Medical Officer Abbreviated Review

Date	September 1, 2015
From	Alan M. Shapiro
Subject	Medical Officer Review
NDA/BLA # **Supplement#**	NDA 206352 S 003 NDA 021567 S038
Applicant	Bristol-Myers Squibb
Date of Submission	March 27, 2015
PDUFA Goal Date	September 25, 2015
Proprietary Name / Established (USAN) names	Reyataz (atazanavir)
Dosage forms / Strength	Reyataz oral powder/ 50 mg / packet
Proposed Indication(s)	Reyataz (atazanavir) is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection for patients 3 months and older weighing at least 5 kg.
Recommended:	Approval with modification of dosing recommendations for patients 5 - < 10 kg

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1. Introduction

This supplement was submitted to provide dosing recommendations for atazanavir (ATV) for pediatric patients at least 3 months old weighing 5 to < 10 kg. Prior pediatric supplements had provided clinical data to support the dosing of ATV capsule formulation for pediatric patients six years and older and the pediatric powder formulation for patients 10 – 25 kg who are older than three months of age. In the prior supplement for the powder formulation, the Applicant was asked to perform additional dose finding for the 5 - <10 kg weight band because there was concern that the previously evaluated dose of 150 mg ATV coadministered with ritonavir (rtv) did not provide adequate pharmacokinetic (PK) exposures. The Applicant has a waiver for studies in subjects less than three months because of concerns for kernicterus with ATV in this age group. ATV increases the level of unconjugated bilirubin and neonates are especially vulnerable to hyper-bilirubinemia-induced neurological damage. Therefore as a safety measure, ATV is not administered to infants younger than three months of age.

2. Background

This supplement represents the completion of the pediatric development program for ATV with drug development that has been ongoing since 2001. The Applicant has evaluated pediatric dosing for both the approved capsule formulation and the powder formulation. Most of the pediatric data was collected in the Pediatric AIDS Clinical Trial Group (PACTG) trial 1020A. PACTG 1020A was a phase 1/2 trial of ATV ± rtv with 2 nucleoside reverse transcriptase inhibitors (NRTIs) (excluding tenofovir DF) in 183 HIV-infected children (91 days to 21 years) from the United States and South Africa to determine the safety, pharmacokinetics (PK), and optimal dosage of ATV powder and capsules. Dosing for the ATV capsule formulation was first approved in March 2008 for pediatric patients 6-18 years of age. Included in the ATV capsule formulation submission were PK and safety data from pediatric studies for the ATV powder formulation, and preliminary PK data for the original powder formulation was done. Clinical Pharmacology reviewers noted that most of the subjects receiving the powder formulation appeared to be under-dosed, based on pharmacokinetic parameters, given the problems with bioavailability of the reconstituted powder.

Based on these PK results, the Applicant revised the pediatric powder formulation to improve bioavailability and conducted another relative bioavailability study against the capsule formulation. The Applicant had originally proposed to (b) (4) Given the need for adequate safety information in pediatric subjects three months to less than six years of age, the Applicant was asked to evaluate PK, safety and antiviral activity in a minimum of 30 subjects using the proposed revised powder formulation dosing regimen. In addition, the Applicant agreed to a descriptive assessment of adherence and tolerability of the powder formulation in their trial.

The Applicant subsequently conducted two trials, AI424397 (PRINCE1) and AI424451 (PRINCE2), to address their US and European regulatory requirements for the powder formulation. AI424397 enrolled pediatric subjects ages three months to less than six years to meet DAVP's request for additional safety information under the Pediatric Research Equity Act (PREA). AI424451 enrolled pediatric subjects ages three months to less than eleven years of age to meet the EMA pediatric requirements.

On July 5, 2012, the Applicant submitted a preliminary summary of their ATV PK data for subjects weighing 5 to 25 kg in the AI424397 trial. Based on Clinical Pharmacology's review, it appeared that pediatric subjects in 5- < 10 kg (treatment group A) were underdosed with the ATZ 150mg + rtv 80 mg regimen. In the August 6, 2012 communication, DAVP recommended the Applicant increase the ATZ/rtv dose to 200/80 mg for subjects weighing 5- < 10 kg in the AI424451 trial. The Applicant responded in their Type B meeting request of August 6, 2012 that they planned to study the increased dose of ATV/rtv 200/80 mg for subjects 5- <10 kg in the AI424451 trial. In the October 19, 2012 meeting package submission, the Applicant propose (b) (4) Following the November 19, 2012 meeting, the Applicant (b) (4). On December 2, 2013, NDA Supplement 206352-S00 was submitted with data supporting the dosing of the powder formulation for pediatric subjects 10 to 25 kg who were at least three months of age. This supplement was approved on June 2, 2014 with a new Pediatric Research Equity Act (PREA) study commitment:

2153-1 Deferred pediatric study under PREA to evaluate ATV oral powder pharmacokinetics, safety, and treatment response in HIV-1 infected pediatric patients 3 months and older who weigh 5 kg to less than 10 kg.

Study Completion: October2014
Final Report Submission: June 2015

The current supplement addresses the above PREA requirement and completes the pediatric drug development for ATV.

3. CMC/Device

There are no current CMC issues with ATV powder formulation.

4. Nonclinical Pharmacology/Toxicology

There are no new pharmacology toxicology issues.

5. Clinical Pharmacology/Biopharmaceutics

HIV pediatric drug development relies on PK exposure matching between adults and pediatric patients and extrapolation of efficacy from adults. Extrapolation depends on the similarity in disease process between adult and pediatric patients. For ATV, the most reliable predictors of efficacy have been Cmin and AUC; while Cmax is predictive of toxicity (specifically hyperbilirubinemia and PR prolongation).

In July of 2012, the Applicant submitted the preliminary PK data for 150 mg ATV powder coadministered with 80 mg rtv for pediatric subjects weighing 5 - < 10 kg. The results suggested that the exposure was suboptimal and the Applicant was asked to dose this population with 200 mg ATV coadministered with 80 mg rtv. Table 1 shows that exposures (Cmin and AUC) obtained with 200 mg ATV powder plus rtv were increased relative to the 150 mg ATV plus rtv. This PK data was supplied by the Applicant and confirmed by the Clinical Pharmacology reviewer Jenny Zheng, Ph.D.

Table 1:

Steady-State Pharmacokinetics of Atazanavir (powder formulation) with Ritonavir in HIV-Infected Pediatric Patients

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%)

Exposures with the 200 mg ATV powder/rtv dose were closer to exposures (Cmin and AUC) observed with 300 mg of ATV capsules coadministered with 100 mg rtv in ARV-experienced HIV-infected adults [(See Table 2 geometric means). The geometric means of Cmin and the AUC for 200 ATV powder/rtv dose were 86% and 78% of the respective values for 300 mg of ATV capsule coadministered with 100 mg rtv in ARV-experienced HIV-infected adults. Exposures with the 150 mg ATV powder/rtv dose exceeded those reported for unboosted ATV 400 mg capsules reported in ARV-naïve HIV-infected adults (see Table 2 geometric means). The geometric means for Cmin and the AUC for the 150 ATV powder/rtv dose were 280% and 220% of the values for 400 mg of ATV capsules in ARV-experienced HIV-infected adults.

Table 2: Steady-State Pharmacokinetics of Atazanavir in Healthy Subjects or HIV-Infected Patients in the Fed State

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

Excerpted from Table 17 of proposed PI

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

Per Clinical Pharmacology's analysis of the PK samples for infants who received either the 150 mg and 200 mg ATV dose coadministered with rtv, non-adherence was a significant issue for infants weighing 5 to < 10kg. For further details, please see review by Clinical Pharmacology Reviewer Jenny Zheng, PhD.

Reviewer Comment: As summarized in Section 7 of this review,the PK data did not provide a clear reason why infants 5 - < 10 kg who received the 200 mg dose of ATV coadministered with rtv did more poorly with regard to efficacy in comparison to infants who had received the 150 mg ATV dose also coadministered with rtv.

6. Clinical Microbiology

In AI424397 and AI424451, there were very few examples of treatment-emergent resistance substitutions that resulted in significant phenotypic resistance to ATV. Treatment-emergent ATV/rtv resistance-associated amino acid substitutions were detected in the isolates of three

subjects who failed treatment, including G16E, M36I, V82A/I/T, I84V, and/or L90M. In addition, one known resistance-associated substitution for other protease inhibitors, V11I, arose in the failure virus from one subject. One virus, obtained from a subject who had emergent protease inhibitor substitutions M46M/V, V82V/I, I84I/V, and L90L/M, acquired phenotypic resistance to rtv (RTV phenotypic fold-change of 3.5, with clinical cutoff of 2.5-fold change). However, no subjects acquired phenotypic resistance to ATV. For further details, please see the review by Clinical Virology Reviewer Sung Rhee, PhD.

7. Clinical/Statistical- Efficacy

ATV dosing in pediatrics is established by extrapolation of efficacy from adults, based on matching PK exposures and confirmation of antiviral efficacy in pediatric subjects. This review highlights the issue of poor antiviral response with the 200 mg ATV dose (coadministered with rtv) in infants 5 - < 10 kg despite having ATV exposures similar to those in adults dosed with ATV 300 mg capsules plus ritonavir 100 mg. Infants weighing 5 - <10 kg dosed with 150 mg ATV had improved efficacy in comparison to those dosed with 200 mg ATV (coadministered with 80 mg rtv in both cases).

Demographics and Baseline Disease Characteristics

Subjects 5 - < 10 kg in the ATV 150 mg and ATV 200 mg cohorts had similar median ages (6 versus 5.5 months) at baseline, gender distribution (50:50 male:female), and percentage of subjects from South Africa (83-84%). Subjects in the ATV 150 mg cohort racial mix consisted of 73% Black/African American, 9.1% White, and 18% other. In contrast, the ATV 200 mg cohort consisted of 50% Black/African American, 17% White, and 33% other. See Table 3 for additional details.

Table 3: Demographics for Subjects

	150 mg ATV N=44	**200 mg ATV N=12**
Age at Baseline		
Mean	7.9	10.5
Median	6	5.5
Min, Max	3, 25	1, 29
Q1, Q3	2, 10	2, 16
Gender		
Male	22 (50%)	6 (50%)
Female	22 (50%)	6 (50%)

Race		
White	4 (9.1%)	2 (17%)
Black/African American	32 (73%)	6 (50%)
Asian	0	0
Other	8 (18%)	4 (33%)
Country		
Argentina	0	1 (8.3%)
Chile	2 (4.5%)	0
Mexico	3 (6.8%)	1 (8.3%)
Peru	1 (2.3%)	0
South Africa	37 (84%)	10 (83%)
USA	1 (2.3%)	0

With regard to baseline HIV disease, the ATV 200 mg cohort had a three-fold (0.5 log) higher median HIV load than the ATV 150 mg cohort. The ATV 200 mg cohort had a higher proportion of subjects with CD4 percentage of 25% or greater than the 150 mg cohort suggesting that subjects in the 200 mg cohort may have been less immunosuppressed at baseline as shown in Table 4 below. There was also a greater proportion of subjects in the 200 mg cohort who were antiretroviral treatment-experienced (see definition of antiretroviral treatment-experienced in subsection 4 below) as compared to the 150 mg cohort, 83% versus 73%, respectively. See Table 4 below for additional details.

Table 4: Baseline HIV Disease Characteristics

	150 mg ATV N=44	**200 mg ATV N=12**
HIV RNA (Log 10 (c/mL))		
Mean	4.7	5.5
Median	5	5.4
Min, Max	2, 5.9	4.4, 5.9
Q1, Q3	4.7, 5.0	5.3, 5.8
HIV RNA Category		
<30,000	9 (21%)	1 (8.3%)
30,000-100,000	5 (11.4%)	1 (8.3%)
>100, 000	30 (68%)	10 (83%)
CD4 Percent		
< 15%	5 (11%)	1 (8.3%)
15 - <25%	10 (23%)	1 (8.3%)
>= 25%	22 (50%)	9 (75%)
Not Reported	7 (16%)	1 (8.3%)

Prior ARV Use		
ARV NAÏVE	12 (27%)	2 (17%)
ARV EXPERIENCED	32 (73%)	10 (83%)

The focus of this summary is to compare efficacy of the 150 mg and 200 mg ATV powder doses co-administered with 80 mg rtv in pediatric subjects 5- < 10 kg. In addition, the efficacy results for subjects weighing 25 to < 35 kg will be examined because recommendations for use of the powder formulation in pediatric patients > 25 kg have been made by the Applicant.

The 150 mg ATV dose was administered to 21 subjects in AI424397 and 23 subjects in AI424451. The 200 mg ATV dose was administered to 12 Subjects in AI42451. All 44 subjects dosed with 150 mg ATV had efficacy data at 48 weeks. However only one subject out of 12 dosed with 200 mg ATV had 48 week efficacy data. Therefore, the best comparison of the 150 mg versus 200 mg dose of ATV for antiviral efficacy is at 24 weeks. Data at 48 weeks for the 150 mg dose of ATV will also be summarized. There were too few subjects in AI424451 who received 200 mg ATV to make a meaningful comparison of efficacy in treatment-naïve versus treatment-experienced subjects in that subgroup. It should be noted that HIV-infected infants have very high baseline viral loads, some over a million copies of HIV per mL; and that HIV RNA cannot be reduced to < 50 copies per mL in 24 weeks in all infants. The comparisons will be as follows:

1) **Virologic success (HIV RNA less than 50 copies/mL and less than 400 copies/mL) by ATV powder/rtv dose at 24 weeks**

Overall, virologic success at 24 weeks (HIV RNA < 50 copies/mL) was somewhat lower among 5- < 10 kg subjects who received 200 mg versus 150 mg ATV powder in both studies combined, 17% (2/12) versus 39 % (17/44, respectively (see Table 5). Similarly, virologic success at 24 weeks (HIV RNA < 400 copies/mL) was lower among subjects who received 200 mg versus 150 mg ATV powder in both studies combined, 42% (5/12) versus 61% (27/44), respectively (Table 5). These differences could not be easily be explained by comparing response in treatment- naïve versus-experienced subjects, as discussed below. However, five out of the twelve 5 – 10 kg subjects receiving the 200 mg ATV dose were discontinued before 24 weeks due to adverse events (n=2) or for other reasons with elevated viral load (N=3). Five out of the forty four 5 – 10 kg subjects receiving the 150 mg ATV dose were discontinued before 24 weeks due to adverse events (n=4) and for other reasons with elevated viral load (N=1). See Table 5 below for additional details.

Table 5: Virologic Success in 5 to < 10 kg Cohort for ATV/rtv Powder by dose at week 24

Trial	HIV RNA <50 (ATV 150 mg)	HIV RNA <50 (ATV 200 mg)	HIV RNA < 400 (ATV 150 mg)	HIV RNA < 400 (ATV 200 mg)
AI424397 Virologic Success	7/21 (33%)	0/0	12/21 (57%)	0/0
AI424451 Virologic Success	10/23 (44%)	2/12 (17%)	15/23 (65%)	5/12 (42%)
Combined Virologic Success	**17/44 (39%)**	**2/12 (17%)**	**27/44 (61%)**	**5/12 (42%)**
Virologic Failure:	23/44 (52%)	8/12 (67%)	13/44 (29%)	7/12 (58%)
HIV RNA > 50 copies/mL OR >400 copies/mL	22/44 (50%)	5/12 (42%)	12/44 (27%)	5/12 (42%)
Discontinued due to virological failure	0/44	0	0/44	2/12 (17%)
Discontinued due to other reasons and HIV RNA > 50 copies/mL OR >400 copies/mL at time of discontinuance	1/44 (8.3%)	3/12 (25%)	1/44 (8.3%)	0/12
No virological data in analysis week window	4/44 (9.1%)	2/12 (17%)	4/44 (9.1%)	2/12 (17%)
Discontinued due to AE OR Death	3/44 (6.8%)	2/12 (17%)	3/44 (6.8%)	2/12 (17%)
Discontinued due to other reasons and HIV > 50 copies/mL OR >400 copies/mL at time of discontinuance	1/44 (2.3%)	0/12	1/44 (2.3%)	0/12
Missing DATA in Window but on Treatment	0/44	0/12	0/44	0/12

These data were reviewed and verified by Clinical and Statistics Reviewer

2) ATV 150 mg in AI424397 versus AI424451 mg snapshot results (HIV-RNA less than 50 and less than 400 copies/mL at 48 weeks)

No meaningful comparison can be made for virologic response at 48 weeks comparing the two ATV doses in the 5 to < 10 kg cohort, because only one subject in the 200 mg ATV cohort reached 48 weeks treatment at the time of data cutoff. Among subjects who received 150 mg ATV plus rtv, in both studies combined 21/44 (48%) subjects achieved an HIV RNA < 50 copies/mL and 28/44 (64%) achieved HIV RNA < 400 copies/mL at 48 weeks. Overall, the virologic success (HIV RNA < 50 copies/mL) at 24 weeks versus 48 weeks among 5- < 10 kg subjects who received 150 mg ATV powder increased from 17/44 (39%) to 21/44 (48%). Using the HIV RNA < 400 copies/mL virological success criterion to compare 24 to 48 weeks, there was a slight increase in virological success from 27/44 (61%) to 28/44 (64%).
See Table 6 below for additional details.

Table 6: Virologic Success in 5 to < 10 kg Cohort for ATV/rtv Powder by Dose at week 48

Trial	HIV RNA < 50 (150 mg)	HIV RNA < 50 (200 mg)	HIV RNA < 400 (150 mg)	HIV RNA < 400 (200 mg)
AI424397 Virological Success	10/21 (48%)	0/0	14/21 (67%)	0/0
AI424451 Virological Success	11/23 (48%)	0/1	14/23 (61%)	1/1 (100%)
Combined Virological Success	**21/44 (48%)**	**0/1**	**28/44 (64%)**	**1/1 (100%)**
Virological Failure	16/ 44 (36)	1/1 (100%)	12/44 (27%)	0/1
HIV RNA > 50 copies/mL OR >400 copies/mL	12/44 (27%)	1/1 (100%)	8/44 (18%)	0/1
Discontinue due to virological failure	2/44 (4.5%)		2/44 (4.5%)	0/1
Discontinued due to other reasons and HIV RNA > 50 copies/mL OR >400 copies/mL at time of discontinuance	2/44 (4.5%)	0/1	2/44 (4.5%)	0/1
				0/1
No virological data in analysis week window	7/44 (16%)	0/1	4/44 (9.1%)	0/1
Discontinued due to AE OR Death	5/44 (11%)	0/1	2/44 (4.5%)	0/1
Discontinued due to other reasons and HIV > 50 copies/mL OR >400 copies/mL at time of discontinuance	1/44 (2.3%)	0/1	1/44 (2.3%)	0/1
Missing DATA in Window but on Treatment	1/44 (2.3%)	0/1	1/44 (2.3%)	0/1

These data were reviewed and verified by Clinical and Statistics Reviewer

4). Comparison of Virologic response in treatment-naïve versus treatment-experienced subjects

For studies AI424397 and AI424451, treatment-experienced subjects were defined by a previous exposure to antiretroviral drugs (ARVs) through either prior treatment for their HIV disease or through a postnatal treatment with ≥ 1 ARVs for the prevention of mother to child transmission (PMTCT). For the purposes of these studies, subjects exposed to ARVs in utero or intra-partum were eligible for the studies, but were considered 'treatment- naive'. Subjects who had been treated with ATV prior to enrollment or had prior history of 2 or more protease inhibitor failures were excluded.

For the ATV 150 mg dose coadministered with rtv 80 mg, virologic success (HIV RNA < 50 copies/mL) at 48 weeks for Studies AI424397 and AI424451 combined was 4/12 (33%) for treatment-naïve and 17/32 (53%) treatment-experienced subjects (see Table 7). For the same dosing regimen, virologic success (HIV RNA < 400 copies/mL) at 48 weeks for Studies AI424397 and AI424451 was 9/12 (75%) for treatment- naïve and 19/32 (59%) treatment-experienced subjects (see Table 7).

Table 7: Virologic Response in 5-10 Kg Cohort for ATV powder in TN and TE subjects at week 48

Trial	HIV RNA < 50 copies/mL		HIV RNA < 50 copies/mL		HIV RNA < 400 copies/mL		HIV RNA < 400 copies/mL	
	ATV/r 150/80 mg		ATV/r 200/80 mg		ATV/r 150/80 mg		ATV/r 200/80 mg	
	TN	TE	TN	TE	TN	TE	TN	TE
AI424397	3/7 (43%)	7/14 (50%)	--	--	6/7 (86%)	8/14 (57%)	--	--
AI424451	1/5 (20%)	10/18 (56%)	0/0	0/1 (0%)	3/5 (60%)	11/18 (61%)	0/0	1/1 (100%)
Combined	4/12 (33%)	17/32 (53%)	--	0/1 (0%)	9/12 (75%)	19/32 (59%)	--	1/1 (100%)

These data were reviewed and verified by the Clinical and Statistics Reviewers

5) Comparison of Viral Load Decrease for ATV 150 mg and 200 mg (both Studies AI424397 and AI424451) at 24 Weeks and 48 Weeks

In comparing the antiviral activity of the 150 mg and 200 mg ATV dose coadministered with rtv in subjects weighing 5- < 10 kg, the drop in HIV viral load from baseline was calculated for 24 weeks and 48 weeks. At 24 weeks, the median $\log_{10}$ (HIV viral load) decrease was -2.49 and -3.68 for the ATV 150 and ATV 200 mg cohorts, respectively. At 48 weeks, the median $\log_{10}$ (HIV viral load) decrease was -3.09 and -3.90 for the ATV 150 and ATV 200 mg cohorts, respectively. See Table 8 below for details.

Table 8: Mean and Median change in log10 HIV RNA for 5-<10 kg Weight Category (Observed Data for AI424397 and AI424451 combined)

ATV Dose	Week 24	Week 48
150 mg	N=39, Mean=-2.25 (sd=1.19) Median=-2.49	N=33 Mean=-2.46 (sd=1.27) Median=-3.09
200 mg	N=7 Mean=-3.07 (sd=1.27) Median=-3.68	N=1 Mean=-3.90 (sd=n/a) Median=-3.90

These data was reviewed and verified by Clinical and Statistics Reviewer

Reviewer Comment: Although the virologic response as measured by HIV RNA < 50 or < 400 copies/mL at 24 weeks was lower for subjects who received 200 mg dose, the mean and median log_{10} decrease in HIV RNA was greater for the 200 mg dose.

Virological Success in 25 - <35 kg Cohort in Study AI424451

Study AI 424451 included subjects 25 kg to less than 35 kg at the request of the EMA to explore the use of the ATV formulation in older pediatric subjects who weighed more than 25 kg. The dose evaluated was 300 mg ATV /100 mg rtv. Only two subjects out of the eight enrolled received 48 weeks ATV powder treatment. Only one out of the two subjects in this weight cohort was a virologic success at 48 weeks, thereby with a virologic success rate of 50%. The other subject with virologic failure had a viral load greater than 400 copies/mL. At 24 weeks, virologic success (HIV RNA <50 copies/ mL) was 5/8 (63%). Two subjects were virologic failures due to HIV viral loads that were greater than 50 copies/mL. One subject discontinued due to an adverse event. Using the criterion of HIV RNA <400 copies/ mL, virological success increased to 6/8 (75%). See Table 9 below for details.

Table 9: Virologic Success in 25 to < 35 kg
300 mg ATV/ 100 mg rtv at 24 weeks for StudyAI424451

	24 Weeks	
Trial	HIV RNA < 50	HIV RNA < 400
AI424451 Virological Success	5/8 (63%)	6/8 (75%)
Virological Failure	2/8 (25%)	1/8 (12%)
HIV RNA > 50 copies/mL OR >400 copies/mL	2/8 (25%)	1/8 (12%)
Discontinue due to virological failure	0	0

Discontinued due to other reasons and HIV RNA > 50 copies/mL OR >400 copies/mL at time of discontinuance	0	0
	0	0
No virological data in analysis week window	1/8 (12%)	1/8 (12%)
Discontinued due to AE OR Death	1/8 (12%)	1/8 (12%)
Discontinued due to other reasons and HIV > 50 copies/mL OR >400 copies/mL at time of discontinuance	0	0
Missing DATA in Window but on Treatment	0	0

These data was reviewed and verified by Clinical and Statistics Reviewer

Reviewer comment: For pediatric patients older than six years of age especially those 25 kg and more, it is preferable that these patients use the ATV capsule formulation rather than the powder formulation. To dose 300 mg of ATV using the powder formulation six 50 mg packets must be mixed into liquid and immediately consumed by patient. The volume of liquid needed to appropriately suspend the ATV powder formulation could make it difficult for the older pediatric patient to take the increased dose. It is the preference of this reviewer to encourage the use of the capsule formulation for patients weighing more than 25 kg by placing the dosing of the powder formulation for pediatric subject > 25 kg as a footnote to the table that summarizes the dosing of the powder formulation for patients 5 - <25 kg. The footnote would give the 300 mg ATV / 100 mg rtv dose for pediatric patients >25 kg who cannot swallow the capsule formulation.

CD4 Counts for Treated Subjects in AI424397 and AI424451

The median increase from baseline in CD4 percentage at Week 24 was 4.5% for subjects weighing 5 kg to less than 10 kg; and the median increase from baseline in absolute CD4 count at Week 24 for this cohort was 115 cells/mm^3. The CD4 results for the 150 mg and 200 mg ATV cohorts at 24 weeks were very similar with median increases in CD4 percentage between 4.0 and 4.5%. The median increase from baseline in CD4 percent at Week 48 was 4.0% for

subjects weighing 5 kg to less than 10 kg; In the prior ATV powder supplement, NDA 206352 S00, the median increase from baseline CD4 percentage at 48 weeks for subjects 10 to < 15 kg and 15 - <25 kg, was 5.0% and 5.9%, respectively. See statistical review of NDA 206352/S00 by Dr. Karen Qi for additional details of CD4 percentages generated from the data from AI 424397 and AI 424451 for subjects weighing 10 to less than 25 kg. The median increase from baseline in absolute CD4 count at Week 48 was 161 cells/mm^3 for 5 kg to less than 10 kg in AI424397 and AI424451.

Reviewer comment: For NDA 206352 for the ATV powder formulation most of the subjects are under six years of age. There is a natural decrease in number of CD4 cells from birth to six years of age which occurs both in healthy children and those infected with HIV. Therefore the use of CD4 percentage is the most accurate determination of changes in CD4 count for those subjects younger than six years of age. The pediatric capsule supplement (NDA 21567 S015) involved subjects older than six years of age, and therefore absolute CD4 count was used as the CD4 measure rather than CD4 percentage. For this review, the comparison of CD4 percentages for patients under six years of age who received the powder supplement is of most importance.

Overall Reviewer Summary

The differences in antiviral activity between 5 to <10 kg subjects who received the 150 and 200 mg ATV doses coadministered with rtv is not easily explained. Infants infected with HIV, in general, have high viral loads that can be a hundred thousand copies/mL to 1 million copies/L or greater. As a group these infants can be difficult to treat because administration of medication has challenges including the amount of volume that can be administered at any time. In addition, these infants have immature immune systems which together with their HIV disease can lead to serious infections and discontinuation from relatively long-term studies. One possible interpretation of the study results is that infants receiving the 200 mg dose of ATV coadministered with rtv had greater difficulty taking four packets of the ATV powder formulation (50 mg per packet) as compared to infants taking 150 mg of ATV who only had to take three packets. In addition, rtv oral solution has a taste which makes it difficult to administer. It is possible that taking four packets of ATV along with the rtv oral solution was just too much for the infants in the 200 mg cohort. The efficacy differences 150 mg and 200 mg dose cohorts could not be explained by differences in treatment experience but the 200 mg dose cohorts subjects did have a higher HIV viral load at baseline. The number of patients in the 200 mg cohort was small (N=12) and the interpretability of the efficacy results were

greatly affected by the discontinuation of five patients due to adverse events and other reasons prior to 24 weeks. The 150 mg cohorts had 3 to 4 times more subjects when subjects from both AI424397 and AI424451 were combined. Based on the examination of drop in viral load for both the ATV 150 and ATV 200 mg cohorts over 24 and 48 weeks for continuing treatment subjects, both regimens have significant anti-HIV activity.

Addressing Efficacy Concerns in Labeling:

After reviewing the efficacy and PK data for both the 150 mg and 200 mg cohorts, one likely explanation, as mentioned above, for the decreased efficacy in the 200 mg cohort is a possibility that subjects had difficulty taking four packets of ATV powder (50 mg/packet) and thereby did not receive the dose necessary for full antiviral effect. The 200 mg ATV dose was found to generate a more favorable PK profile (Cmin and AUC) then the 150 mg ATV dose based on intensive PK sampling early in the study. Given the 150 mg dose result in a PK profile that would be likely sufficient to provide an adequate exposure of ATV for antiretroviral-naïve infants, it could serve as an alternative to the 200 mg dose for patients five to less than 10 kg who are protease inhibitor naïve and unable to tolerate the full 200 mg ATV dose. The Applicant has expressed concerns that infants grow so fast that they would outgrow the 150 mg dose by reaching 10 kg of weight before they could fully adjust to it. This reviewer does not concur with the Applicant. Infants newly diagnosed with HIV are followed very closely in pediatric HIV clinics when they first started on antiretroviral drugs. Therefore there should be a window of time of 4 to 6 months in which the patient could be dosed at 150 mg and have their viral load monitored closely prior to the time the patient's weight reaches 10 kg.

8. Safety

A total of 56 pediatric subjects 5- to<10 kg were treated with ATV powder formulation either 150 mg or 200 mg coadministered with 80 mg rtv in Studies AI424397 and AI424451. Note that ATV 200 mg dose was studied only in AI424451. Twenty one subjects from Study AI424397 and 23 subjects from Study AI424451 received the 150 mg ATV dose; and 12 subjects from Study AI424451 received the 200 mg ATV dose.

For subjects weighing 5 to < 10 kg there was no new safety signal apparent with either the 150 mg or 200 mg ATV doses coadministered with rtv. There were no deaths. There were five discontinuations due to AEs (5/44, 11%) for subjects that received 150 mg and two discontinuations due to AEs (2/12, 17%) for subjects that received 200 mg [see Table 10]. Three out of the six total discontinuations (50%) were due to infections that are not uncommon in young infants, especially in developing countries where these trials were conducted.

Table 10: Discontinuations due to AE in subjects 5 to < 10kg at baseline

	150 mg ATV	200 mg ATV
	N=44	N=12
Total	5/44 (11%)	2/12 (17%)
Amylase Abnormality	1/44 (2.3%)*	1/12 (8.3%)
Elevated Transaminase	1/44 (2.3%)	0/12
Meningitis	1/44 (2.3%)	0/12
Tuberculosis	1/44 (2.3%)	1/12 (8.3%)
Lymphadenitis	1/44 (2.3%)	0/12

*Diagnosed with pancreatitis

SAEs were reported in 7/77 (16%) subjects that received 150 mg ATV and in 4/12 (33%) subjects that received 200 mg ATV [see Table 11]. Seven out of the 11 SAEs were due to infections.

Table 11: On Treatment SAE in subjects 5- <10kg

	ATV 150 mg	ATV 200 mg
All	7/44 (16%)	4/12 (33%)
Infections#	4/44 (9.1%)	3/12 (25%)
Increased transaminases	1/44 (2.3%)	1/12 (8.3%)
Neutropenia	1/44 (2.3%)	0/12
Acute Pancreatitis*	1/44 (2.3%)	0/12

Infections in 150 mg ATV group: pneumonia (1), gastroenteritis (1), pneumonia/lymphadenitis (1), meningitis (1)
infections in 200 mg ATV group: gastroenteritis (1), lower respiratory tract infection (1), pulmonary TB (1)
*Subject discontinued due to pancreatitis (NRTI backbone was ZDV/3TC)

As shown in Table 12, seven Grade 3-4 AEs were reported in subjects that received 150 mg ATV, all of which were laboratory-related AEs (see Table 13). In subjects who received 200 mg ATV, a total of 6 Grade 3-4 AEs were reported, of which four were laboratory-related AEs and two were infection-related including oral candidiasis and a helminthic infection.

Table 12: Grade 3-4 AEs

	150 mg	**200 mg**
All	7/44 (16%) (all laboratory abnormality-related)	6/12 (50%) (4/12 lab abnormality-related)
Infections	0/44 (11%)	2/12 (17%)

helminthic infections (1), oral candidiasis (1)

Table 13 shows treatment-emergent Grade 3-4 laboratory abnormalities. Treatment--emergent laboratory AEs were reported in 16/44 (36%) of the subjects treated with 150 mg ATV. These AEs included transaminase increase (27%), lipase increase (16%), bilirubin increase (11%), and neutrophil decrease (9.1%). A total of 4/12 (33%) of the subjects who received 200 mg ATV had Grade 3-4 laboratory AEs, including increased transaminase (17%), increased lipase (17%), increased alkaline phosphatase (8.3%), and increased pancreatic amylase (8.3%). Hyperbilirubinemia, a known dose-dependent effect of ATV was not observed in subjects 5 to <10 kg who received 200 mg ATV; but was reported in 5/44 (11%) subjects who received 150 mg ATV.

Table 13: On treatment Grade 3-4 Laboratory AEs excluding non-pancreatic amylase

	150 mg	200 mg
ALL	16/44 (36%)	4/12 (33%)
AST/ALT Increased	12/44 (27%)	2/12 (17%)
Lipase Increased	7*/44 (16%)	2/12 (17%)
Bilirubin Increased	5/44 (11%)	0/12
Neutrophils Decreased	4/44 (9.1%)	0/12
Platelets Decreased	2/44 (4.5%)	0/12
Bicarbonate Decreased	2/44 (4.5%)	0/12
Phosphorus Decreased	2/44 (4.5%)	0/12
Alk Phos Increased	1/44 (2.3%)	1/12 (8.3%)
Pancreatic Amylase Increased	1*/44 (2.3%)	1/12 (8.3%)
Potassium Increased	1/44 (2.3%)	0/12
Glucose Increased	1/44 (2.3%)	0/12

*Same subject had increased lipase and pancreatic amylase

Reviewer Summary of Safety:

No significant safety issues were identified in the 5 - < 10 kg weight cohort. As compared to 10 - < 25 kg cohort taking the ATV powder formulation there were higher degree of increased transaminases and lipases, respectively 4/89 (4.5%) and 3/89 (3.4%). However increased transaminases led to study drug discontinuation in only one subject weighing 5 to < 10 kg. All other subjects with increased transaminases were managed without discontinuation of study drug. Overall, the safety data in the 5 to 10 kg weight group is also similar to those subjects weighing 15 kg and above who were administered the capsule form of ATV coadministered with rtv. Pediatric subjects, in general, have a similar safety profile to adults except that rash is more common in pediatric subjects.

9. Advisory Committee Meeting

Non-applicable

10. Pediatrics

This submission has met the terms of the Pediatric Written Request originally issued on August 2, 2001and last amended on May 20, 2013. On June 23, 2015, the Pediatric Exclusivity Board granted Pediatric Exclusivity for Reyataz.

The Pediatric Review Committee (PeRC) met on July 1, 2015 and concurred with the Division of Antiviral Products that the Applicant had met their PREA requirements and tentatively agrees with the Division's proposal for labeling of ATV for infants 5 - < 10 kg.

11. Other Relevant Regulatory Issues

Applicant submitted Debarment Certification and Certification of Financial Interests and Arrangements of Clinical Investigators.
See Appendix for Clinical Investigator Financial Disclosure Review.

12. Labeling

The main purpose of this supplement is

- Update clinical data to support dosing of the ATV powder for pediatric patients 5 - < 10 kg
- Provide dosing recommendations for ATV powder in patients weighing 5 to < 10 kg.
- Update Labeling Sections 8.1 and 8.3 to be compliant with the Pregnancy& Lactation Labeling Rule

Summary of Major Changes Applicable to Clinical Review Team:

Section 2.3: The Applicant proposed changes in Section 2.3 which described powder dosing in adult patients who cannot swallow capsules. The review team merged the instructions for dosing the powder formulation in adults into Section 2.2, which included the general description of dosing of the capsule formulation in adults

Section 2.5: The Applicant proposed changes in the pediatric oral powder section to expand dosing of the powder formulation to patients weighing 5 kg and to patients heavier than 25 kg. The review team has recommended that patients 5 - <10 kg be started on 200 mg ATV coadministered with rtv and if they cannot tolerate four packets (50 mg/packet) then the dose can be decreased down to 150 mg in patients who have not previously received protease inhibitors and with close monitoring of viral load. DAVP recommends that a footnote be added to the dosing table to provide ATV powder dosing recommendations in pediatric patients > 25 kg who cannot swallow capsules.

Section 6.2: the applicant proposed changes in the adverse reaction pediatric patients: Reyataz oral powder which included the safety data for subjects 5 to <10 kg and combined with the data for all the pediatric subjects studied with the powder formulation in studies AI424397 and AI424451. Given there was no unique safety signals in the subjects 5 to < 10 kg, the review team agreed with the Applicant's proposed changes to the label.

Section 8.1: The Applicant proposed changes to the pregnancy section to make it compliant with the Pregnancy Lactation Labeling Rule (PLLR). The Applicant made changes to the first section which had to deal with the pregnancy exposure registry, reformatting it to meet specifications. They revised the risk summary to include data from the Metropolitan Atlanta congenital defects program for the background birth defect rate; and they made some minor changes to the clinical considerations section. They added a maternal adverse reactions and fetal/neonatal adverse reactions section to be compliant with the PLLR. The human data Section 8.1 was modified to update the data from the antiretroviral pregnancy registry and again use data from the Metropolitan Atlanta congenital defects program. The review team used wording recommended by CDER guidance to describe the background rate of birth defects and miscarriage and included animal data into the risk summary section. The human data section was updated with the latest information from the antiretroviral pregnancy registry. In addition changes were made to the animal data section by the pharmacology toxicology team.

Section 8.3: the Applicant made some minor changes in format to the lactation section. The review team requested that the applicant include information about the presence of ATV in breast milk and included information about the effects of ATV on nursing animals.

Section 14.3: The Applicant included combined virologic success data from both trials for the powder formulation for subjects 5 to 35 kg at 48 weeks by prior antiretroviral treatment experience. The review team concurred with the summary of the virologic success data for pediatric subjects 5 to 35 kg for HIV RNA less than 50 copies/mL and less than 400 copies/mL endpoints. For CD4 counts, (b) (4) The review team has recommended the use of LOCF at 48 weeks comparing the change in absolute CD4 count and CD4 percentage comparing those that are antiretroviral-naïve and antiretroviral-experienced.

13. Recommendations/Risk Benefit Assessment

- Recommend approving the supplement with 200 mg ATV coadministered with 80 mg rtv for treatment of infants 5 to < 10 kg. If the infant has any difficulty tolerating the 200 mg dose, the infant can be switched to 150 mg dose if the infant has not previously been treated with an HIV protease inhibitor.

- The risk of HIV therapy failure and development of HIV protease inhibitor resistance in infants 5 to < 10kg must be balanced against the benefits of a once a day HIV protease inhibitor which has, in the past, has been tolerated better than lopinavir/rtv. The improved tolerability refers to the capsule formulation and the use of the powder formulation in patients 10 to < 25 kg. Efavirenz is another option that can be used in infants 5 to <10 kg stead of an HIV protease inhibitor such as ATV.

  Reviewer Comment: It is best to try to facilitate as many options as possible for ART in infants 5 - < 10 kg, and finding an effective way to use ATV therapy in this age/weight cohort would be advantageous.

APPENDIX Clinical Investigator Financial Disclosure Review

Application Number: NDA 206352

Submission Date(s): March 27, 2015

Applicant: Bristol-Myers Squibb

Product: Reyataz

Reviewer: Alan M Shapiro

Date of Review: August 27, 2015

Covered Clinical Study (Name and/or Number): AI424397 and AI424451

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: AI424397: 87 AI424451: 112		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): **N/A** Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements: **N/A**	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided: **N/A**	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: **N/A**	Yes ☐	No ☐ (Request explanation from applicant)

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/s/

ALAN M SHAPIRO
09/01/2015

MARY E SINGER
09/02/2015
I agree with Dr. Shapiro's review and recommendations.