 mg/m² (powder formulation) in children ages 3 months–2 years achieved average ATV exposures that approximated, but did not meet protocol targets; there was greater variability in exposures among children in this age range. This study was unable to find an unboosted ATV dose with acceptable exposures in children ages 3 months to 13 years using ATV powder. Additional studies on the use of ATV powder are proceeding, using only ATV/r.

On average, ATV pharmacokinetics in the ritonavir-boosted and unboosted dosing cohorts of IMPAACT P1020A that satisfied protocol-defined pharmacokinetic criteria, approximated values for ATV in adults. Geometric mean (%CV) adult historic values for ATV AUC_{0–24hr}, C_{max}, and C₂₄ following a ritonavir-boosted dose of 300mg (176 mg/m²) are 44.2 mcg*hr/mL (34), 4427 ng/mL (28), and 709 ng/mL (60), respectively.[12] As illustrated in Figure 1a, ATV CL/F is faster in infants and children less than 12 years of age relative to adults.[10] This could be due to a number of physiologic factors including, but not limited to, decreased bioavailability, increased drug transporter expression or activity, and/or greater hepatic enzyme capacity or function in younger children. Unboosted ATV CL/F appears similar for children ages 6–13 years with historical data in adults; CL/F is faster, however, in adolescents 13–22 years (Figure 1b). As noted, we were not able to find a dose of unboosted ATV powder that satisfied our pharmacokinetic parameters for children between 3 months to 13 years. This likely arose because of a combination of factors including low bioavailability, fast clearance and wide intersubject variability in these pharmacokinetic characteristics.

Once a BSA-based dose was identified that satisfied protocol-defined pharmacokinetic criteria for the various age and formulation cohorts, day seven (steady-state) ATV exposures

were not predicted by or correlated with age, BSA, weight, formulation and ritonavir-boosting. There were also no racial or gender differences in exposures. However, there were significant differences in ATV exposures at day seven between American and South African children. This difference was driven primarily by the two groups on unboosted ATV (groups 3 and 4) and infants 3–6 months on ATV/r (5A). The South African children in these groups had faster BSA-adjusted ATV CL/F than the American children (Table 4). The reasons for faster CL/F in South African children are unclear. It may be a consequence of differences in type and amount of food consumed for the intensive pharmacokinetic visits (as meals were not standardized). *Helicobacter pylori* is more prevalent in South African children relative to the United States, which may give rise to poorer ATV absorption because of a higher gastric pH in South African children.[13] Finally, genetic differences in drug metabolizing enzyme or transporter expression or function between American and South African children could provide an explanation.

The unboosted ATV capsule doses, which satisfied protocol-defined pharmacokinetic criteria in these children, are higher than the FDA-approved unboosted ATV dose for adults (520 and 620 mg/m² vs. 235 mg/m²), and in general, C_{max} and C₂₄ were higher and lower, respectively compared with ATV/r cohorts. The data from this study provided the basis for the FDA-approved ritonavir-boosted ATV dosing regimen in children ages 6–18 years. However, the FDA-recommended doses are based on body weight rather than BSA. The approved dose is also capped at the adult ritonavir-boosted dose, 300mg once daily. There were 33 children ages 6–18 years in ritonavir-boosted dosing cohorts that passed our protocol-defined pharmacokinetic criteria (Groups 6, 7, and 8). We compared the starting doses of these 33 children in our study with the FDA-approved weight-based dose. Fourteen (42%) children would have received different starting doses of ATV when based on weight vs. BSA. Twelve of 14 (86%) would have received a lower dose based on body weight than they received in the study with the BSA-based dose. This may lead to differences in therapeutic outcomes in practice relative to those observed in this clinical trial.

There are limitations to this study that may impact generalizability. First, both abacavir and tenofovir disoproxil fumarate were excluded. ATV concentrations are reduced with concomitant tenofovir disoproxil fumarate administration; thus, if tenofovir disoproxil fumarate was coadministered with ATV (and ritonavir) in children, concentrations of ATV would be expected to be lower than those observed in this study.[14] Additionally, gastric acid modifiers were not exclusionary medications to participation in the study. However, only three children (all from the United States) were receiving gastric acid modifiers during the day seven intensive pharmacokinetic visits. Two of these children were in group 5.

This study demonstrated once daily BSA-determined doses using the capsule formulation of ATV, when given with and without ritonavir, can provide ATV exposures in children that approximate concentrations in adults receiving ATV/r. Once daily unboosted ATV powder was unable to achieve protocol-defined pharmacokinetic targets. While the powder formulation of ATV when given with ritonavir met protocol-defined pharmacokinetic criteria for children ages 2–13 years, there was significant variability in exposures in those less than 2 years of age, driven primarily by lower exposures in South African infants. Additional studies are needed in this age group to determine if an appropriate ritonavir-boosted dose can be identified. Studies are also needed to elucidate the explanation for lower unboosted ATV exposures in South African children relative to American children. A manuscript describing the safety and efficacy of ATV and ATV/r in P1020A is forthcoming. An investigation of pharmacokinetic-dynamic relationships at the conclusion of the study may provide additional guidance for future studies of ATV dosing in children.

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J.J.K. and C.V.F. were protocol pharmacologists, R.M.R. was protocol chair, P.S. and T.F. were protocol statisticians, B.G. was the protocol data manager, G.A. was protocol vice-chair, L.M.M. and E.S. provided regulatory oversight for the study, S.S. was the pharmaceutical company representative, R.C.B. was involved in study design and pharmacokinetic analyses. All authors reviewed and edited this manuscript.

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Figure 1.

- a. Mean (SD) Ritonavir-Boosted ATV Apparent Oral Clearance (L/hr/m²) in Dosing Cohorts which Met Protocol-Defined ATV Pharmacokinetic Targets Relative to Historical Data in Adults
- b. Mean (SD) ATV Apparent Oral Clearance (L/hr/m²) in Dosing Cohorts which Met Protocol-Defined Pharmacokinetic Targets Relative to Historical Data in Adults (Unboosted ATV)

Table 1

Dosing Cohorts

Age	Unboosted ATV	ATV/r	Formulation
91 d to $\leq$ 2 yrs (5A: 91 d-6 mos)	Group 1	Group 5 (5A)	Powder
>2 yrs to $\leq$ 13 yrs	Group 2	Group 6	Powder
>2 yrs to $\leq$ 13 yrs	Group 3	Group 7	Capsules
>13 yrs to $\leq$ 21 yrs	Group 4	Group 8	Capsules

Table 2

Dosing Cohorts that Passed Protocol-Defined Pharmacokinetic and Safety Criteria. Data presented as medians (IQR).

Group	ATV Dose/m ²	Formulation	N	Age (yrs)	Weight (kg)	BSA (m ²)	Dose/m ²	Dose (mg)	CL/F (L/hr/m ²)	AUC (ng*hr/mL)	C _{max} (ng/mL)	C ₂₄ (ng/mL)
3	520	Capsules	20	8.1 (4)	24.1 (16.4)	0.89 (0.41)	509 (42)	475 (200)	12.8 (10.55)	40653 (24287)	6463 (3213)	173 (218)
4	620	Capsules	21	14.6 (2.9)	52 (18.8)	1.54 (0.29)	620 (38)	900 (200)	11.4 (6.7)	51781 (25659)	7006 (3399)	510 (516)
5*	310	Powder	17	1.3 (0.9)	8.5 (1.4)	0.42 (0.06)	335 (82)	150 (50)	7.9 (6.9)	44243 (41664)	6501 (5865)	482 (433)
5A*	310	Powder	11	0.4 (0.1)	6.2 (0.5)	0.32 (0.02)	309 (26)	100 (0)	8.3 (16.8)	38928 (42778)	4952 (4706)	596 (672)
6*	310	Powder	21	4.5 (1.8)	15 (4.1)	0.64 (0.13)	312 (35)	200 (0)	5.3 (4.4)	52199 (37148)	5593 (3397)	947 (759)
7*	205	Capsules	21	8.8 (4.2)	28.8 (12.5)	0.98 (0.32)	206 (23)	200 (100)	4.7 (2)	45680 (20028)	5013 (2301)	575 (469)
8*	205	Capsules	14	17.1 (2.4)	62.3 (34.9)	1.73 (0.55)	195 (11)	350 (100)	4.8 (1.7)	42835 (18910)	4095 (2616)	885 (799)

* Ritonavir-boosted ATV

Table 3

Dosing Cohorts that Failed to Meet Protocol-Defined Pharmacokinetic Targets

Group #	N	ATV Dose (mg/m ²)	Median Dose (mg)	Median Dose (mg/m ²)	Median AUC _{0-24hr} (ng*hr/mL)	# subjects AUC _{0-24hr} < 15	# subjects AUC _{0-24hr} > 30	# subjects AUC _{0-24hr} > 90	Median C ₂₄ (ng/mL)	C ₂₄ ≥ 60 (ng/mL)
1	5	310	100	329	6354	3	1	0	27	2
1	2	620	300	610	11208	1	0	0	21	0
2	5	310	200	314	17182	1	2	0	293	5
2	5	620	500	589	37314	1	4	0	167	4
3	5	310	300	309	33070	0	3	0	238	5
3	5	415	400	399	30645	1	3	0	165	4
4	5	310	400	236	15023	2	0	0	73	3
4	5	520	600	369	28634	2	2	0	194	3
7*	5	310	400	296	73755	0	5	2	2071	5
8*	5	310	500	286	62403	0	5	0	1108	5

* Ritonavir-boosted ATV

Table 4

Atazanavir Pharmacokinetics by Country. Data presented as medians (IQR).

Group	ATV Dose/m ²	Formulation	Country	N	Age (yrs)	Weight (kg)	BSA (m ²)	Dose/m ²	Dose (mg)	CL/F (L/hr/m ²)	AUC (ng*hr/mL)	C _{max} (ng/mL)	C ₂₄ (ng/mL)
3	520	Capsules	US	10	10.2 (4.2)	35.2 (18)	1.18 (0.38)	511 (42)	600 (100)	12.5 (4.6)	42315 (21713)	7158 (2470)	317 (408)
			SA	10	6.9 (2.3)	20 (3.1)	0.8 (0.13)	505 (36)	400 (0)	21.1 (18)	25498 (27474)	5414 (4579)	123 (188)
4	620	Capsules	US	11	14.6 (2.9)	55.7 (11.1)	1.58 (0.24)	600 (122)	900 (200)	8.9 (7.1)	55287 (49174)	6808 (7300)	644 (715)
			SA	10	14.6 (3.5)	40.2 (26)	1.28 (0.51)	620 (17)	800 (350)	12.9 (5.9)	47325 (24337)	7573 (2717)	259 (517)
5*	310	Powder	US	6	1 (0.8)	8.7 (1.6)	0.43 (0.07)	328 (78)	150 (50)	9.2 (9.2)	40717 (64507)	5413 (9572)	425 (661)
			SA	11	1.6 (0.8)	8.5 (2.1)	0.42 (0.07)	344 (84)	150 (50)	7.9 (5.9)	44243 (41664)	7374 (5865)	482 (433)
5A*	310	Powder	US	3	0.4 (0.1)	6.2 (0.5)	0.32 (0.02)	311 (23)	100 (0)	7.4 (3.8)	40919 (30625)	6071 (2319)	648 (811)
			SA	8	0.5 (0.1)	6.3 (0.9)	0.33 (0.03)	307 (27)	100 (0)	18.7 (22.05)	16296 (40331)	1648 (3920)	464 (653)
6*	310	Powder	US	11	4.3 (4.6)	16.3 (8.2)	0.67 (0.24)	293 (39)	200 (50)	5.3 (2.6)	52199 (30488)	5593 (3267)	1134 (989)
			SA	10	4.7 (1.7)	14.2 (1.4)	0.61 (0.04)	328 (23)	200 (0)	6.5 (5.9)	55152 (47730)	5656 (5348)	729 (946)
7*	205	Capsules	US	10	10.3 (3.3)	34.1 (17.1)	1.15 (0.37)	212 (19)	250 (100)	4.6 (1.6)	46620 (13153)	5094 (2038)	821 (588)
			SA	11	6.9 (2.7)	21.3 (8.1)	0.82 (0.23)	203 (25)	150 (50)	4.9 (4.3)	45680 (35921)	5013 (3367)	389 (404)
8*	205	Capsules	US	12	17.1 (2.4)	72.7 (34.8)	1.85 (0.51)	199 (13)	375 (75)	4.9 (1.85)	41449 (22679)	3840 (2339)	888 (1083)
			SA	2	18.7 (5.3)	55.3 (1.0)	1.56 (0.02)	193 (1)	300 (0)	3.95 (1.1)	49992 (13342)	6374 (45)	710 (601)

* Ritonavir-boosted ATV