CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 206352 S-03; 21567 S-38
Submission Date: 03/27/2015
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

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I. Executive Summary

Atazanavir (ATV) 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 at least 6 years of age in combination with other antiretrovirals. ATV is also approved in a Powder for Oral Use (POU) formulation in pediatric patients who are at least 3 months and weigh 10 to <25 kg. This sNDA is being submitted for the treatment of HIV infection in pediatric patients who are at least 3 months and weigh 5 to < 10 kg and ≥ 25 kg using POU, based on the additional data from the same clinical trials (AI424397 and AI424451) used for approval for pediatric patients at least 3 months and weighing 10 to <25 kg. As studies AI424397 and AI424451 have already been submitted and reviewed as part of the original NDA submission for the powder formulation, they will only be summarized for the purposes of this review.

In addition, the applicant proposed to use ATV POU for adult patients who cannot swallow capsules. The Week 24 and 48 efficacy results and pooled safety, PK and efficacy analysis for Studies AI424397 (PRINCE I), and AI424451 (PRINCE II) were included in this submission.

A. Recommendation

The Office of Clinical Pharmacology has reviewed the information submitted to NDA 206352 S-03 and NDA 21567 S-38. The data provided in these applications support the ATV dosing recommendations for the POU formulation in HIV-infected pediatric patients who weigh 5 to <10

kg and ≥25 kg. The new recommended dosing regimens for pediatric patients at least 3 months of age and weight at least 5 kg are shown in Table 1 below.

Table 1: Recommended Dosage of REYATAZ Oral Powder and Ritonavir in Pediatric Patients (at least 3 months of age and weighing 5 to less than 25 kg)[a, b]

Body Weight	Daily Dosage of REYATAZ Oral Powder	Daily Dosage of Ritonavir Oral Solution
5 kg to less than 15 kg	200 mg (4 packets)[c,d]	80 mg[e]
15 kg to less than 25 kg	250 mg (5 packets)[c]	80 mg[e]

[a] The same recommendations regarding the timing and maximum doses of concomitant PPIs and H2RAs in adults also apply to pediatric patients. See *Drug Interactions (7)* for instructions concerning coadministration of acid reducing medications (eg, H2RA or PPIs), and other antiretroviral drugs (eg, efavirenz, tenofovir, and didanosine).
[b] Reyataz oral powder (300 mg) and ritonavir (100 mg) can also be used for pediatric patients who weigh at least 25 kg if they cannot swallow the capsules.
[c] Each packet contains 50 mg of REYATAZ.
[d] For patients weighing 5 to less than 10 kg who have not previously received protease inhibitors and cannot tolerate four packets (50 mg/packet), the dose can be decreased down to 150 mg with close monitoring of viral load.
[e] Ritonavir oral solution.

In addition, the applicant also proposed to provide use of the POU for adult patients (who cannot swallow the capsules) at the same recommended adult dosage as the capsules. The proposal is acceptable.

B. Phase IV Commitments

None.

C. Summary of Clinical Pharmacology Findings

ATV is currently approved 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 at least 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 mg) 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	ATV dose	RTV 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.

ATV is also approved as a POU formulation for pediatric patients who are at least 3 months and weigh 10 to <25 kg (Table 3) based on the PK, safety and efficacy data from Studies AI424397 and AI424451. ATV oral powder must be mixed with food or beverage for administration and ritonavir must be given immediately afterwards.

Table 3: Recommended Dosage of ATV Oral Powder and Ritonavir in Pediatric Patients (at least 3 months of age and weighing at least 10 kg and less than 25 kg)[a]

Body Weight Solution	Daily Dosage of REYATAZ Oral Powder	Daily Dosage of Ritonavir Oral
10 kg to less than 15 kg	200 mg (4 packets)[b]	80 mg
15 kg to less than 25 kg	250 mg (5 packets)[b]	80 mg

[a] The same recommendations regarding the timing and maximum doses of concomitant PPIs and H2RAs in adults also apply to pediatric patients. See *Drug Interactions (7)* for instructions concerning coadministration of acid reducing medications (eg, H2RA or PPIs), and other antiretroviral drugs (eg, efavirenz, tenofovir, and didanosine).
[b] Each packet contains 50 mg of ATV

The applicant originally included pediatric subjects with body weight of 5 to <10 kg at ATV/RTV dose of 150/80 mg; however, the ATV exposures were too low based on the preliminary PK analysis. The applicant was requested to increase the dose for this weight band to 200/80 mg to match the exposure to other weight groups and adults. Additional PK, safety and efficacy data at ATV/RTV 200/80 mg were collected from Study AI424451 (PRINCE II). In addition, the applicant also submitted the safety, efficacy and PK data for pediatric subjects with body weight of 25 to <35 kg. Based on these data, the dosing for pediatric patients who weigh 5 to <10 kg and ≥25 kg were determined. The following sections summarize the study design and PK results from PRINCE I and PRINCE II.

Study AI424397 (PRINCE I)

This study was a prospective single arm, open-label, international, multicenter, 2-stage study to evaluate the safety, efficacy and pharmacokinetics of ATV 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 or a prior history of 2 or more PI failures). In Stage 1, 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/ (b) (4) and RTV was administered as an oral solution (80 mg/mL). Subjects who reached a weight of 25 kg or Age 6 during Stage 1

must have been immediately entered into Stage 2 and been switched to the capsule formulation of ATV and the corresponding capsule/tablet formulation of RTV. Subjects who did not reach a weight of 25 kg or Age 6 during Stage 1 continued on the powder formulation of ATV through the end of the 48-week period of Stage 1 and then moved into Stage 2 while remaining on the powder formulation. (See Individual Study Reviews for the original NDA submission).

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 post-dose 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. 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. Table 3 shows the summary statistics of ATV PK parameters for Study AI424397.

Table 4: Summary Statistics of ATV PK Parameters (Week 2) following ATV powder formulation/RTV –PRINCE I

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.

Study AI424451 (PRINCE II)

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 or a prior history of 2 or more PI failures). In Stage 1, ATV was administered once daily as oral powder based on the body weight of the subjects: 150 mg and 200 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/ (b) (4) 300 mg for 25 to <35 kg. RTV was administered at 80 mg QD (80 mg/ml oral solution) for body weight of 5 to <25 kg and at 100 mg QD (100 mg/ml oral solution,100 mg tablets or 100 mg capsules) for body weight of 25 to <35 kg for a minimum of 24 weeks or a maximum of 48 weeks. Subjects who reached a weight ≥ 35 kg during Stage 1

must have been immediately entered into Stage 2 and been switched to the capsule formulation of ATV and the corresponding capsule/tablet formulation of RTV. Subjects who did not reach a weight ≥ 35 kg during Stage 1 continued on the powder formulation of ATV through the end of the 48-week period of Stage 1 and then moved into Stage 2 while remaining on the powder formulation. Subjects who did not have the opportunity to reach Week 48 or a weight ≥ 35 kg during Stage 1 by the time the last treated subject reached Week 24 had a final Stage 1 status assessment performed and immediately moved into Stage 2 while remaining on ATV powder. (See Individual Study Reviews for the original NDA).

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 3 months to < 11 years of age weighing 5 to < 35 kg. It was agreed upon between the applicant and the agency that sufficient PK data from PRINCE I for pediatric subjects 5 to < 10 kg at ATV 150 mg +RTV and 10 to <15 kg at ATV 200 mg + RTV (November 19, 2012), no additional PK data from these weight bands are needed from PRINCE II.

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. Summary statistics for ATV PK parameters from the subjects in the 5 to < 35 kg weight bands are presented in Table 7. The exposures are similar to the observed ATV exposures in PRINCE I for the same weight range at the same dose (15 to <25 kg group).

Table 5: Summary Statistics of ATV PK Parameters (Week 2) following ATV powder formulation/RTV –PRINCE II

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 [10]	4466 (59) 607-12200	39519 (54) 6268-93597	550 (60) 101-1330	1.60 (1.4-4.0)	5.06 (122) 2.1-31.9	0.66 (105) 0.3-3.4
C [17]	4789 (55) 1480-11400	51027 (53) 19309-121141	675 (70) 177-2570	2.72 (1.5-8.0)	4.90 (64) 2.1-12.9	0.24 (64) 0.1-0.6
D [8]	4209 (52) 1160-8950	44329 (63) 7172-117805	468 (104) 51.2-3010	3.42 (1.5-6.1)	6.77 (127) 2.5-41.8	0.25 (107) 0.1-1.2

Treatments: A = 5 to < 10 kg: ATV 200 mg Powder + RTV 80 mg Oral Solution; C = 15 to < 25 kg; ATV 250 mg Powder + RTV 80 mg Oral Solution; D = 25 to < 35 kg: ATV 300 mg Powder + RTV 100 mg.
Abbreviations: CV = coefficient of variation; Geo.Mean = geometric mean; Max = maximum; and Min = minimum

Pooled PK Analysis from PRINCE I and PRINCE II

Because the study design and the PK results for PRINCE I and PRINCE II are similar, the applicant pooled the PK data from 2 studies as shown in Table 6. The adults PK data are also included in the table for comparison purposes.

Table 6: Summary Statistics of Pooled ATV PK Parameters (Week 2) of PRINCE I and PRINCE II

Body Weight (range in kg) [n]	atazanavir/ritonavir Dose (mg)	C_{max} ng/mL Geometric Mean (CV%)	AUC ng•h/mL Geometric Mean (CV%)	C_{min} ng/mL Geometric Mean (CV%)
5 to <10 [20]	150/80	4131 (55%)	32503 (61%)	336 (76%)
5 to <10 [10]	200/80	4466 (59%)	39519 (54%)	550 (60%)
10 to <15 [18]	200/80	5197 (53%)	50305 (67%)	572 (111%)
15 to <25 [32]	250/80	5394 (46%)	55687 (45%)	686 (68%)
25 to <35 [8]	300/100	4209 (52%)	44329 (63%)	468 (104%)
Adult Patients	300/100	4422 (58)	46073 (66)	636 (97)
Adult Patients	400 (ATV)	2298 (71)	14874 (91)	120 (109)

Due to higher apparent oral clearance of ATV in pediatric patients relative to adults, higher Cmax values relative to adults may be observed in order to ensure target ATV Cmin and AUC values are met. The predicted mean (10th to 90th percentile) ATV Cmax for adult patients treated with ATV/RTV 300/100 mg QD is 4175 ng/mL (1405 ng/mL to 12,242 ng/mL). Out of both pediatric studies, only 1 of 18 subjects (6%) in the 10 - < 15 kg weight band (ATV/RTV 200/80 mg) had an ATV Cmax that exceeded the 90th percentile of the prediction interval in adult patients. No subject in any other weight band or treatment regimen demonstrated an ATV Cmax above the 90th percentile of the prediction interval in adult patients. Furthermore, geometric mean ATV Cmax values at the proposed ATV oral powder doses in pediatric patients (when given with RTV) are largely similar to that observed in adults. These data suggest that for safety events related to ATV exposure, the safety profile of ATV in pediatric patients is expected to be similar to that in adults.

The exposures of ATV are comparable among pediatric patients with body weight of 5 to <15 kg at ATV/RTV 200/80 mg, with body weight of 15 to 25 kg at ATV/RTV 250/80 mg, and with body weight of 25 to <35 kg at 300/100 mg, as well as adult patients at ATV/RTV 300/100 mg. Other than the group with body weight of 5 to <10 kg at ATV/RTV 150/80 mg, the exposures in other groups are also comparable to predicted exposures for capsules at the approved doses in pediatric patients with body weight of ≥15 kg (Table 7). These data support the use of ATV oral powder/RTV 200/80 mg in patients who weigh 5 - <10 kg, and ATV oral powder/RTV 300/100 mg in patients who weigh 25 to <35 kg. For pediatric patients with body weight of 5 to <10 kg, the Cmin for ATV/RTV 150 /80 mg is 47% lower as compared to adult patients at ATV/RTV 300 /100 mg, but is about 3-fold higher than the value observed in adult patients at ATV 400 mg (approved for treatment-naïve patients).

It is postulated that Cmin is the pharmacodynamically linked PK parameter of interest for efficacy. Based on a previous analysis of the Cmin values for subjects taking the ATV/RTV 150/80 mg dose, the data suggested that ATV/RTV 150/80 mg may not be sufficient for patients with body weight of 5 - <10 kg who are HIV protease inhibitor (PI)-experienced, but may be used for patients who are PI-naïve if they cannot tolerate the 200 mg dose of ATV oral powder with RTV.

Table 7: Predicted Steady-State Pharmacokinetics of Atazanavir (capsule formulation) with Ritonavir at Approved Doses in HIV-Infected Pediatric Patients

Body Weight (range in kg)	Atazanavir/Ritonavir 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%)

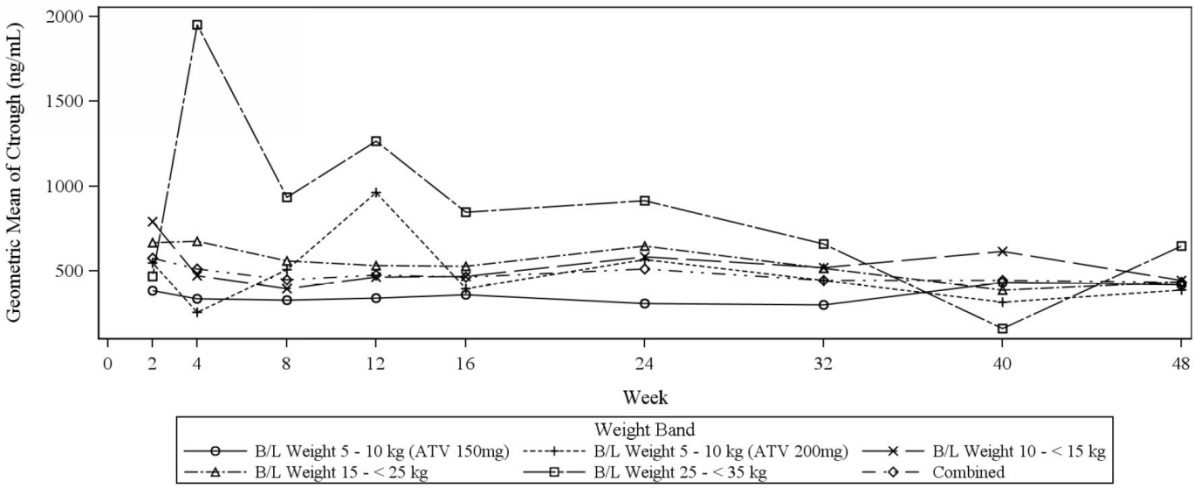
While PRINCE II had an upper body weight limit of 35 kg, the proposed dose of ATV powder for subjects weighing > 35 kg who cannot swallow ATV capsule is 300 mg (with 100 mg of RTV), the same dose as for subjects weighing 25 - < 35 kg. The currently recommended capsule dose of ATV in pediatric subjects weighing 40 kg or more is 300 mg as well, and given the similar bioavailability demonstrated in Study AI424025 between the oral powder and capsule, a dose of 300 mg oral powder is expected to provide exposures in pediatric subjects between 35 and 40 kg that are similar to adults treated with ATV/RTV 300/100 mg. Because a large amount (6 packets for 300 mg) of ATV powder would have to be consumed for patients ≥25 kg, capsules are preferred for patients weighing ≥25 kg, but the powder can be used in this population if patients cannot swallow capsules.

Atazanavir Ctrough is summarized by week and weight band in Table 8 and Figure 1. The data show that the variability in Ctrough among different weeks is large, suggesting there was the possibility of an adherence issue.

Table 8: Summary Statistics for ATV Trough Concentrations by Weight Band

Weight Band	Week 2	Week 4	Week 8	Week 12	Week 16	Week 24	Week 32	Week 40	Week 48
	Geometric Mean (%CV) [N]								
5 to < 10 kg	385	340	330	342	361	310	303	434	422
(ATV 150 mg)	(162)	(156)	(66)	(90)	(67)	(94)	(110)	(89)	(119)
	[20]	[34]	[29]	[33]	[32]	[32]	[31]	[29]	[30]
5 to < 10 kg	550	259	512	964	399	572	446	320	391
(ATV 200 mg)	(60)	(233)	(59)	(145)	(44)	(154)	(12)	(96)	(N/A)
	[10]	[7]	[6]	[4]	[6]	[5]	[3]	[3]	[1]
10 to < 15 kg	793	475	400	467	469	585	523	617	446
	(134)	(108)	(121)	(128)	(115)	(61)	(111)	(82)	(123)
	[17]	[33]	[35]	[33]	[28]	[29]	[30]	[27]	[27]
15 to < 25 kg	670	677	562	532	530	649	520	389	437
	(69)	(113)	(98)	(115)	(78)	(110)	(134)	(99)	(59)
	[32]	[43]	[41]	[42]	[40]	[37]	[37]	[33]	[36]
25 to < 35 kg	468	1952	935	1267	848	917	662	162	650
	(104)	(72)	(78)	(73)	(73)	(108)	(105)	(140)	(N/A)
	[8]	[7]	[5]	[5]	[6]	[5]	[4]	[2]	[1]

Figure 1: Geometric Mean of ATV Ctrough by Week in Pooled PRINCE I and PRINCE II Safety PK Dataset



Note 1: Ctrough is defined as the plasma concentration 24 hours post-dose.

Trough ATV plasma concentrations were also analyzed by inhibitory quotient (IQ). Individual subject IQs were generated by dividing ATV Ctrough by the protein binding-adjusted EC90 for ATV at baseline. Composite IQ, derived by taking the geometric mean of IQs at each visit week for each subject was generated. Table 9 presents summary statistics for composite IQ and baseline EC90 by baseline weight band.

Table 9: Summary Statistics for ATV Composite IQ and Baseline EC_{90}

	5 to <10 kg (ATV 150 mg)	5 to <10 kg (ATV 200 mg)	10 to <15 kg	15 to <25 kg	25 to <35 kg	Combined
Inhibitory Quotient	**N = 42**	**N = 10**	**N = 37**	**N = 46**	**N = 8**	**N = 143**
Geometric Mean (%CV)	7.23 (73.1)	12.5 (75.9)	10.7 (83.3)	11.4 (68.7)	17.2 (71.4)	10.1 (79.8)
Baseline EC_{90} (ng/mL)	**N = 43**	**N = 10**	**N = 37**	**N = 48**	**N = 8**	**N = 146**
Geometric Mean (%CV)	44.4 (27.0)	35.3 (34.9)	43.8 (24.3)	46.8 (33.6)	44.5 (23.2)	44.3 (29.7)

Source: Tables 9.2.1-2 from the Applicant's Integrated PK/PD Report

Geometric mean composite IQ appears to be lower in the 5 - < 10 kg weight band treated with 150 mg relative to the same weight band treated with ATV 200 mg + RTV 80 mg as well as the remaining weight bands. Composite IQ is largely similar between the 5 - < 10 kg weight band (ATV 200 mg), 10 - < 15 kg weight band, and the 15 - < 25 kg weight band, and was somewhat higher in the 25 - < 35 kg weight band. These IQ values were lower to reported (45) for adult treatment-naïve patients following administration of ATV/RTV 300/100 mg (Lambert-Niclot, et. al., HIV Medicine, 2010). However, it is not clear what threshold IQ value is associated with antiviral activity for ATV. Baseline EC90s were consistent across weight bands with the 5 - < 10

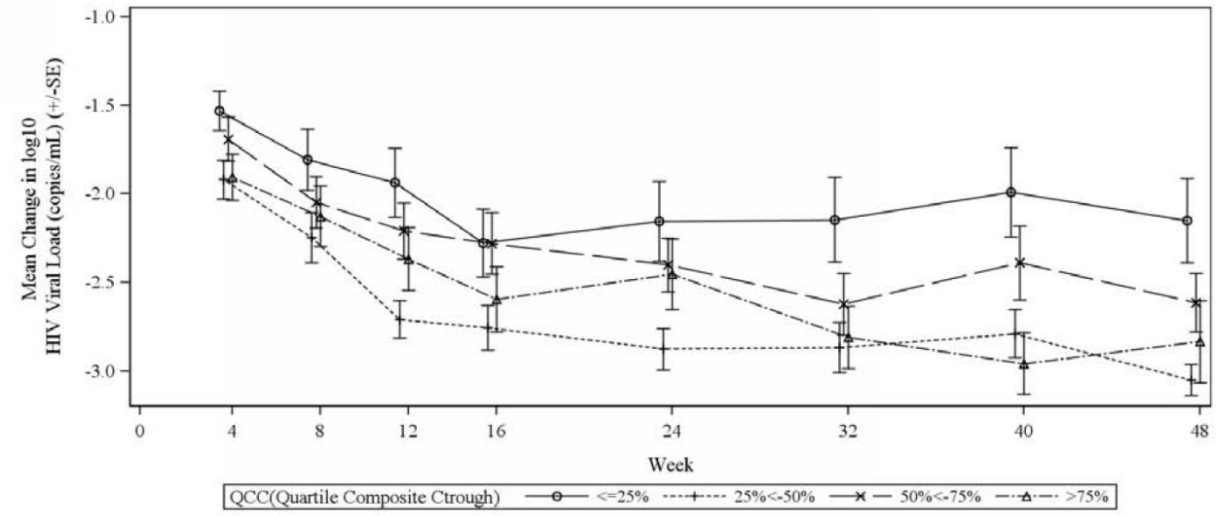
kg weight band treated with ATV 200 mg + RTV 80 mg having a slightly lower geometric mean baseline EC90.

Pooled PK/PD Analysis from PRINCE I and PRINCE II

- *Relationship Between ATV Trough Concentration and HIV RNA*

The pooled efficacy dataset from PRINCE I AND PRINCE II was used to explore the relationship between ATV Ctrough and HIV RNA. Composite Ctroughs, defined as the within subject geometric mean of all available Ctroughs, was used for the analysis. The mean change in log10 HIV RNA from baseline versus week by ATV Quartile Composite Ctrough (QCC) for all subjects combined is presented in Figure 2. The data show that subjects in the <25% ATV QCC had the least mean decline in RNA over time (open circle, solid line).

Figure 2: Mean (± SE) Change in Log10 HIV RNA vs. Week by ATV QCC



Based on body weight, the groups with body weight of 5-<10 kg had the most subjects in the lowest QCC (40% for ATV/RTV 150/80 mg, 30% for ATV/RTV 200/80 mg) as compared to body weights of 10-<15 kg, 15-<25 kg, and 25-<35 kg with 24%, 13% and 12% in the lowest QCC, respectively. The data also show that the largest changes in log10 HIV RNA were observed over the first 12-16 weeks of therapy for all ATV QCC bands, after which the rate of decline was reduced.

According to the FDA guidance for Industry (Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment), "In treatment-naïve trials and trials in treatment-experienced patients with multiple remaining approved drug options, the primary efficacy endpoint should be the proportion of patients with HIV-RNA below the limit of assay detection at 48 weeks (or 24 weeks for drugs with a likely treatment advantage over available options for treatment experienced patients) using a sensitive, FDA-approved viral load assay." Therefore, the percentage of subjects with HIV RNA < 400 copies/mL and HIV RNA < 50 copies/mL at Week 48 by ATV QCC for all subjects combined was analyzed and is presented in Figure 3 (*source: statistical reviewer, Fraser Smith*). Because there are only limited data at Week 48 for PRINCE II, particularly in patients with body weight of 5 - <10 kg (n=1) and 25 -<35 kg (n=2), we will focus on the percentage of subjects with HIV RNA < 400 copies/mL and HIV RNA < 50 copies/mL at Week 24 for these 2 groups (Figure 4; *source: statistical reviewer, Fraser Smith*).

Figure 3: Week 48 Antiviral Activities by Weight Category from PRINCE I AND PRINCE II

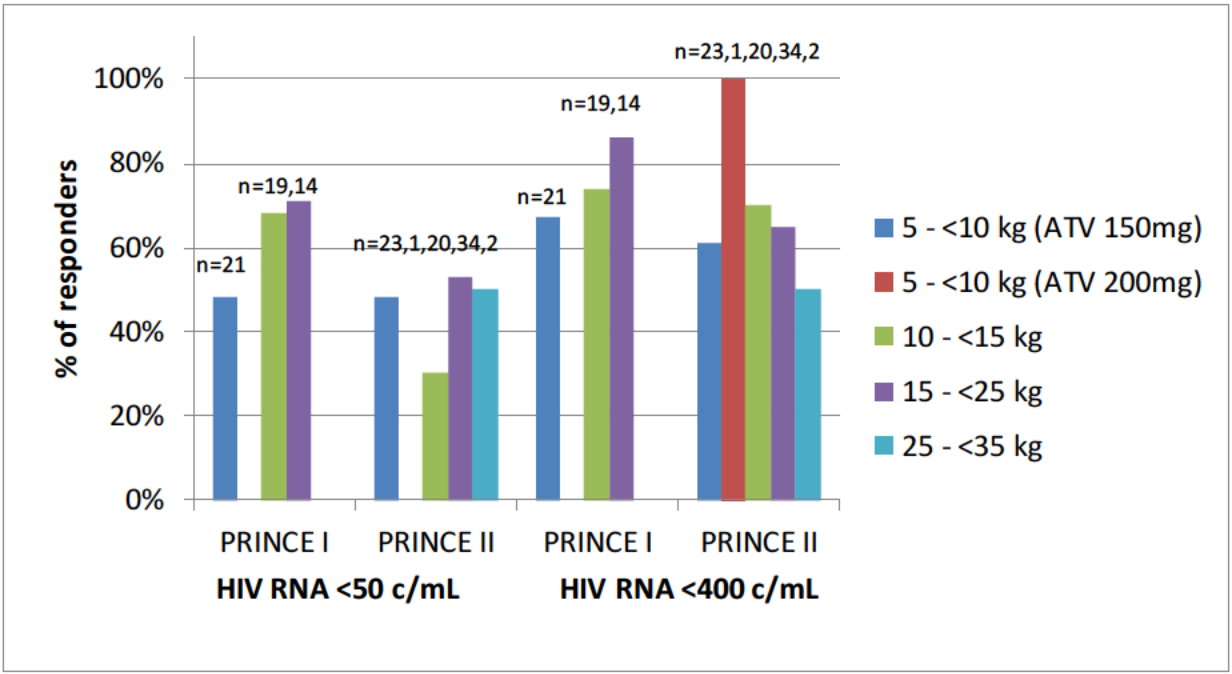
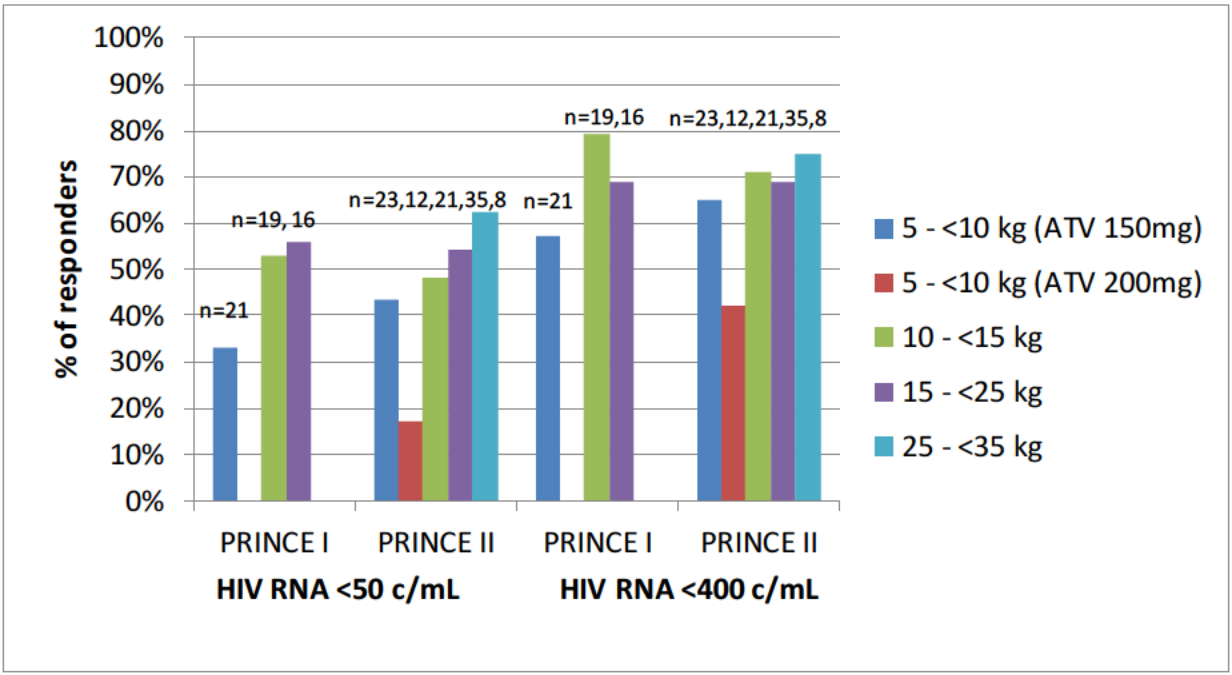


Figure 4: Week 24 Antiviral Activities by Weight Category from PRINCE I AND PRINCE II



In general, the antiviral activities were generally similar between Prince I and Prince II at Week 24 (within each weight group) and trends were consistent between Week 24 and Week 48. For subjects with body weight of 25 - <35 kg, the antiviral activities were similar to subjects with body weight of 10 to 25 kg at the approved doses, which is consistent with the PK results. However, for subjects with body weight of 5 -<10 kg, the virologic success rate was lower following 200 mg ATV(+RTV) as compared to 150 mg ATV (+RTV): 17% (2/12) versus 39 %

(17/44) and 42% (5/12) versus 61% (27/44) at 24 weeks using HIV RNA < 50 copies/mL and HIV RNA < 400 copies/mL, respectively. These data cannot be explained by Week 2 intense PK data or trough concentrations. Of note, any trough concentrations that is below the lower limit of quantification (< LLQ (10 ng/mL)) were treated as missing data by the applicant. Although it is reasonable to treat <LLQ as missing data to more accurately represent the PK data without confounding by non-compliance, it limits the interpretation of the exposure-response data. It needs to be noted that 5 out of the 12 (41.7%) subjects with body weight of 5 –< 10 kg receiving 200 mg ATV dose were discontinued before 24 weeks versus 5 out of 44 (11.4%) for subjects with body weight of 5 –< 10 kg receiving 150 mg ATV dose. Out of these 5 subjects in the 200 mg ATV group, 2 subjects discontinued due to adverse events, 1 was due to lost to follow-up, 1 was due to subject withdrawing consent, and 1 was due to subject no longer meeting study criteria (none were for virologic failure). Of the remaining subjects, only 2 failed due to virologic failure (had HIV Viral Load ≥ 400 at Week 24). Therefore, a high discontinuation rate also contributed to the low virologic response rate for the 200 mg ATV dose.

To investigate the possible reasons that contribute to the lower virologic success following 200 mg ATV(+RTV) as compared to 150 mg ATV (+RTV), baseline viral load, prior treatment status and compliance were also evaluated.

Baseline Viral Load
At baseline, the overall median HIV RNA was 5.00 $\log_{10}$ c/mL for all weight groups, and 54% of subjects had HIV RNA >100,000 c/mL. Subjects in the 5 -< 10 kg weight band administered the 200 mg ATV dose had the highest baseline median HIV RNA of 5.43 $\log_{10}$ c/mL. Subjects in the lower weight bands generally tended toward higher baseline HIV RNA levels, which may partially explain the lower antiviral activities in these groups. The Medical Officer for this NDA indicated that HIV-infected infants have much higher baseline viral loads as compared to adults, and viral load cannot be reduced to less than 50 copies/mL in some infants by 24 weeks, even with effective therapy. Therefore, the antiviral results with the criteria of <50 copies/mL at week 24 for the youngest subjects (body weight of 5 -< 10 kg) should be interpreted cautiously.

Prior Treatment Status
There were too few subjects in PRINCE II who received 200 mg ATV to make a meaningful comparison of efficacy in treatment naïve versus treatment experienced subjects.

Compliance
Compliance to study regimens is an important predictor of efficacy; however, compliance was not incorporated into the exploratory PK/PD assessments. The applicant indicated nearly all subjects (97%) in PRINCE I and PRINCE II had self-reported compliance rates > 90%. Because the compliance was based on self-reporting and the non-compliance was defined by a fairly conservative criterion of >3 consecutive days of reported dosing error, it may not be accurate and the criteria may not capture all non-compliant subjects.

The reviewer reevaluated the non-compliance rate based on the ATV and RTV trough concentration data. Non-adherence was re-defined as at least 2 occasions of LLOQ for Ctrough measurements for either ATZ or RTV throughout the study. Based on this criteria, we found that 3 out of 4 failurers (who had HIV Viral Load ≥ 400 at Week 24) with body weight of 5-<10 kg at 150 mg ATV dose in Prince I and 4 out 6 failurers (who had HIV Viral Load ≥ 400 at Week 24 and have PK data) with body weight of 5-<10 kg at 150 mg ATV dose in Prince II were non-compliant. Combining the 2 studies, 70% of failurers with body weight of 5-<10 kg at 150 mg ATV dose had compliance issues; while only 7 out of 29 (24%) of successes (who had HIV Viral Load < 400 at Week 24 and have PK data) with body weight of 5-<10 kg at 150 mg ATV dose

had compliance issues. For the body weight of 5-<10 kg at the 200 mg ATV dose, 2 out of 2 (100%) failurers (who had HIV Viral Load ≥ 400 at Week 24) had compliance issues while none of 5 successes had a compliance issue. There was no clear relationship between VL and Ctrough. Therefore, the failure could be partially due to non-compliance in the 5-<10 kg body weight groups, without regard to the dose.

- *Relationship Between ATV Trough Concentration and CD4 Cell Count*

There is no clear relationship between change in CD4 cell count and ATV QCC. CD4 levels appear to remain largely consistent over 48 weeks within each ATV QCC as well as across ATV QCC quartiles.

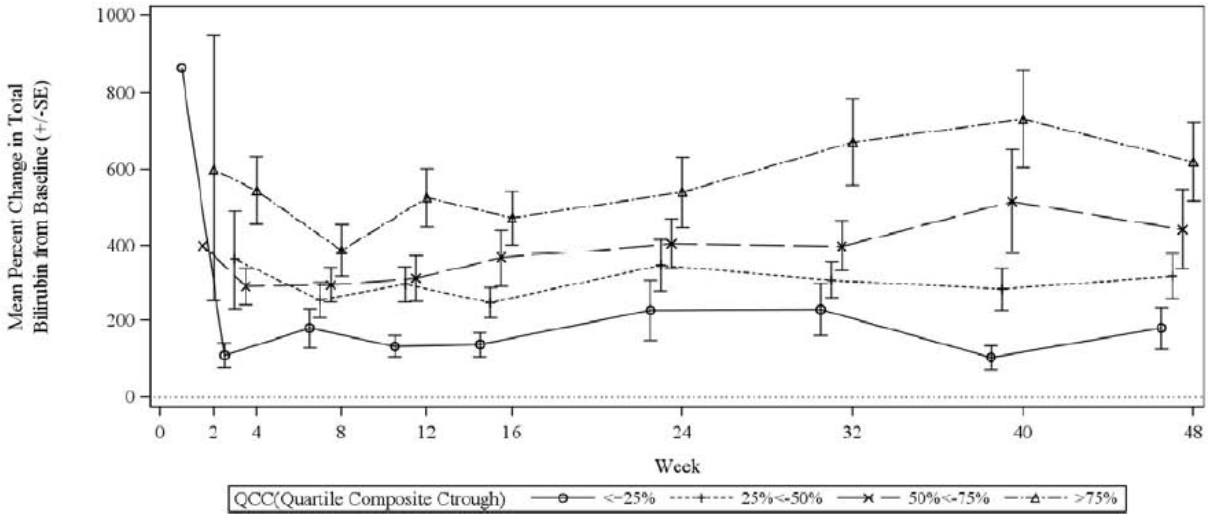
- *Relationship Between ATV Trough Concentration and Safety*

Overall, 155 subjects were treated, and 136 subjects (88%) continued in the study on or after Week 24. The most common reason for discontinuation of ATV powder was adverse events (9 subjects [6%]).

The applicant assessed the relationship between ATV composite Ctrough and changes from baseline in selected laboratory parameters (total bilirubin, total amylase, and total lipase).

As shown in Figure 5, ATV plasma concentration-dependent increases in total bilirubin were observed in pediatric subjects, with increased frequency of hyperbilirubinemia at higher ATV plasma concentration. These findings are consistent with adults, and are due to a reduced systemic clearance of bilirubin via UGT1A1 that is inhibited by ATV in a plasma concentration-dependent manner.

Figure 5: Mean (±SE) Percent Change in Total Bilirubin vs. Week by ATV QCC



There is no clear relationship between ATV plasma concentration and total amylase or total lipase.

Consistent with adults, the incidence of rash is higher at higher plasma concentrations of ATV in pediatric subjects.

The relationship between the frequencies of selected AEs (rash, hyperbilirubinemia, diarrhea, and nausea) and ATV QCC were assessed by the applicant. As shown in Table 10, there appears to be a slight trend with increased frequency of rash with increasing ATV exposure (as measured by composite Ctrough). Frequency of hyperbilirubinemia increases with increasing ATV exposure. There does not appear to be a clear trend between frequency of diarrhea and ATV exposure; however, diarrhea occurred less frequently in subjects in the lowest ATV QCC quartile. Reports of nausea were minimal, with no apparent relationship with ATV exposure.

Table 10: Frequency of Selected AE by ATV QCC

Adverse Event	ATV Quartile Composite Ctrough (QCC)			
N (%)	< 25%	25% to ≤50%	50% to ≤75%	≥75%
Rash	3 (8.3%)	4 (11.1%)	6 (16.7%)	6 (17.1%)
Hyperbilirubinemia	1 (2.8%)	4 (11.1%)	5 (13.9%)	13 (37.1%)
Diarrhea	4 (11.1%)	9 (25.0%)	9 (25.0%)	8 (22.9%)
Nausea	1 (2.8%)	1 (2.8%)	0 (0%)	0 (0%)

Conclusion for POU in Pediatrics

The proposed doses by the applicant for pediatric patients with body weight of 5-<10 kg (ATV/RTV 200/80 mg RTV) and for pediatric patients with body weight of ≥ 25 kg (ATV/RTV 300/100 mg) are appropriate based on the PK data. A higher drop-out rate, a higher non-compliance rate and higher baseline viral loads may contribute to the lower antiviral activities observed in subjects with body weight of 5-<10 kg at ATV 200 mg (+RTV) as compared to ATV 150 mg (+RTV). The exposure-response relationships in pediatrics were similar to adults and observed adverse events were similar to that observed in adults.

POU in Adults:

The applicant also proposed to provide use of the POU for adult patients (who cannot swallow the capsules) at the same recommended adult dosage as the capsules. The proposal is acceptable, because we have determined that when administered under fed conditions, ATV exposures are similar between the POU and the capsule formulation (See the Clinical Pharmacology Review for original NDA 206352).

II. Question Based Review

Not applicable for this supplement.

III. Labeling Recommendations

Under negotiation

IV. Individual Study Reviews

See individual study reviews for original NDA for ATV POU (NDA 206352).

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/s/

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09/03/2015

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09/03/2015