CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 206352
Submission Date: 12/02/2013
Brand Name: Reyataz®
Generic Name: Atazanavir sulfate
Formulation: Powder for Oral Use (50 mg packet)
Applicant: Bristol-Myers Squibb Company
Reviewer: Jenny H. Zheng, Ph.D.,
Team Leader: Shirley Seo, Ph.D.
OCP Division: DCP IV
OND Division: DAVP

Table of Contents

I. Executive Summary

Atazanavir is a protease inhibitor approved in a capsule dosage form (150 mg, 200 mg, 300 mg) for the treatment of HIV-1 infection in adults and pediatric patients ≥ 6 years of age in combination with other antiretrovirals. This NDA was submitted to provide pharmacokinetics, safety and limited efficacy data from Studies AI424397 and AI424451 to support of an indication for a new Powder for Oral Use (POU) formulation in pediatric patients who weigh 10 to <25 kg.

A. Recommendation

The Office of Clinical Pharmacology has reviewed the information submitted to NDA 206352. The data provided in this application support the atazanavir (ATV) dosing recommendations for the new POU formulation in HIV-infected pediatric patients who weigh 10 to <25 kg, as shown in Table 1.

Table 1: Dosage for Pediatric Patients (10 kg to less than 25 kg) for REYATAZ Powder with Ritonavir[a]

Body weight	REYATAZ dose	ritonavir[b] dose
10 kg to less than 15 kg	200 mg (4 packets)	80 mg
15 kg to less than 25 kg	250 mg (5 packets)	80 mg

[a] The REYATAZ and ritonavir dose should be taken together once daily with food.

[b] Ritonavir solution.

B. Phase IV Commitments:

None.

C. Summary of Clinical Pharmacology Findings

Atazanavir is currently approved in the in the US in capsule dosage forms (150 mg, 200 mg, 300 mg) for the treatment of HIV-1 infection in adults and pediatric patients ≥ 6 years of age in combination with other antiretrovirals. The recommended dosing regimen for adults is 300 mg ATV with 100 mg ritonavir (RTV) once daily (ATV/RTV 300/100) with food. For treatment-naïve adult patients, ATV 400 mg once daily can be used if patients are unable to tolerate RTV. The current recommended daily dosage of ATV capsules for pediatric patients (6 to less than 18 years of age) is based on body weight (Table 2) and should not exceed the recommended adult dosage.

Table 2: Dosage for Pediatric Patients (6 to less than 18 years of age) for REYATAZ Capsules with Ritonavir[a]

Body weight	REYATAZ dose	ritonavir dose
15 kg to less than 20 kg	150 mg	100 mg
20 kg to less than 40 kg	200 mg	100 mg
at least 40 kg	300 mg	100 mg

[a] The REYATAZ and ritonavir dose should be taken together once daily with food.

The pharmacokinetics, safety and limited efficacy were evaluated in Studies AI424397 and AI424451 to support the proposed ATV indication of a new POU formulation in pediatric patients who weigh 10 to < 25 kg.

Study AI424397

This study was a prospective single arm, open-label, international, multicenter study to evaluate the safety, efficacy and pharmacokinetics of ATV powder boosted with RTV liquid with an optimized NRTI background therapy, in HIV infected pediatric patients greater than or equal to 3 months to less than 6 years. Subjects can be ARV naive or experienced (without prior exposure to ATV). ATV was administered once daily (QD) based on the body weight of the subjects: 150 mg for 5 to < 10 kg; 200 mg for 10 to < 15 kg; 250 mg for 15 to < 25 kg as oral powder (50 mg/sachet) and RTV was administered as an oral solution (80 mg/mL). At Week 2, serial blood

samples were collected over a 24-hour period for plasma concentrations in order to assess the steady-state PK of ATV and RTV.

The PK of ATV was characterized in 53 pediatric subjects weighing 5 to < 10 kg (N=20), 10 to < 15 kg (N=18), and 15 to < 25 kg (N=15) following administration of ATV Oral Powder with RTV liquid at doses of 150/80 mg, 200/80 mg, and 250/80 mg, respectively. Characterization of ATV following administration of ATV 150 mg/RTV 80 mg included 9 subjects aged ≥ 3 months to < 6 months of age. Tables 3 and 4 show the summary statistics of ATV PK parameters for Study AI424397 and the summary statistics of ATV PK parameters for the subgroup aged 3 to less than 6 months. Due to unacceptably lower exposures obtained in the 5 to <10 kg group, the sponsor was requested to include this weight group in their study AI424451 (PRINCEII) and increase the dose for this group to ATV/RTV 200/80 mg.

Note: Study AI424451 was not requested by FDA. The sponsor decided to conduct this study due to a request from the EMA for additional pediatric data.

Table 3: Summary Statistics of ATV PK Parameters –Study AI424397

Treatment Group [N]	Cmax (ng/mL) Geo.Mean (%CV) Min - Max	AUC(TAU) (ng•h/mL) Geo.Mean (%CV) Min - Max	Cmin (ng/mL) Geo.Mean (%CV) Min - Max	Tmax (h) Median (Min - Max)	CLT/F (L/h) Geo.Mean (%CV) Min - Max	CLT/F/kg (L/h) Geo.Mean (%CV) Min - Max
A [20]	4131 (55) 1110 - 9660	32503 (63) 10441 - 94352	336 (76) 11.4 - 1330	1.58 (1.4 - 12.0)	4.61 (60) 1.6 - 14.4	0.65 (62) 0.2 - 1.8
B [18]	5197 (53) 390 - 15000	50305 (67) 6697 - 189971	572 (111) 11.2 - 4870	1.97 (1.0 - 6.0)	3.98 (118) 1.1 - 29.9	0.32 (122) 0.1 - 2.6
C [15]	6172 (37) 3560 - 10400	61485 (36) 31599 - 117171	698 (67) 238 - 2410	1.83 (1.4 - 6.0)	4.07 (36) 2.1 - 7.9	0.24 (38) 0.1 - 0.5

Treatments:
A = 5 to < 10 kg: 150 mg ATV Powder + 80 mg RTV Oral Solution
B = 10 to < 15 kg: 200 mg ATV Powder + 80 mg RTV Oral Solution
C = 15 to < 25 kg: 250 mg ATV Powder + 80 mg RTV Oral Solution
Abbreviations: AUC(TAU) = area under the curve (over the dosing interval); Cmax = maximum observed concentration of drug; Cmin = minimum observed concentration of drug; CV = coefficient of variation; Geo. Mean = geometric mean; Tmax = time to maximum observed concentration of drug.

Table 4: Summary Statistics of ATV PK Parameters in Subjects Aged 3 to Less Than 6 Months–Study AI424397

Treatment A Subset [N]	Cmax (ng/mL) Geo.Mean (%CV) Min - Max	AUC(TAU) (ng•h/mL) Geo.Mean (%CV) Min - Max	Cmin (ng/mL) Geo.Mean (%CV) Min - Max	Tmax (h) Median (Min - Max)	CLT/F (L/h) Geo.Mean (%CV) Min - Max	CLT/F/kg (L/h/kg) Geo.Mean (%CV) Min - Max
3 months to < 6 months [9]	3240 (61) 1110 - 7960	25875 (57) 15635 - 57672	383 (64) 235 - 1040	1.5 (1.4 - 12.0)	5.80 (41) 2.6 - 9.6	0.87 (47) 0.3 - 1.6

Treatment: ATV: 150 mg ATV Powder + 80 mg RTV Oral Solution

Abbreviations: AUC(TAU) = area under the curve (over the dosing interval); Cmax = maximum observed concentration of drug ; Cmin = minimum observed concentration of drug; CV = coefficient of variation; Geo. Mean = geometric mean; Tmax = time to maximum observed concentration of drug; Min = minimum; Max = maximum.

See Individual Study Report Review (Section IV) for additional details.

Study AI424451

This study is an ongoing Phase 3b prospective, international, multicenter, nonrandomized, 2-stage study of a cohort of HIV-infected pediatric subjects ≥ 3 months to < 11 years and weighing ≥ 5 to < 35 kg treated with ATV powder and RTV optimized regimens. Subjects can be ARV naive or experienced (without prior exposure to ATV). ATV was administered once daily based on the body weight of the subjects: 150 mg for 5 to < 10 kg; 200 mg for 10 to < 15 kg; 250 mg for 15 to < 25 kg as oral powder (50 mg/sachet) and RTV was administered as an oral solution (80 mg/mL). Serial blood samples were collected over a 24-hour period for plasma concentrations in order to assess the steady-state PK of ATV and RTV for subjects 6 to < 11 years of age weighing 15 to < 25 kg.

Summary statistics for ATV PK parameters from the subjects in the 15 to < 25 kg weight band (6 to 7.3 years of age) are presented in Table 7. The exposures are similar to the observed exposures in Study AI424397 for the same weight range.

Table 5: Summary Statistics of ATV Pharmacokinetic Parameters

Treatment Group [N]	Cmax (ng/mL) Geo. Mean (%CV) Min - Max	AUC(TAU) (ng•h/mL) Geo. Mean (%CV) Min - Max	Cmin (ng/mL) Geo. Mean (%CV) Min - Max	Tmax (h) Median (Min - Max)	CLT/F (L/h) Geo. Mean (%CV) Min - Max	CLT/F/kg (L/h/kg) Geo. Mean (%CV) Min - Max
ATV/RTV 250 /80 mg QD 15 to < 25 kg [16]	4741 (57) 1480 - 11400	50464 (55) 19309 - 121141	661 (73) 177- 2570	2.65 (1.50 - 8.00)	4.95 (64) 2.06 - 12.95	0.25 (64) 0.10 - 0.64

See Individual Study Report Review (Section IV) for additional details.

The exposures of ATV at the proposed doses for POU for subjects 3 month to 7 years at BW of 10 to 25 kg are in the range of the predicted steady-state exposures of ATV for capsule formulation at the approved dose with RTV in HIV-infected pediatric patients ≥6 years of age.

Table 6: Predicted Steady-State Pharmacokinetics of Atazanavir (capsule formulation) with Ritonavir in HIV-Infected Pedatric Patients

Body Weight (range in kg)	ATV/RTV Dose (mg)	C_{max} ng/mL Geometric Mean (CV%)	AUC ng•h/mL Geometric Mean (CV%)	C_{min} ng/mL Geometric Mean (CV%)
15 to <20	150/100	5213 (78.7%)	42902 (77.0%)	504 (99.5%)
20 to <40	200/100	4954 (81.7%)	42999 (78.5%)	562 (98.9%)
≥40	300/100	5040 (84.6%)	46777 (80.6%)	691 (98.5%)

The exposures are also in the range of the observed values in HIV-infected adult patients (N=10) at ATV/RTV 300/100 mg QD (Cmax: 4422 (58) ng/mL, AUC: 46073 (66) ng.h/mL, and Cmin: 636 (97) ng/mL).

Office of Scientific Investigations is conducting the inspection on 3 clinical sites and the analytical site for Study AI424397 and Study AI424451, and the results are pending.

II. Question Based Review

1. *What is the proposed therapeutic indication?*

ATV is approved as a capsule dosage form (150 mg, 200 mg, 300 mg) for the treatment of HIV-1 infection in adults and pediatric patients ≥ 6 years of age in combination with other antiretrovirals. This NDA was submitted for the treatment of HIV-1 infection with a new POU formulation in combination with other antiretrovirals in pediatric patients who have body weight between 10 to < 25 kg.

2. *Is the proposed dose appropriate for the targeted population?*

Yes. The proposed ATV doses for the new POU formulation in pediatric patients are weight based as shown in the following table:

Body weight	ATV dose	RTV dose
10 kg to less than 15 kg	200 mg (4 packets)	80 mg
15 kg to less than 25 kg	250 mg (5 packets)	80 mg

ATV and RTV should be taken together once daily with food.

The proposed ATV/RTV doses of the new POU formulation in pediatric patients who weigh 10 to < 25 kg have been evaluated in Studies AI424397 and AI424451. The objectives of these two studies are to identify any new safety concerns in pediatrics as compared to adults or pediatrics 6 year and above taking ATV capsules in combination with RTV and determine if the PK with the proposed doses are similar to those observed in adults administered ATV capsules in combination with RTV. Limited efficacy data were also collected to support the proposed indication (See Summary of Clinical Pharmacology Findings and individual study reviews for detailed study design information).

As shown in the following table, the results from the combination of Studies AI424397 and AI424451 show ATV exposures in these pediatric subjects were similar to those observed in adults administered RTV-boosted ATV. In addition, the limited efficacy data and the safety data show there are no clinically significant differences between the results from these two studies and the historical data observed for ATV capsules in combination with RTV (Refer to Dr.

Shapiro's review). Therefore, the proposed dose is appropriate for pediatric patients who weigh 10 to < 25 kg.

PK Parameter	10 to < 15 kg ATV/RTV 200/80 mg QD (N=18)	15 to < 25 kg ATV/RTV 250/80 mg QD (N=31)	HIV-infected Adults ATV/RTV 300/100 mg QD (N=10)
Cmax (ng/mL)	5197 (53)	5386 (47)	4422 (58)
AUC (ng.h/mL)	50305 (67)	55525 (46)	46073 (66)
Cmin (ng/mL)	572 (111)	678 (69)	636 (97)

3. *What are the formulations of the drug product as they relate to clinical pharmacology review?*

The composition of the proposed commercial ATV POU is presented in the following table.

Commercial Formulation for ATV POU (b) (4) 50 mg, as the Free Base

Ingredient	% w/w
Atazanavir sulfate	(b) (4)
Aspartame[a]	
Sucrose	
Orange vanilla flavor	
Total	100.00

(b) (4)

A relative bioavailability study (Study# AI424-025) was conducted to compare the Reyataz® capsule formulation (2 x 200 mg) to the pediatric POU formulation, (400 mg) containing (b) (4) aspartame. Relative to the capsule, the bioavailability of ATV POU ((b) (4) aspartame formulation), with respect to ATV AUC_{INF}, when administered to healthy adults with applesauce or water was similar. Although a 30% lower Cmax was observed for this pediatric POU formulation, this is not considered clinically significant.

A biowaiver for conducting a bioequivalence study between the (b) (4) aspartame formulation and the proposed commercial (b) (4) aspartame (b) (4) formulation was granted by the FDA in November, 2012.

4. *If the inspection was conducted, are the inspection results acceptable?*

Pending

III. Labeling Recommendations

Under negotiation

IV. Individual Study Reviews

Study AI424397: A Prospective Single Arm, Open-label, International, Multicenter Study to Evaluate the Safety, Efficacy and Pharmacokinetics of Atazanavir (ATV) Powder Boosted with Ritonavir (RTV) Liquid with an Optimized NRTI Background Therapy, in HIV Infected Pediatric Patients Greater Than or Equal to 3 Months to Less Than 6 Years (Pediatric Atazanavir International Clinical Evaluation: The PRINCE I Study)

Objectives: To evaluate the safety, efficacy and pharmacokinetics of atazanavir (ATV) powder boosted with ritonavir (RTV) liquid with an optimized nrti background therapy, in HIV infected pediatric patients greater than or equal to 3 months to less than 6 years.

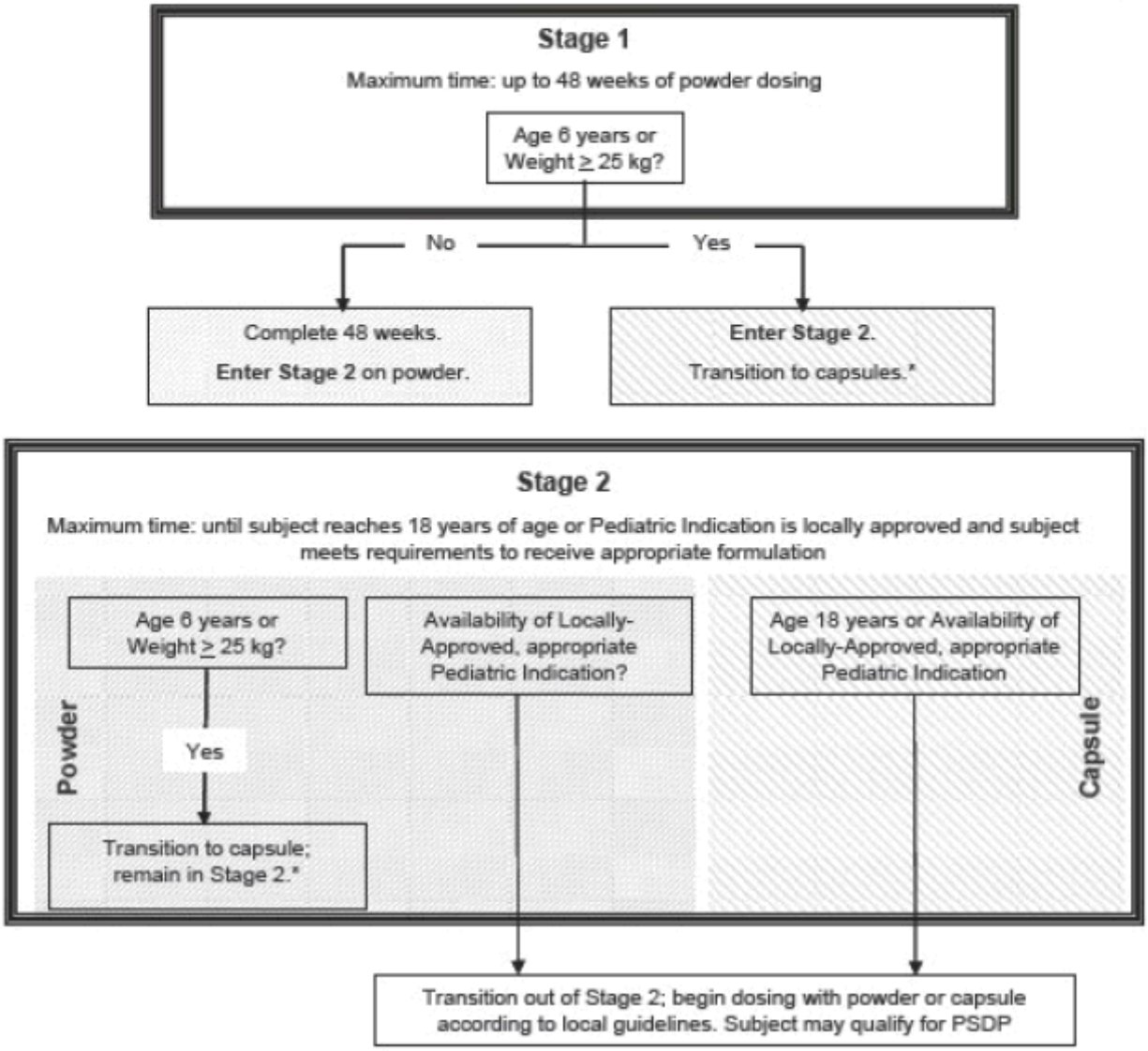
Study Design: This is a Phase 3b prospective, international, multicenter, nonrandomized, 2-stage study of a cohort of HIV-infected pediatric subjects ≥ 3 months to < 5 years and 6 months of age, treated with ATV powder and RTV optimized regimens. Subjects can be ARV naive or experienced (without prior exposure to ATV).

Nucleoside backbone therapy is determined by the investigator on the basis of the viral resistance profile and the subject's treatment history. It consists of 2 nucleoside reverse transcriptase inhibitor (NRTIs) approved for pediatric use and dosed as per the local country label (tenofovir (TDF) is excluded). A total of approximately 50 children were to be treated with the ATV powder formulation boosted with RTV oral solution.

Figure 1 shows the 2 stages of the study.

Figure 1: Study AI424397 Schema

Age ≥ 3 months to < 5 years, 6 months: 50 subjects treated with powder formulation				
Body Weight (kg)	Target # of Subjects	ATV Dose (mg)	RTV Dose (mg)	
5 to less than 10	min of 6* and max of 20	150	80	+ approved NRTI backbone (tenofovir is prohibited)
10 to less than 15	min of 10 and max of 20	200	80	
15 to less than 25	min of 10 and max of 20	250	80	
* A minimum of 6 subjects from this weight band must be ≥ 3 months to < 6 months of age.				



*Subjects who are unable to swallow the capsule formulation after an 8 week transition period must be discontinued from the study.

The atazanavir powder is administered by either mixing with a food substance or water and taken with a light meal. Throughout the study, the majority of subjects took their dose of ATV mixed with milk or water.

Formulation:
ATV capsules (150, 200, and 300 mg) - Batch nos.: 1C71210, 1E68055, 1G64963, and 1J67509;
ATV Oral Powder (50 mg/sachet) - Batch nos.: 0K65490, 1C70482, 1C70483, 1H60026, 1K68747, and 9L53247;
RTV capsules or tablets (100 mg) - Batch nos.: 0G62043; RTV tablet - 1H56045, 945518D, 945518D.1A;
RTV oral solution (80 mg/mL) - Batch nos.: 0M45380, 1A67697, 1A67835, 1F65790, 6011660.0A, 60159251A, 6017033, 6017033.1A, 6017931, 6017931.1A, 6019612, 6019612.1A, 6020639, 6020639.1A, 6021274, 6021274.2A, 6022881, 6022881.2A, 6023188, 6023188.2A, 6024219, 6024219.2A, 6024614, 6024614.2A, 6025250, 6025250.2A, 6026130, 6026130.2A, 6026788, 6026788.2A, IA67697.

PK Sampling: An intensive PK assessment was conducted at Week 2 (Day 14). Serial plasma concentrations were collected at predose, and 0.5, 2.5, 4, 6, 8, 12, and 24 hours postdose to assess the steady state PK of ATV and RTV. A PK Trough sample (Ctrough) was collected for ATV and RTV at each scheduled visit thereafter through Week 48.

Analytical Methods: Atazanavir and RTV in human potassium ethylenediaminetetraacetic acid (K2EDTA) plasma were simultaneously assayed using a validated liquid chromatography (LC)-mass spectrometry (MS)/MS method during the period of known analyte stability. The standard curve and QC data indicated that the plasma assay method for ATV and RTV were precise and accurate as shown in the following table.

Table 1: Summary of Quality Control (QC) Results

Analyte	LLOQ (ng/mL)	ULOQ (ng/mL)	Between-run %CV[a]	Within-run %CV[a]	Mean % Deviation from Nominal Concentration[a]
Atazanavir	10.0	10,000	≤ 4.2	≤ 3.2	± 7.0
Ritonavir	5.00	5,000	≤ 3.4	≤ 4.4	± 2.8

[a] Maximum value from analytical quality controls.
CV = coefficient of variation; LLOQ = lower limit of quantitation; ULOQ = upper limit of quantitation.

Pharmacokinetic Results: The PK of ATV was characterized in 53 pediatric subjects weighing 5 to < 10 kg (N=20), 10 to < 15 kg (N=18), and 15 to < 25 kg (N=15) following administration of ATV Oral Powder with RTV liquid at doses of 150/80 mg, 200/80 mg, and 250/80 mg, respectively. Characterization of ATV following administration of ATV 150 mg/RTV 80 mg included 9 subjects aged ≥ 3 months to < 6 months of age.

The summary statistics for ATV PK parameters from the 3 treatments are presented in Table 2. The summary statistics for ATV PK parameters in subjects ≥ 3 months to < 6 months of age are presented in Table 3.

Table 2: Summary Statistics of ATV PK Parameters

Treatment Group [N]	Cmax (ng/mL) Geo.Mean (%CV) Min - Max	AUC(TAU) (ng•h/mL) Geo.Mean (%CV) Min - Max	Cmin (ng/mL) Geo.Mean (%CV) Min - Max	Tmax (h) Median (Min - Max)	CLT/F (L/h) Geo.Mean (%CV) Min - Max	CLT/F/kg (L/h) Geo.Mean (%CV) Min - Max
A [20]	4131 (55) 1110 - 9660	32503 (63) 10441 - 94352	336 (76) 11.4 - 1330	1.58 (1.4 - 12.0)	4.61 (60) 1.6 - 14.4	0.65 (62) 0.2 - 1.8
B [18]	5197 (53) 390 - 15000	50305 (67) 6697 - 189971	572 (111) 11.2 - 4870	1.97 (1.0 - 6.0)	3.98 (118) 1.1 - 29.9	0.32 (122) 0.1 - 2.6
C [15]	6172 (37) 3560 - 10400	61485 (36) 31599 - 117171	698 (67) 238 - 2410	1.83 (1.4 - 6.0)	4.07 (36) 2.1 - 7.9	0.24 (38) 0.1 - 0.5

Treatments:
A = 5 to < 10 kg: 150 mg ATV Powder + 80 mg RTV Oral Solution
B = 10 to < 15 kg: 200 mg ATV Powder + 80 mg RTV Oral Solution
C = 15 to < 25 kg: 250 mg ATV Powder + 80 mg RTV Oral Solution
Abbreviations: AUC(TAU) = area under the curve (over the dosing interval); Cmax = maximum observed concentration of drug; Cmin = minimum observed concentration of drug; CV = coefficient of variation; Geo. Mean = geometric mean; Tmax = time to maximum observed concentration of drug.

Table 3: Summary Statistics of ATV PK Parameters in Subjects Aged 3 to Less Than 6 Months

Treatment A Subset [N]	Cmax (ng/mL) Geo.Mean (%CV) Min - Max	AUC(TAU) (ng•h/mL) Geo.Mean (%CV) Min - Max	Cmin (ng/mL) Geo.Mean (%CV) Min - Max	Tmax (h) Median (Min - Max)	CLT/F (L/h) Geo.Mean (%CV) Min - Max	CLT/F/kg (L/h/kg) Geo.Mean (%CV) Min - Max
3 months to < 6 months [9]	3240 (61) 1110 - 7960	25875 (57) 15635 - 57672	383 (64) 235 - 1040	1.5 (1.4 - 12.0)	5.80 (41) 2.6 - 9.6	0.87 (47) 0.3 - 1.6

Treatment: ATV: 150 mg ATV Powder + 80 mg RTV Oral Solution
Abbreviations: AUC(TAU) = area under the curve (over the dosing interval); Cmax = maximum observed concentration of drug ; Cmin = minimum observed concentration of drug; CV = coefficient of variation; Geo. Mean = geometric mean; Tmax = time to maximum observed concentration of drug; Min = minimum; Max = maximum.

The summary statistics of RTV PK parameters at Week 2 are presented in Table 4.

Table 4: Summary Statistics of RTV PK Parameters

Treatment Group [N]	Cmax (ng/mL) Geo.Mean (%CV) Min - Max	AUC(TAU) (ng•h/mL) Geo.Mean (%CV) Min - Max	Cmin (ng/mL) Geo.Mean (%CV) Min - Max	Tmax (h) Median (Min - Max)	CLT/F (L/h) Geo.Mean (%CV) Min - Max	CLT/F/kg (L/h/kg) Geo.Mean (%CV) Min - Max
A [19]	2919 (65) 188 - 9160	17439 (66) 1322 - 56864	41.8[a] (115) 12.7 - 311	1.8 (1.3 - 11.9)	4.59 (173) 1.4 - 60.5	0.65 (156) 0.2 - 7.5
B [18]	2634 (102) 163 - 17700	20510 (148) 971 - 229777	143[b] (146) 14.2 - 1610	2.9 (1.0 - 8.0)	3.90 (223) 0.3 - 82.4	0.32 (212) 0.04 - 5.9
C [15]	1838 (54) 582 - 4960	13640 (56) 3376 - 40806	51.0 (135) 9.0 - 468	4.0 (1.5 - 6.0)	5.87 (74) 2.0 - 23.7	0.35 (73) 0.1 - 1.4

[a] N = 18.
[b] N = 16.
Treatments:
A = 5 to < 10 kg: 150 mg ATV Powder + 80 mg RTV Oral Solution
B = 10 to < 15 kg: 200 mg ATV Powder + 80 mg RTV Oral Solution
C = 15 to < 25 kg: 250 mg ATV Powder + 80 mg RTV Oral Solution

The PK data show:

- Geometric mean ATV Cmax and AUC(TAU) increased with increasing dose, with the greatest values observed following administration of 250 mg ATV with 80 mg RTV.
- The ATV Cmax and AUC(TAU) for Groups B and C are within the range of observed values for the approved adult and pediatric (above 6 years of age) doses with ATV capsule formulations.
- Geometric mean ATV Cmin values were similar to those observed in adults (636 ng/mL) administered 300/100 mg ATV/RTV (approved dosing regimen) following doses of 200 and 250 mg ATV, while geometric mean ATV Cmin values appeared to be relatively lower in the 150 mg ATV dosing group.
- Apparent oral clearance of ATV (CLT/F) was similar between the 3 treatment groups, while ATV clearance adjusted for body weight (CLT/F/kg) was highest in Treatment A (lowest weight band, 5 to < 10 kg) and decreased as the weight band increased.
- The variability in the PK parameters from Treatments A and B was relatively high, with Treatment B demonstrating the highest variability, while variability was considerably lower in Treatment C. The variability in Cmin was large for all groups, with the greatest variability observed within Treatment B.
- Subjects aged ≥ 3 months to < 6 months in the 5 to < 10 kg group administered ATV/RTV 150/80 mg had lower geometric mean Cmax and AUC(TAU) values, but similar Cmin values as compared to older subjects in the 5 to < 10 kg group.
- In the 2 lowest ATV dose groups (150 and 200 mg), mean RTV Cmax and AUC were comparable, but were slightly greater than those parameters observed at the ATV 250 mg dose, which was attributed to administration of the same RTV dose over the weight range of 5 to 25 kg.

Reviewer's Note: On July 17, 2012, DAVP recommended that the sponsor study patients with body weight between 5 to <10 kg using a higher dose of ATV/RTV (200/80 mg) in PRINCE II,

because the preliminary data from PRINCE I study showed that the ATV exposures at ATV/RTV 150/80 mg in this body weight group is considerably lower than targeted exposures (the observed ATV exposure for adults at the approved ATV/RTV 300/100 mg dose). The apparent oral clearance of ATV (CLT/F) was similar between all 3 treatment groups, thus it is expected that 200/80 mg ATV/RTV would reach the targeted concentrations

The Medical Officer (MO) indicated there were no additional safety concerns identified in this study as compared to adults or pediatrics 6 years and above. See the MO's review for details.

Conclusion: The proposed doses of 200/80 mg and 250/80 mg ATV POU/RTV for pediatrics with BW of 10 to <15 kg and 15 to <25 kg, respectively, are appropriate.

Study AI424451: A Prospective Single Arm, Open-label, International, Multicenter Study to Evaluate the Safety, Efficacy and Pharmacokinetics of Atazanavir (ATV) Powder Boosted with Ritonavir (RTV) with an Optimized NRTI Background Therapy, in HIV Infected, Antiretroviral, Naive and Experienced Pediatric Subjects From 3 Months to Less Than 11 Years (Pediatric Atazanavir International Clinical Evaluation: The PRINCE II study)

Objectives:

- To describe the safety and efficacy of ATV powder formulation boosted with RTV based highly active antiretroviral (ARV) therapy regimens in pediatric subjects dosed through 48 weeks
- To describe the pharmacokinetic (PK) profile of ATV powder formulation with RTV in pediatric subjects weighing 25 - < 35 kg and/or 6 to < 11 years of age and for new 5 - < 10 kg cohort (200 mg ATV and 80 mg RTV)

Study Design: This is an ongoing Phase 3b prospective, international, multicenter, nonrandomized, 2-stage study of a cohort of HIV-infected pediatric subjects 3 months to < 11 years and weighing 5 to < 35 kg treated with ATV powder and RTV optimized regimens. Subjects can be ARV naive or experienced (without prior exposure to ATV). This interim report summarizes the results through the data cutoff date of 07-Jun-2013 (with a last patient last visit [LPLV] date for this data cutoff of 18-Apr-2013).

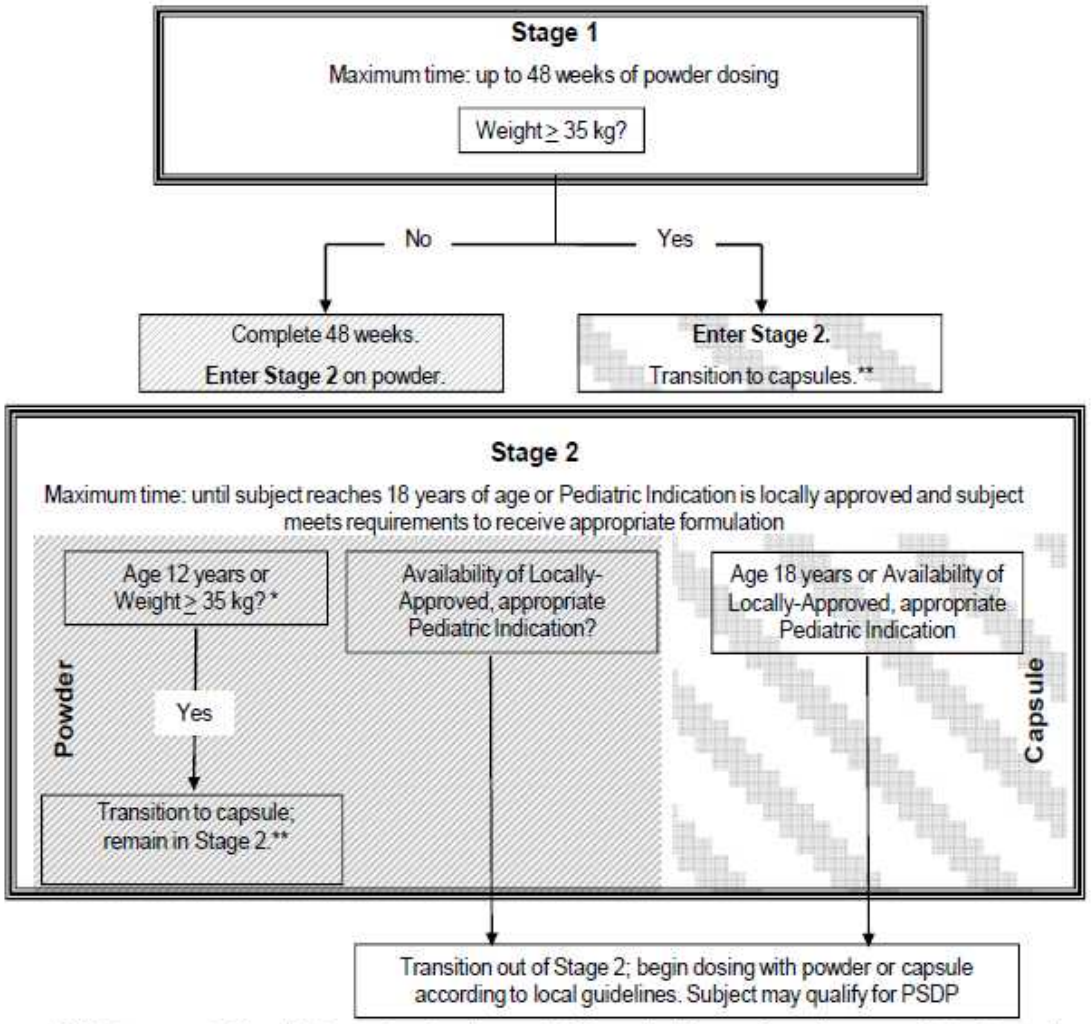
Nucleoside backbone therapy is determined by the investigator on the basis of the viral resistance profile and the subject's treatment history. It consists of 2 nucleoside reverse transcriptase inhibitor (NRTIs) approved for pediatric use and dosed as per the local country label (tenofovir [TDF] is excluded).

Approximately 95 subjects will be treated with the ATV powder formulation boosted with RTV oral solution (or RTV capsules/tablets for the 25 to < 35 kg weight band only) in order to have a minimum number of 56 treated subjects with 48 weeks follow up on the ATV powder formulation.

Figure 1 shows the 2 stages of the study.

Figure 1: Study AI424451 Schematic

Age ≥ 3 months to < 11 years: Minimum 56 subjects treated with ATV powder formulation for 48 weeks				
Body Weight (kg)	Target # of Subjects	ATV Dose (mg)	RTV Dose (mg)	
5 to less than 10	Minimum of 5	150	80	+ approved NRTI backbone (tenofovir is prohibited)
	Minimum of 6	200	80	
10 to less than 15	Minimum of 10	200	80	
15 to less than 25	Minimum of 10	250	80	
25 to less than 35	Minimum of 6	300	100	
The study will commit to enroll a minimum of 30 ARV experienced patients .				



* Subjects are required to switch to capsules when they reach 35 kg and/or 12 years of age. However, subjects who reach a weight of 25 kg and/or 6 years of age during Stage 2 may, at the discretion of the investigator and caregiver, choose to attempt switch to the solid dosage forms of ATV/RTV. Careful consideration should be given to the time of switch as subjects who are unable to swallow capsule after an 8-week transition period must be discontinue from Stage 2.

** Subjects who are unable to swallow the capsule formulation after an 8 week transition period must be discontinued from the study.

Intensive PK sampling was conducted at Week 2 only for subjects who fit in one of the following categories:

- subjects who entered the study weighing 25 to < 35 kg
- subjects who became 6 years of age during Stage 1 of the study and received an increase in the ATV dose and had intensive PK sampling approximately 2 weeks after initiation of the new dose
- subjects who became 6 years of age during Stage 1, but did not increase their dose of ATV, and intensive PK sampling was conducted at a regularly scheduled Stage 1 visit
- subjects who enrolled in the new 5 to < 10 kg weight band receiving ATV 200 mg with RTV 80 mg

The atazanavir powder is administered by either mixing with a food substance or water and taken with a light meal.

Formulation:
ATV capsules (200mg) - Batch nos.: *1J67509 and 2H61672*;
ATV Oral Powder (50 mg/sachet) - Batch nos.: *0K65490, 1C70482, 1C70483, 1H60026, 1K68747, 2H61925, 2H61926, and 9L53247;*
RTV capsules (100 mg) - Batch nos.: *02137AF, 03249AF, 03249F, 04175AI, 06150AF, 10144AF, 11081AF, 14167AF, 15103AF, 16174AF, 201218F, 20121AF, 25073AF, 6020632, 6021266, 6021267, 6022877, 6023187, 6023248, 6023799, 6024612, 6025248, 6026128, 6026787, 6027506, 6028592, 6029211, 6030150, 6030689, 6031580, 6032652, 6032756, 6033652;*
RTV tablets (100 mg) - Batch nos.: *095938D.2A, 196828D, and 196828D.2D;*
RTV oral solution (80 mg/mL) - Batch nos.: *6017931, 6017931.1A, 6019612, 6019612.1A, 6020639, 6020639.1A, 6021274, 6021274.2A, 6022881, 6022881.2A, 6023188, 6023188.2A, 6024219, 6024219.2A, 6024614, 6024614.2A, 6025250, 6025250.2A, 6026130, 6026130.2A, 6026788, 6026788.2A, 6027510, 6027510.2A, 6028597, 6028597.2A, 6029216, 6029216.2A, 6030114.2A, 6030693, 6030693.3A, 6031584, 6031584.3A.*

PK Sampling: An intensive PK assessment was conducted at Week 2 (Day 14). Serial plasma concentrations were collected at predose, and 1.5, 2.5, 4, 6, 8, 12, and 24 hours postdose to assess the steady state PK of ATV and RTV. A PK Trough sample (Ctrough) was collected for ATV and RTV at each scheduled visit thereafter through Week 48.

Analytical Methods: Atazanavir and RTV in human potassium ethylenediaminetetraacetic acid (K2EDTA) plasma were simultaneously assayed using a validated liquid chromatography (LC)-mass spectrometry (MS)/MS method during the period of known analyte stability. The standard curve and QC data indicated that the plasma assay method for ATV and RTV were precise and accurate as shown in the following table.

Table 1: Summary of Quality Control (QC) Results

Analyte	LLOQ (ng/mL)	ULOQ (ng/mL)	Between-run %CV[a, b, c]	Within-run %CV[a, b, c]	Mean % Deviation from Nominal Concentration[a, b, c]
BMS-232632	10.0	10000	≤ 6.7 (6.7)	≤ 3.8 (19.0)	± 9.6 (9.6)
Ritonavir	5.00	5000	≤ 5.0	≤ 11.2	± 4.7

a: Maximum value from analytical QCs.
b: Statistics in parentheses represent accuracy and precision with an outlying value from Run 1 included. Statistics outside of parentheses present the accuracy and precision data with the outlying value excluded.
c: Run 7 and 8 (ISR) were extracted together and reported separately in Watson.

PK Results: At the time of database lock for the interim CSR for Study AI424451, 16 subjects with evaluable intensive PK data were between the ages of 6 and 7.3 years; however, they were in the 15 to < 25 kg weight band, and were treated with ATV/RTV 250/80 mg QD. Only 1 subject (6.7 years) was within the 25 to < 35 kg weight band (ATV/RTV 300/100 mg QD) at the time of the intensive PK visit. At the time of the interim CSR, there were no subjects with available PK data in the 5 to < 10 kg weight band treated with ATV 200 mg with RTV. The summary statistics for ATV PK parameters from the 15 to < 25 kg weight band are presented in Table 2.

Table 2: Summary Statistics of ATV Pharmacokinetic Parameters in Study AI424451

Treatment Group [N]	Cmax (ng/mL) Geo.Mean (%CV) Min - Max	AUC(TAU) (ng•h/mL) Geo.Mean (%CV) Min - Max	Cmin (ng/mL) Geo.Mean (%CV) Min - Max	Tmax (h) Median (Min - Max)	CLT/F (L/h) Geo.Mean (%CV) Min - Max	CLT/F/kg (L/h/kg) Geo.Mean (%CV) Min - Max
15 to < 25 kg [16]: ATV/RTV 250 /80 mg QD	4741 (57) 1480 - 11400	50464 (55) 19309 - 121141	661 (73) 177- 2570	2.65 (1.50 - 8.00)	4.95 (64) 2.06 - 12.95	0.25 (63) 0.10 - 0.64

The exposures are in the range of the observed exposures in Study AI424397 for the same weight range and are similar to those observed in HIV-infected adult patients (N=10) at ATV/RTV 300/100 mg QD (Cmax: 4422 (58) ng/mL, AUC: 46073 (66) ng.h/mL, and Cmin: 636 (97) ng/mL).

Conclusion: The proposed dose of 250/80 mg ATV/RTV for pediatrics with BW of 15 to <25 kg using the ATV powder formulation is appropriate.

Study AI424-025: A Pilot Study to Assess the Bioavailability of BMS-232632 from an Oral Powder Formulation Relative to Capsule Formulation in Healthy Adult Subjects

Objectives:

- To determine the bioavailability of atazanavir (ATV) oral powder formulation relative to capsule formulation in the present of a light meal in healthy volunteer
- To determine the bioavailability of ATV from the contents of 2 x 200 mg capsules mixed with applesauce, relative to a capsule formulation, in the presence of a light meal

Study Design: This was an open-label, randomized, four-treatment, four-period, single-dose, crossover study. Eight (8) healthy adult volunteers, aged 18 to 50 years, were enrolled and received the following treatments in random sequence:

- 400 mg of ATV oral powder formulation mixed with 4 oz applesauce, administered within 5 minutes after a light meal
- 400 mg of ATV oral powder formulation mixed with 50 mL of water, administered within 5 minutes after a light meal
- 400 mg of ATV capsules (2 x 200 mg) given with water, administered within 5 minutes after a light meal (reference)
- The contents of 2 x 200 mg ATV capsules mixed with 4 oz applesauce, administered within 5 minutes after a light meal

The periods were separated by ≥ 72 hours and < 2 weeks.

Formulation:
ATV 400 mg in a (b) (4) oral powder formulation ((b) (4) aspartame): Batch #N00006
ATV 200-mg capsules: Batch #C99274

Reviewer's note: A formal biowaiver request by BMS, for the waiver of a bioequivalence study to be conducted between the (b) (4) aspartame formulation and the proposed commercial (b) (4) aspartame (b) (4)) formulation was submitted and granted by the FDA. .

PK Sampling: ATV PK samples were collected prior to dosing and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 18, and 24 h after dosing.

Analytical Methods: ATV plasma samples were analyzed by a validated LC/MS method. The standard curve and QC data indicated that the plasma assay method for ATV was precise and accurate as shown in the following table. Samples were analyzed within these periods of known stability.

Table 1: Summary of Quality Control (QC) Results

Analyte	Linear Range (ng/mL)	Between Run Precision (%CV)	Between Run Bias (% Deviation)	Stability
ATV	1 – 1000 R^2 >0.991	≤ 2.4	< ± 3.0	2 weeks at -20° C

PK Results: The PK of ATV is summarized by treatment in Table 2. The results of the statistical analysis are presented in Table 3. The data show that the AUCinf of ATV for the powder formulation administered with applesauce or water and the contents of the 2 x 200 mg capsule formulation mixed with applesauce was comparable to AUCinf of ATV for the capsule formulation, with 22% to 28% reduced Cmax for the powder formulation administered with applesauce or water or the contents of the 2 x 200 mg capsule formulation mixed with applesauce. The differences are not considered clinically significant.

Table 2: Summary of ATV PK parameters

Pharmacokinetic Parameter	Treatment[a] A (n = 7)[b]	B (n = 7)[b]	C (n = 7)[b]	D (n = 7)[b]
Cmax (ng/mL) Geometric Mean (C.V.%)	2244.19 (55.03)	2112.54 (31.71)	2912.09 (34.36)	2078.61 (41.95)
AUC(INF) (ng·h/mL) Geometric Mean (C.V.%)	9932.67 (39.65)	10424.46 (30.70)	10114.80 (42.19)	9226.57 (41.50)
Tmax (h) Median (Min, Max)	1.50 (1.00, 2.00)	1.50 (1.50, 3.00)	1.50 (1.00, 2.00)	2.00 (1.50, 3.00)
T-half (h) Mean (SD)	4.48 (0.78)	4.68 (0.60)	5.05 (1.61)	4.90 (0.94)

(b) (4)

(b) (4)

Table 3: Statistical Summary of ATV PK parameters

Pharmacokinetic Parameter	Treatment[a]	Adjusted Geometric Mean[b]	Ratio of Geometric Means Relative to Capsule Point Estimate (90% C.I.)[b]
Cmax (ng/mL)	A	2360.79	0.777 (0.610, 0.990)
	B	2205.30	0.726 (0.570, 0.925)
	C	3037.65	--
	D	2178.75	0.717 (0.563, 0.913)
AUC(INF) (ng·h/mL)	A	10184.18	0.998 (0.867, 1.149)
	B	10668.97	1.046 (0.908, 1.204)
	C	10204.40	--
	D	9362.17	0.917 (0.797, 1.056)

(b) (4)

(b) (4)

Conclusion: When administered under fed conditions, ATV exposures are similar among the powder formulation administered with applesauce or water, the contents of the 2 x 200 mg capsule formulation mixed with applesauce, and the capsule formulation.

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/s/

HUIMIN ZHENG
05/13/2014

SHIRLEY K SEO
05/13/2014