CLINICAL REVIEW

Application Type	SE5
Application Number(s)	NDA 21-567 S026
Priority or Standard	S
Submit Date(s)	12/17/2010
Received Date(s)	12/17/2010
PDUFA Goal Date	10/17/2011
Division / Office	DAVP/ OAP
Reviewer Name(s)	Alan M. Shapiro, MD, Ph.D.
Review Completion Date	September 22, 2011
Established Name	Atazanavir (ATV)
(Proposed) Trade Name	Reyataz
Therapeutic Class	HIV Protease Inhibitor
Applicant	Bristol Myers Squibb
Formulation(s)	Capsule
Dosing Regimen	400mg or 300mg orally daily plus ritonavir (RTV) 100mg daily
Indication(s)	Treatment of HIV-1 infection
Intended Population(s)	Pediatric Patients

Template Version: March 6, 2009

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Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

FDA review of the Applicant's pharmacokinetic modeling and 96 week safety and antiviral activity in pediatric subjects supports the Applicant's proposed revised dosing of atazanavir (ATV) capsules and updating of pediatric labeling. The Applicant's proposed dosing streamlined the boosted (co-administered with ritonavir) ATV capsule dosing for pediatric patients by:

1) combining two dosing regimens: one for antiretroviral (ARV)-naïve and the other for ARV-experienced pediatric patients into a single regimen
2) allowing for all pediatric patients to use the 100mg dose of RTV
3) allowing for dosing of ARV-experienced patients weighing 15-25kg, for whom a dose was not specified in the previously (March 2008) approved pediatric ATV capsule prescribing information, because of concerns about decreased ATV exposure.

With regard to efficacy and safety, the Applicant's proposed label changes are acceptable. There are no new safety concerns. The Applicant updated the label with safety data up to 96 weeks. Therefore, this reviewer recommends approval of the supplement.

1.2 Risk Benefit Assessment

This supplement involves simplification of dosing for pediatric patients ages 6 to < 18 years old (see above), and inclusion of a dosing regimen for treatment experienced patients, age 6 years and above, weighing 15-25kg to the approved dosing regimen based on pharmacokinetic modeling and simulation performed by the applicant. No new safety signal was identified on review of the 96 week data; therefore, the risk-benefit assessment made with the March 25, 2008 Clinical Review of NDA 21-567 S015 remains favorable.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies (REMS)

No REMS is recommended for this supplement.

Recommendations for Postmarket Requirements and Commitments (PMC)

If approved, this supplement will allow the Applicant to complete their post-marketing commitment from their March 2008 pediatric capsule approval using the proposed

simplified dosing regimen for pediatric patients ages 6 to < 18 years old. No new PMR is recommended for this supplemental application.

2 Introduction and Regulatory Background

2.1 Product Information

Established Name: Atazanavir
Trade Name: Reyataz
Chemical: $C_{38}H_{52}N_6O_7 \bullet H_2SO_4$
Class: Protease Inhibitor
Formulation: Capsules (100 mg, 200 mg, 300 mg, 400 mg)

Adult Dosage:

1) 300 mg daily and RTV 100 mg daily for treatment-naïve and treatment-experienced adults
2) 400 mg daily for treatment-naïve adults who are intolerant to ritonavir
3) 400 ATV and 100mg RTV for treatment experienced patients who are receiving concomitant tenofovir and an H_2-receptor antagonist
4) ATV-boosted RTV should not be co-administered with proton-pump inhibitors or efavirenz in treatment-experienced patients

Pediatric Dosage:
The following table shows currently approved dosing in treatment-naïve pediatric patients ages 6 to < 18 years old (Table 1):

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

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

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

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

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

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

[c] Ritonavir liquid.

[d] Ritonavir capsule or liquid.

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

Therapy-Experienced Pediatric Patients

The currently approved dosing of REYATAZ with ritonavir in treatment-experienced patients ages 6 to < 18 years old is shown in Table 2.

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

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

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

[b] The dosage was calculated as REYATAZ 7 mg/kg with ritonavir 4 mg/kg once daily with food not to exceed REYATAZ 300 mg and ritonavir 100 mg.

[c] Ritonavir capsule or liquid.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 3 shows the antiretroviral agents currently approved for use in pediatric patients.

Table 3: Approved Pediatric Antiretrovirals

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)			
Brand Name	**Generic Name(s)**	**Manufacturer Name**	**Pediatric Use Labeling**
Combivir	lamivudine (LMV) and zidovudine (ZDV),	GlaxoSmithKline	≥12 years
Emtriva	emtricitabine, FTC	Gilead Sciences	0-3 months and above
Epivir	lamivudine, 3TC, LMV	GlaxoSmithKline	≥3 months
Hivid	zalcitabine, ddC, dideoxycytidine	Hoffmann-La Roche	≥13 years
Retrovir	zidovudine, ZDV, azidothymidine, AZT	GlaxoSmithKline	≥ 6 weeks
Trizivir	abacavir (ABC), zidovudine (ZDV), and lamivudine (LMV)	GlaxoSmithKline	Adolescents > 40kg
Videx	didanosine, ddI, dideoxyinosine	Bristol Myers-Squibb	≥ 2 weeks
Zerit	stavudine, d4T	Bristol Myers-Squibb	Birth-13 days and above
Ziagen	abacavir, ABC	GlaxoSmithKline	≥ 3 months
Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)			
Brand Name	**Generic Name**	**Manufacturer Name**	**Pediatric Use Labeling**

Rescriptor	delavirdine, DLV	Pfizer	≥ 16 years
Sustiva	efavirenz, EFV	Bristol Myers-Squibb	≥3 years
Viramune	nevirapine, NVP, BI-RG-587	Boehringer Ingelheim	≥ 2 months
Protease Inhibitors (PIs)			
Brand Name	**Generic Name(s)**	**Manufacturer Name**	**Pediatric Use Labeling**
Agenerase	amprenavir, APV	GlaxoSmithKline	≥ 4 years
Aptivus	Tipranavir, TPV	Boehringer Ingelheim	≥ 2 years
Invirase	saquinavir mesylate, SQV	Hoffmann-La Roche	≥16 years
Kaletra	lopinavir and ritonavir, LPV/RTV	Abbott Laboratories	≥ 14 days
Lexiva	Fosamprenavir Calcium, FOS	GlaxoSmithKline	≥ 2 years
Norvir	ritonavir, ABT-538, RTV	Abbott Laboratories	>1 month
Prezista	Darunavir, DRV, TMC-114	Tibotec, Inc.	>6 years
Viracept	nelfinavir mesylate, NFV	Agouron Pharmaceuticals	≥2 years
Fusion Inhibitors			
Brand Name	**Generic Name**	**Manufacturer Name**	**Pediatric Use Labeling**
Fuzeon	enfuvirtide, ENF, T-20	Hoffmann-La Roche & Trimeris	≥ 16 years
CCR5 Co-receptor Antagonist –HIV entry inhibitor			
Brand Name	**Generic Name(s)**	**Manufacturer Name**	**Pediatric Use Labeling**
Selzentry	maraviroc, MVC	Pfizer	≥ 16 years
HIV Integrase Inhibitor			
Brand Name	**Generic Name**	**Manufacturer Name**	**Pediatric Use Labeling**

Isentress	raltegravir, RAL	Merck and Co.	≥ 16 years

2.3 Availability of Proposed Active Ingredient in the United States

The active moiety is currently approved and available for use in the US.

2.4 Important Safety Issues with Consideration to Related Drugs

Class-related adverse events/laboratory abnormalities and potential for significant drug-drug interaction potential are common for the approved protease inhibitors (PIs). Ritonavir (RTV) has significant drug-drug interactions due to its potent inhibition of CYP3A4 metabolism. As with other PIs, the ATV label includes warnings and precautions for new onset diabetes, hyperglycemia, hepatotoxicity, rash, lipodystrophy, hypertriglyceridemia, hypercholesterolemia, hemolytic anemia, increased bleeding episodes in patients with hemophilia, and fat redistribution.

Summary of Presubmission Regulatory Activity Related to Submission

On March 25, 2008 the applicant was released from the following original Phase 4 commitment, which was agreed upon July 6, 2004:

> "A pediatric study or studies under PREA for the treatment of HIV infection in pediatric patients ages greater than or equal to 3 months to 18 years to determine safe and appropriate dosing".

In NDA 21-567 SE5-015 (letter date: September 27, 2007), the Applicant submitted data for the ATV capsule formulation in patients six years to 18 years of age. In that submission, the Applicant requested a partial pediatric deferral of the requirement specific to pediatric patients between the ages of three months to less than six years old. A partial waiver of PREA requirements for pediatric patients younger than three months was previously granted due to the potential issue of neonatal and/or infant hyperbilirubinemia. The clinical review team recommended granting the partial deferral pending the submission of the pediatric supplement for the powder formulation. From a preliminary review of the data from pediatric patients who received the powder formulation, the review team was concerned that the Applicant would not have the safety data for a minimum of 100 patients treated at or above the recommended ATV dose for 24 weeks. On March 25, 2008, the review team recommended the following PREA requirement that was accepted by the Applicant:

> "Deferred pediatric study or studies under PREA for the treatment of HIV-1 infection in pediatric patients ages ≥ 3 months to 18 years to obtain a minimum of 100 patients followed for safety for a minimum of 24 weeks at the recommended dose or any higher doses studied during pediatric development".

On July 29, 2009, the Applicant responded with a PMC study protocol that incorporated an unapproved streamlined capsule dosing regimen.

On November 18, 2009, DAVP informed the Applicant that the streamlined doing regimen must be approved via an NDA supplement before the regimen could be used in the PMC study for fulfillment of the PREA requirement.

On January 19, 2010, DAVP agreed to the delayed start of the PMC study to allow time for the submission and review of an NDA containing the revised pediatric capsule dosing.

Studies currently planned or ongoing to fulfill PREA requirements and Pediatric Written Request:

Ongoing:
Study AI424397: Single arm, PK, safety and activity study of ATV powder formulation co-administered with ritonavir in pediatric patients ≥ 3 months and <6 years of age.

Planned:
Study AI424452: Single arm safety study of ATV capsule co-administered with ritonavir, using the streamlined dosing included in the current supplement, in pediatric patients ≥ 6 years to <17 years of age.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

There were no major concerns with the current submission that necessitated an inspection.

Compliance with Good Clinical Practices

As stated in the interim Clinical Study Report (Study AI424020):

1) A total of 36 sites enrolled or provided care for subjects in US and South Africa.

2) The Investigator at each site was responsible for conducting the study according to the protocol and International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines.

3.3 Financial Disclosures

Form FDA 3454 and list of investigators with financial disclosure information was reviewed and found to be acceptable.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

This sNDA contained no new chemistry, manufacturing and controls (CMC) data. Please refer to the original NDA review for CMC information.

4.2 Clinical Virology

As reviewed previously, 51% (n=25) of treatment-experienced (TE) subjects in Study AI424020 had PI resistance-associated substitutions at baseline and of these 88% (n=22) failed. Please refer to list of subjects with baseline PI resistance in Dr. Lisa Naeger's virology review of 3/19/08. No new resistance data were included in this submission.

4.3 Preclinical Pharmacology/Toxicology

This sNDA contained no new preclinical pharmacology/toxicology data. Please refer to the original Pharmacology/Toxicology review of the NDA for additional information.

Clinical Pharmacology

This supplement was submitted mainly for the purpose of revising pediatric capsule dosing. The revised pediatric ATV/RTV dosing recommendations in this supplement were mainly based on comparisons of pharmacokinetic parameters in HIV-infected pediatric subjects and adults treated with ATV or ATV/RTV. The exposures in adults after 400 mg of ATV once daily for treatment-naive subjects (Study 008) and after 300/100 mg of ATV/RTV once daily (ATV/RTV 300/100) for treatment-experienced subjects (Studies 074, 089, and 137) were used as a reference for this comparison. The applicant also conducted simulations based on their population PK model.

Drs. Jiang Liu and Pravin Jadhav reviewed the PK modeling and simulation provided in this submission and concluded that the following proposed changes in ATV/RTV dosing were acceptable:

1. Extend the use of ATV/RTV to treatment-experienced patients weighing 15 to 25 kg
2. Simplify the current 250 mg ATV dosing that requires two different capsule strengths, (100-mg and 150-mg ATV capsules) in 32 to 40 kg weight patients to avoid two different capsule strengths.

4.4.1 Mechanism of Action

ATV is an azapeptide HIV-1 protease inhibitor (PI). The compound selectively inhibits the virus-specific processing of viral Gag and Gag-Pol polyproteins in HIV-1 infected cells, thus preventing formation of mature virions.

4.4.2 Pharmacodynamics

No pharmacodynamic analysis was provided with this submission.

4.4.3 Pharmacokinetics

See Clinical Pharmacology review by Drs. Jiang Liu and Pravin Jadhav review for details.

5 Sources of Clinical Data

This review is primarily based on data from one Phase 1/2 study, AI424020, conducted by the Applicant.

5.1 Tables of Studies/Clinical Trials

Only one clinical study, AI424020, was included with this sNDA application, as summarized in the following table (Table 4).

Table 4: Clinical Study AI424020 Summary

Study	Study Type	Country or Continent	Design	Dose and Duration	Total No. of Subjects	Status
Phase 1/2 Study						
AI424020	Pharmacokinetics, safety and efficacy	North America, including Puerto Rico and, South Africa	Ongoing multicenter, open-label study to determine the safety, PK, and optimal dose of ATV powder and capsules, administered with or without RTV, in pediatric subjects aged 91 days to 21 years infected with HIV	The starting dose of ATV was 310 mg/m^2 orally QD in the morning. ATV (with or without RTV) was administered in combination with 2 NRTIs, excluding abacavir sulfate and tenofovir disoproxil fumarate. Up to 96 weeks (Step 1) and until the study therapy was approved and readily available in South Africa (Step 2)	105 subjects in the ATV Capsule Cohort (63 treated with ATV alone and 42 treated with ATV/RTV). This cohort also includes the 7 subjects treated with ATV/RTV capsule using the newly proposed dosing regimen.	In progress

ATV/RTV, atazanavir/ritonavir

5.2 Review Strategy

Review of safety data included assessment and analysis of the adverse event database, case report tabulations and case report forms, when applicable.

5.3 Discussion of Individual Studies/Clinical Trials

Discussion of Individual Studies

Study AI424020 was originally reviewed with the submission of NDA 21-567 S015 September 2007(see Clinical Review of NDA 21-567 S015 March 25, 2008). In this submission, the Applicant focused on the assessment of data collected at 24 weeks of ATV (± RTV) therapy, following an initial period of dose finding. The September 2007 submission focused on the patients receiving the capsule formulation (ages ≥6 year to < 18 years of age) but the submission also included pharmacokinetic, safety and antiviral activity for the powder formulation. The safety data from patients receiving the powder formulation was reviewed in support of the capsule formulation; however the Applicant was not seeking an indication for the powder formulation at that time. Pediatric studies for the ATV powder formulation are ongoing currently. On March 25, 2008, pediatric dosing for the ATV capsule formulation for pediatric patients ≥6 year to < 18 years of age was approved (see Section 2.1).

TITLE OF STUDY

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

STUDY PERIOD:
Study Initiation Date: 12-Jun-2000
Study Completion Date: Ongoing: Data cut-off of 21-Sep-2010 for this submission

Methodology: This study (AI424020) was conducted by the Pediatric AIDS Clinical Trials Group (PACTG), and was a multicenter, open-label study conducted in the U.S. and South Africa to determine the safety, PK and optimal dose of ATV powder and capsules, administered with or without RTV, in HIV-infected pediatric subjects between the ages of 91 days to 21 years. Eligible subjects were assigned to treatment groups, stratified by age, ATV formulation, and concomitant administration of RTV (see Table 5 and Figures 1-2):

Table 5: Definition of Treatment Groups

Stratification and Regimens Used

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

Five subjects were to be enrolled in each group to receive the starting dose of ATV in the appropriate formulation and with or without RTV. If prospectively defined dose acceptance criteria, based upon intensive PK assessments made at Week 1 and safety data collected through Week 4, were not met, the ATV starting dose was either decreased or increased in the same group of 5 subjects (see (Figures 1 and 2). If dose acceptance criteria were met, an additional 5 subjects were enrolled at the same dose and the regimen was evaluated once more with 10 total subjects. If the dose acceptance criteria were still satisfied after 10 subjects, the group fully enrolled at that dosing cohort and treatment in Step 1 continued until 96 weeks after the last subject was enrolled in the respective study part (Part A: ATV alone; Part B: ATV with RTV).

Nucleoside backbone therapy was determined on the basis of the viral genotypic and phenotypic resistance profile and/or the subject's treatment history (abacavir and tenofovir use was not permitted). All groups began at 310 mg/m^2 of ATV daily; the boosted groups also received RTV 100 mg/m^2 daily (liquid, up to 100 mg daily or 100 mg capsule). All groups escalated or decreased ATV doses based on PK exposure targets and safety criteria.

Repeat 24-hour PK evaluations were done 2 weeks after initiation of a new ATV dose; in the event that further dose changes were needed at this time. Subjects automatically had dose increases based on an increase in body weight of ≥ 25%.

Figure 1: Study A424020 Dose Finding Algorithm

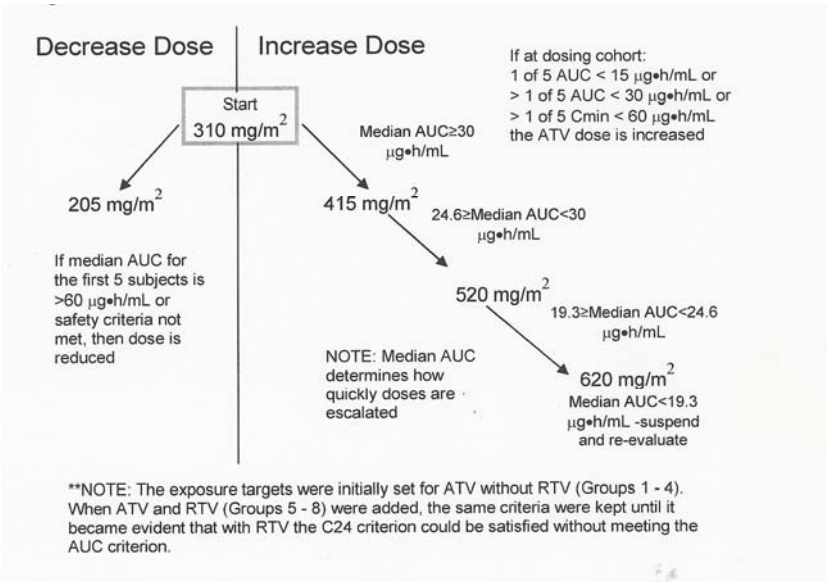
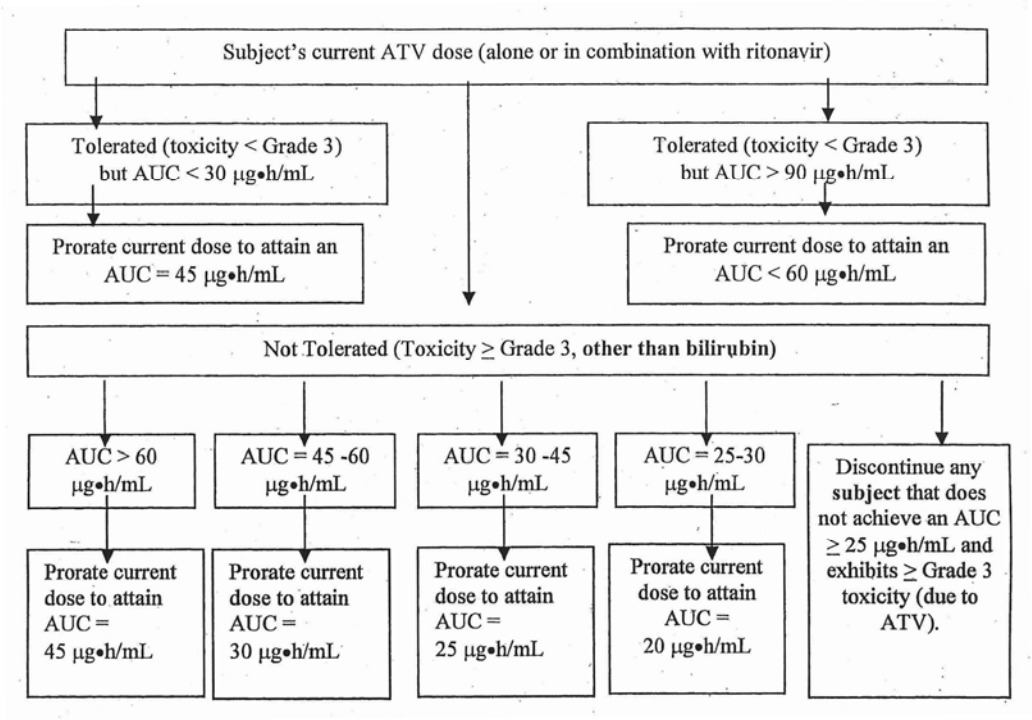


Figure 2: Study A424020 Dose Finding Decision Tree



Repeat 24-hour PK evaluations were done 2 weeks after initiation of a new ATV dose; in the event that further dose changes were needed at this time. Subjects automatically had dose increases based on an increase in body weight of ≥ 25%.

OBJECTIVES OF CURRENT SUBMISSION:

The current submission of the Applicant proposed a new ATV capsule dosing regimen for pediatric patients ages 6 years to less than 18 years and provided safety and ATV antiviral activity results up to 96 weeks to incorporate into labeling.

This Applicant's clinical study report (CSR) focuses on data from subjects dosed with ATV Capsules and treated with atazanavir (ATV) alone or with ritonavir (RTV), as well as a subgroup of subjects in this cohort treated with a newly proposed simplified ATV/RTV capsule dosing regimen. Data from prior studies involving patients dosed with ATV powder formulation were not included.

Primary Objectives Addressed in the Current Submission

To describe the safety and tolerability of ATV and ATV/RTV capsules in combination with 2 nucleoside reverse transcriptase inhibitors (NRTIs) in human immunodeficiency

virus (HIV)-infected pediatric subjects 6 to ≤ 18 years of age, and specifically in a subset of subjects treated with a newly proposed simplified ATV/RTV capsule dosing regimen.

To describe the pharmacokinetic (PK) profile and dosing schedule of ATV capsules with RTV in combination with 2 NRTIs in HIV-infected pediatric subjects treated with a newly proposed simplified ATV/RTV capsule dosing regimen.

Secondary Objectives Addressed in the Current Submission

- To assess the antiretroviral (ARV) activity of ATV and ATV/RTV containing regimens as measured by viral load response when given to protease inhibitor (PI) treatment-experienced and -naive study subjects

- To assess the ARV activity of ATV and ATV/RTV containing regimens as measured by duration of maximum response when given to PI treatment-experienced and -naive study subjects

- To assess the immunologic response of ATV and ATV/RTV containing regimens.

(See Section 5.3 of March 25, 2008 Clinical Review of NDA 21-567 S015 for additional details for Study AI424020)

6 Review of Efficacy

6.1 Indication

Reyataz (atazanavir sulfate) is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in patients six years and older. No new indication was proposed in this NDA supplement.

6.1.1 Methods

This review focuses primarily on the updated 96 week safety and efficacy data submitted for Study AI424020 including a separate analysis for seven (7) subjects who weighed between 15 to < 20 kg and 20-25 kg, who received the newly proposed dose or higher. The Applicant initially provided efficacy analyses using "Virological Response" (VR) and"Virological response – Observed Cases" (VR-OC) [see definitions below]. In the VR analysis, subjects with missing measurements were treated as failures; while in the VR-OC analysis, subjects with missing measurements were excluded from the analysis. Because the VR-OC analysis did not take into account missing data due to virological failure, background drug substitutions and adverse events (AEs), the review team requested that the Applicant submit efficacy results using the " Snapshot Analysis," which separates discontinuations due to virological failure and/or AEs from other causes of discontinuations such as loss to follow-up and withdrawal of consent. Please see the statistical review and evaluation of efficacy data was done by Dr. Lie Nie.

Reviewer Comment: The snapshot analysis of efficacy was not used to evaluate the adult data that is currently described in labeling. Therefore, it is not possible to make a direct comparison between the efficacy data from adults to the pediatric efficacy data evaluated with this supplement. In addition, the pediatric study was an uncontrolled open-label study, in contrast to many of the adult studies which are blinded and controlled.

Definitions:

VR *(*Virologic Response*)*: This analysis classified subjects who remained on study therapy as responders according to a single HIV RNA measurement < 50 c/mL or

<400c/mL closest to the planned week 96 visit and within a pre-defined visit window. The denominator was based on subjects who enrolled into the study. Subjects with HIV RNA ≥ 50 c/mL or ≥ 400 c/mL or subjects with missing measurements (for whatever reasons) were considered failures.

VR-OC *(*Virologic Response - Observed Cases*)*: This analysis classified subjects who remained on study therapy as responders according to a single HIV RNA measurement < 50 c/mL or < 400 c/mL closest to the planned week 96 visit and within a pre-defined visit window. The denominator was based on subjects who remained on study therapy through week 96. In this analysis, subjects with HIV RNA ≥ 50 c/mL or > 400 c/mL were considered failures. Subjects who remained on study therapy and were missing their week 96 measurement were responders only if the previous and subsequent measurements were < 50 c/mL or < 400c/mL.

6.1.2 Demographics

There were 105 subjects in the ATV Capsule Cohort (63 treated with ATV alone and 42 treated with ATV/RTV). The demographics of the capsule cohort was discussed in the Clinical Review of NDA 21-567 S015 (please see March 25, 2008 Clinical Review of NDA 21-567 S015 for additional details). This cohort also includes a subset of 7 subjects treated with ATV/RTV capsule at the newly proposed doses, as shown in Table 6.

Table 6: ATV/RTV Capsule Low Weight Cohort (Subset on Newly Proposed Dosing Regimen; n=7)

On Newly Proposed Dose (15 - < 20kg)					On Newly Proposed Dose (20- 25kg)		
Subject	Age (yrs)	Body Wt. (kg)	Time on Proposed Dose (wks)		Age (yrs)	Body Wt. (kg)	Time on Proposed Dose (wks)
(b) (6)	5.95	15.0	128.3				
					9.06	22.7	60.7
					6.98	21.5	41.0
	6.84	17.7	35.0		8.06	22.0	80.3
					8.87	20.9	57.3
					6.91	21.8	48.1
	6.47	17.0	23.7		7.00	20.5	76.1

6.2.1 Analysis of Efficacy Endpoint(s)

HIV RNA Level
Applicant's Analysis:
The Applicant reported a VR (Virologic Response) and VR-OC (Virologic Response - Observed Cases) analysis, as described below. Among 105 subjects in the ATV Capsule Cohort (6 to < 18 years of age) treated with the ATV capsule formulation, with or without RTV, the overall proportions by VR-OC analysis of antiretroviral (ARV)-naive and -experienced subjects with HIV RNA < 400 copies/mL at Week 96 were 78% (21/27) and 66% (21/32), respectively. The overall proportions of ARV-naive and -experienced subjects with HIV RNA < 50 copies/mL at Week 96 were 74% (20/27) and 47% (15/32), respectively.

Table 7 shows the applicant's VR and VR-OC analyses of virologic response results by ARV experience.

Table 7: Applicant's Analysis of Virologic Response (VR) /VR-OC by ARV Experience*

Method and LOQ	**ARV-naïve N = 43 (n/N%)**	**ARV-experienced N = 62 (n/N%)**
VR at Week 96		
<400 c/mL	21/43 (49)	21/62 (34)
<50 c/mL	20/43 (47)	15/62 (24)
VR-OC at Week 96		
<400 c/mL	21/27 (78)	21/32 (66)
<50 c/mL	20/27 (74)	15/32 (47)

Reference: Table 7.3.1. Study report.
n= number of subjects with HIV RNA <400 c/mL or < 50 c/mL at week 96
N= number of subjects (VR= number who enrolled into the study, VR-OC = number who remained on study therapy through week 96)
*see Section 6.1.1 for definition of VR and VR-OC
VR= virological response analysis
VR-OC= virological response – observed cases analysis
LOQ= limit of quantification for HIV RNA

Among 105 subjects in the ATV Capsule Cohort (6 to < 18 years of age), the overall proportion of subjects with HIV RNA < 400 copies/mL at Week 96 were 60% (21/35) and 88% (21/24), in those treated with ATV alone or ATV/RTV, respectively using the VR-OC analysis. The overall proportions of subjects with HIV RNA < 50 copies/mL at Week 96 were 49% (17/35) and 75% (18/24) in those treated with ATV alone or ATV/ RTV , respectively.

Table 8 shows the applicant's VR and VR-OC analyses of virologic response results by treatment

Table 8: Applicant's Analysis of Virologic Response (VR) /VR-OC by Treatment*

Method and LOQ	**ATV N = 63 (n/N%)**	**ATV/RTV N = 42 (n/N%)**
VR at Week 96		
<400 c/mL	21/63 (33)	21/42 (50)
<50 c/mL	17/63 (27)	18/42 (43)
VR-OC at Week 96		
<400 c/mL	21/35 (60)	21/24 (88)
<50 c/mL	17/35 (49)	18/24 (75)

Reference: Table 7.3.1. Study report.
n= number of with HIV RNA <400 c/mL or < 50 c/mL at week 96
N= number of subjects (VR= number who enrolled into the study, VR-OC = number who remained on study therapy through week 96)
*see Section 6.1.1 for definition of VR and VR-OC
VR= virological response analysis
VR-OC= virological response – observed cases analysis
LOQ= limit of quantitation for HIV RNA

Reviewer Comments: 1) The Applicant's VR analysis and DAVP's snapshot analysis generated the same success rate (< 50c/mL) for ARV-naive (47%) and ARV-experienced subjects (24%) at week 96 (see DAVP analysis below).
2) The VR analysis is similar to DAVP's snapshot analysis because it is an intent to treat (ITT) analysis with missing data for the week 96 window counted as failure.
3) The VR-OC analysis differed from DAVP's analysis because of differences in denominators. The VR-OC analysis is similar to per-protocol analysis since it uses only those subjects that complete 96 weeks of therapy for the denominator while snapshot analysis uses all treated subjects.

DAVP "Snapshot" Analysis:
The overall proportions of ARV-naive and -experienced subjects with HIV RNA < 50 copies/mL at Week 96 were 47% (20/43) and 24% (15/62), respectively. The overall proportions of ARV-naive and -experienced subjects with virologic failure at Week 96 were 30% (13/43) and 58% (36/62), respectively. The overall proportions of ARV-naive and -experienced subjects discontinued due to AEs prior to Week 96 were 12% (5/43) and 18% (11/62), respectively. Note that AEs count for all discontinuations due to reasons other than virologic failure in ARV-experienced subjects; while 5/43 (12%) ARV-naïve subjects discontinued for other reasons. See Table 9 for detail.

Table 9: DAVP "Snapshot" Analysis of Virologic Response by ARV experience

Virologic Response	**ARV-naive N = 43**	**ARV-experienced N = 62**
Success (HIV RNA < 50 c/mL)	**20 (47%)**	**15 (24%)**
Failure (HIV RNA ≥ 50 c/mL)	**13 (30%)**	**36 (58%)**
No Virologic Data at 96 week Window	10 (23%)	11 (18%)
AEs	5 (12%)	11 (18%)
Other Reasons*	5 (12%)	0

*Other reasons for missing data: lost to follow up, disallowed medications, site closure, and subject request withdrawal

Reviewer Comments: (1) *The success rate in pediatric ARV-naïve subjects (47%) is lower than what has been observed in adults at 96 weeks in Study 138 (75%) [see Dr. Chan-Tack's Clinical Review of NDA 21-567/S019 of September 22, 2009; however the clinical trials were of different design [e.g. randomized (adults) versus non-randomized (pediatric)], and were different with regard to background regimens and study conduct. In addition, the patient populations were different and the pediatric study was quite small in comparison to the larger adult study. Pediatric patients, in general, are different than adults because of growth and developmental stages (e.g. adolescence). Concerns in pediatrics include outgrowing the dose of their antiretrovirals and changes in adherence to antiretroviral therapy related to their psychosocial development.*

The following table (Table 10) shows the DAVP "snapshot" analysis of virologic response by treatment. In this analysis, both treatment-naïve and treatment-experienced subjects received either ATV alone or ATV/RTV.

Table 10: DAVP "Snapshot" Analysis of Virologic Response by treatment

	ATV N=63	**ATV/RTV N=42**
Success (< 50 c/mL)	**17 (27%)**	**18 (43%)**
Failure (≥ 50 c/mL)	**33 (52%)**	**16 (38%)**
No Virologic Data at week 96 Window	**13 (21%)**	**8 (19%)**
AE	10 (16%)	6 (14%)
Other Reasons	3 (5%)	2 (5%)

Reference: Dr. Lie Nie's statistical analysis

All but one of the seven (7) capsule cohort subset subjects who were administered the newly proposed dosing regimen had virologic success. The failed subject had HIV suppression during the study, but rebounded and reached < 50 c/mL again, ultimately remaining above 50 c/mL.

Reviewer Comments: DAVP's snapshot analysis of virologic response by treatment (ATV vs. ATV/RTV) is more conservative, with lower success rates, than the Applicant's VR-OC analysis because of the difference in denominators, as described above. DAVP's snapshot analysis results are closer to the Applicant's VR analysis, which is similar to an ITT analysis.

CD4 Cell counts
The applicant reported the observed case analysis as described above (similar to VR-OC). The mean increase from baseline in absolute CD4 count at 96 weeks of therapy was 394 cells/mm^3 in ARV-naive subjects and 252 cells/mm^3 in ARV-experienced subjects. However, subjects with missing measurements were excluded from the analysis; and therefore the applicant's analysis does not provide the best description of the efficacy results.

6.3 Efficacy Summary

See Dr. Lie Nie's Statistical review for full details.

In the applicant's reported Virological Response –Observed Cases (VR-OC) analysis, among 105 subjects in the ATV Capsule Cohort (6 to < 18 years of age) treated with the ATV capsule formulation, with or without RTV, the overall proportions of antiretroviral (ARV)-naive and -experienced subjects with HIV RNA < 400 copies/mL at Week 96 were 78% (21/27) and 66% (21/32), respectively. The overall proportions of ARV-naive and -experienced subjects with HIV RNA < 50 copies/mL at Week 96 were 74% (20/27) and 47% (15/32), respectively.

In the applicant's reported Virological Response analysis, among 105 subjects in the ATV Capsule Cohort (6 to < 18 years of age) treated with the ATV capsule formulation, with or without RTV, the overall proportions of antiretroviral (ARV)-naive and -experienced subjects with HIV RNA < 400 copies/mL at Week 96 were 49% (21/43) and 34% (21/62), respectively. The overall proportions of ARV-naive and -experienced subjects with HIV RNA < 50 copies/mL at Week 96 were 47% (20/43) and 24% (15/62), respectively.

In the DAVP analysis, using the "snap-shot" method, the overall proportions of ARV-naive and -experienced subjects with HIV RNA < 50 copies/mL at Week 96 were 47% (20/43) and 24% (15/62), respectively. The overall proportions of ARV-naive and -experienced subjects with virologic failure at Week 96 were 30% (13/43) and 58% (36/62), respectively. The overall proportions of ARV-naive and -experienced subjects discontinued due to AEs prior to Week 96 were 12% (5/43) and 18% (11/62), respectively.

Reviewer's Comment: In the statistical reviewer's subset analysis, virologic response was higher at the South African site in comparison to the U.S. site. However, because the numbers were small, the clinical significance of this finding is not known. The applicant suggested that it may be due to differences in adherence. Adherence was not measured at the South African site, so this hypothesis could not be explored.

7.0 Review of Safety

7.1 Methods

7.1.1 Categorization of Adverse Events

Adverse events were graded using the December 2004 Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.

7.2 Adequacy of Safety Assessments

The ATV capsule pediatric Study AI424020 included 105 subjects (63 treated with ATV alone and 42 treated with ATV/RTV). Seven (7) subjects were treated with ATV/RTV capsule at the newly proposed dosing regimen (ATV/RTV Capsule Low Weight Cohort). The Applicant provided updated 96 week safety data to include in product labeling. Because the information provided is an update, the adequacy of the data primarily relies on the original pediatric capsule submission which was approved in March of 2008 (please see the March 25, 2008 Clinical Review of NDA 21-567 S015 for additional details).

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In Study AI424020, 63 subjects were treated with ATV capsule alone and 42 were treated with ATV capsule /RTV for a total of 105 subjects. Of these subjects, 35 who were treated with ATV capsule alone (56%), and 24 who were treated with ATV capsule/RTV (57%), completed at least 96 weeks of treatment.

7.2.2 Explorations for Dose Response

As summarized in the original review of the pediatric capsule submission (see March 25, 2008 Clinical Review of NDA 21-567 S015), the adverse reactions of unconjugated hyperbilirubinemia and PR interval prolongation were dose- dependent in pediatric patients in a similar fashion to that observed in adults.

7.2.4 Routine Clinical Testing

See March 25, 2008 Clinical Review of NDA 21-567 S015 for details of routine testing.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Adverse events observed with the class of HIV protease Inhibitors (PIs) include new onset diabetes, hyperglycemia, hepatotoxicity, rash, lipodystrophy, hypertriglyceridemia, hypercholesterolemia, hemolytic anemia, increased bleeding episodes in subjects with hemophilia, and fat redistribution. These adverse events were extensively reviewed with the September 2007 supplement NDA 21-567 S015. Please see the March 25, 2008 Clinical Review of NDA 21-567 S015 for additional details.

7.3 Major Safety Results

7.3.1 Deaths

There were three deaths in Study AI424020. Two of the 3 subjects who died received the ATV capsule formulation alone without RTV. Both deaths occurred more than 56 days after the end of therapy and were not considered related to ATV by the investigators. The third death was in a 23 month old patient with a complicated past medical history treated with the ATV powder formulation who developed fever, vomiting and seizure while on therapy, subsequently developed respiratory distress and died of pneumonia and renal failure. These three deaths were extensively reviewed and discussed in the March 25, 2008 Clinical Review of NDA 21-567.

7.3.2 Nonfatal Serious Adverse Events (SAEs)

Nonfatal SAEs reported at 96 weeks were similar to those reported at 24 weeks, reviewed previously in March of 2008 (see Clinical Review of NDA 21-567 S015). However, as shown in Table 10, the number of SAEs increased over time, as expected. SAEs in patients treated with ATV capsule are shown in Table 11. Of note, there was an apparent increase from 5 to 10 SAEs in the Cardiac System Organ Class (SOC) for patients treated with ATV alone when comparing the 96 week results in the current pediatric submission compared to the September 2007 submission NDA 21-567 S015. However, on detailed review, none of the five additional cardiac SAEs were new. Two of these SAEs were ECG abnormalities that were originally classified as SAEs under the Investigations SOC. Another of these cardiac SAEs was previously listed as an AE that resulted in patient discontinuation from study (prolonged PR interval and low resting heart rate). The remaining two additional cardiac SAEs were the result of an updated narrative that reclassified the cardiac AEs as SAEs.

Table 11: Serious Adverse Events Identified in Prior (2007) and in Current Submission (2010) in both Treatment-Naïve and Treatment-Experienced Subjects Treated with ATV Capsules

SYSTEM ORGAN CLASS	ATV 2007	ATV 2010	ATV/RTV 2007	ATV/RTV 2010	TOTAL 2007	TOTAL 2010
PREFERRED TERM	(N = 63)	(N=63)	(N = 42)	(N = 42)	(N = 105)	(N = 105)
Any Adverse Experience	**31 (49)**	**41 (65)**	**22 (52)**	**28 (66)**	**53 (51)**	**69 (66)**
Cardiac Disorders including ECG abnormalities	**5 (8)**	**10 (16%)**	**0**	**0**	**5 (5)**	**10 (10%)**
Atrioventricular block (one subject: 2nd degree)	3 (5)	5 (8)	0	0	3 (3)	5 (5)
Congestive Heart Failure#	2 (3)	2 (3)	0	0	2 (2)	2 (2)
Cardiomyopathy#	1 (1)	1 (1)	0	0	1 (1)	1 (1)
Left Atrial Dilatation %	0	1 (2)	0	0	0	1 (1)
ECG QT prolongation	0	3 (5)	0	0	0	3 (3)
Gastrointestinal Disorders	**1 (2)**	**3 (5)**	**1 (2)**	**3 (5)**	**2 (2)**	6 (6)
Pancreatitis	1 (2)	1 (2)	0	0	0	1 (1)
Stomatitis	0	0	1 (2)	0	0	1 (1)
Diarrhea	0	0	0	1 (2)	0	1 (1)
Constipation	0	1 (2)	0	0	0	1 (1)
Vomiting	0	1 (2)	0	1 (2)	0	2 (2)
General Disorders OK	**0**	**0**	**1 (2)**	**1 (2)**	**1 (1)**	**1 (1)**
Pyrexia	0	0	1 (2)	1 (2)	1 (1)	1 (1)
Hepatobiliary Disorders	**0**	**1 (2)**	**1 (2)**	**1 (2)**	1 (1)	2 (2)
Jaundice	0	1 (2)	1 (2)	1 (2)	1 (1)	2 (2)
Infections and Infestations	**1 (2)**	**3 (5)**	**0**	**2 (5)**	**1 (1)**	5 (5)
Gastroenteritis	**0**	**0**	**0**	1 (2)	**0**	1 (2)
Pneumonia/Bronchopneumonia	1 (2)	2 (3)	0	1 (2)	1 (1)	3 (3)
Urinary Tract Infection	**0**	1 (2)	0	0	0	1 (2)

Injury, Poisoning, and Procedural Complications	0	0	0	2 (5)	0	2 (2)
Hand Fracture	0	0	0	1 (2)	0	1 (1)
Head Injury	0	0	0	1 (2)	0	1 (1)
Investigations	**27 (43)**	**27 (43)**	**21 (51)**	**22 (54)**	**48 (46)**	**49 (47)**
Blood bilirubin (including unconjugated) abnormal or increased (or hyperbilirubenemia)	25(40)	27 (43)	20 (49)	22 (54)	45 (43)	49 (47)
Bilirubin conjugated increased	0	2 (3)	0	0	0	2 (2)
Blood creatinine increased	0	0	1 (2)	1 (2)	1 (1)	1 (1)
Blood glucose increased	0	0	1 (2)	1 (2)	1 (1)	1 (1)
Blood potassium increased	0	0	1 (2)	1 (2)		
Blood Sodium decreased	1	1	0	0	1 (1)	1 (1)
Gamma-glutamyl transferase increased	1	1	1 (2)	1 (2)	1 (1)	1 (1)
Neutrophil count decreased			1 (2)	1 (2)		
Liver function test abnormal or hepatic enzyme increased	1	1	1	1	2 (2)	2 (2)
Metabolic and Nutrition Disorders	0	**2 (3)**	0	**0**	1 (2)	**3 (3)**
Hyponatremia or Blood Sodium decreased	0	2 (3)	0	1 (2)	0	3 (3)
Pregnancy, Puerperium and Perinatal	0	1 (2)	0	0	0	1 (1)
Spontaneous Abortion	0	1 (2)	0	0	0	1 (1)
Psychiatric Disorders	0	0	0	1 (2)	1 (2)	1 (1)
Attention Deficit/Hyperactivity Disorder	0	0	0	1 (2)	0	1 (1)
Suicidal Ideation	0	1 (2)	0	0	0	0
Renal and Urinary Disorders	0	1 (2)	0	0	0	0
Proteinuria	0	1 (2)	0	0	0	0
Skin and subcutaneous tissue disorder	0	**1 (2)**	0	**1 (2)**	0	**2 (2)**
Facial Wasting	0	1 (2)	0	0	0	1 (1)

Rash	0	0	0	1 (2)	0	1 (1)

Same patient with two cardiac preferred terms.
This patient subsequently died.
% patient also had a conduction disorder AE

Based on the results summarized in Table 11, there were no apparent differences in the SAE profile at week 24 or 96; however the numbers were small.

In the ATV/RTV capsule Low Weight Cohort four out of the seven subjects had SAEs while on the recommended dose. These are shown in Table 12. No pattern consistent with drug related causality was observed.

Table 12: ATV/RTV LOW WEIGHT COHORT SAEs

SYSTEM ORGAN CLASS	**(N = 7)**
PREFERRED TERM	
Any Adverse Experience	**4 (57%)**
Gastrointestinal Disorders	**1 (14%)**
Diarrhea	1 (14%)
Hepatobiliary Disorders	**2 (29%)**
Hyberbilirubinemia	2 (29%)
Infections and Infestations	**1 (14%)**
Pneumonia/Bronchopneumonia	1 (14%)
Injury, Poisoning, and Procedural Complications	1 (14%)
Head Injury	1 (14%)

Investigations	**1 (14%)**
Blood bilirubin (including unconjugated) abnormal or increased (or hyperbilirubenemia)	1 (14%)
Metabolic and Nutrition Disorders	**1 (14%)**
Hyponatremia or Blood Sodium decreased	1 (14%)
Psychiatric Disorders	1 (14%)
Attention Deficit/Hyperactivity Disorder	1 (14%)

7.3.3 Dropouts and/or Discontinuations

There was one additional discontinuation (due to prolonged PR interval and low resting heart rate) since the prior review in March of 2008. The pattern of toxicity-related discontinuation did not change.

7.3.4 Significant Adverse Events

Grade 2 to 4 AEs

The most common Grade 2-4 AEs (≥ 5% in any group) in the ATV Capsule Cohort were very similar to what was previously summarized in March 2008 (see Clinical Review of NDA 21-567 S015). The Applicant modified Section 6.2 Clinical Trial Experience in Pediatric Patients of their proposed labeling with updated numbers and proportion of subjects with adverse events (see Appendix).

While the 7 subjects of the ATV capsule cohort subset were on the newly proposed dose, they all had Grade 2-4 AEs (see Table 11), as shown in Table 13. The pattern of AEs was similar to the overall rate of Grade 2-4 AEs for the entire cohort. The most common Grade 2-4 AEs were abnormal or increased blood bilirubin and increased unconjugated blood bilirubin.

Table 13: Adverse Events (Grade 2-4) - ATV/RTV Capsule Low Weight Cohort Occurring up to 56 Days after Last Dose of Drug while on Proposed Dose

SYSTEM ORGAN CLASS	**(N = 7)**
PREFERRED TERM	
Any Adverse Experience	**7 (100 %)**
Cardiac Disorders including ECG abnormalities	**1 (14)**
Conduction Disorder	1 (14)
Gastrointestinal Disorders	**2 (29)**
Diarrhea	1 (14)
Vomiting	1 (14)
Hepatobiliary Disorders	**2 (29)**
Jaundice	2 (29)
Investigations	**6 (86)**
Alanine aminotransferase increase	1 (14)
Blood bilirubin (including unconjugated) abnormal or increased (or hyperbilirubenemia)	4 (57)
Bilirubin conjugated increased	1 (14)
Bilirubin unconjugated increased	4 (57)
Blood glucose decreased	1 (14)
Blood potassium abnormal	1 (14)
Bllood potassium increased	1 (14)
Blood Sodium decreased	1 (14)
Hemoglobin increased	3 (43)
Metabolic and Nutrition Disorders	**1 (14)**
Hyponatremia or Blood Sodium decreased	1 (14)
Psychiatric Disorders	1 (14)
Attention Deficit/Hyperactivity Disorder	1 (14)
Respiratory Disorder	1 (14)
Tachypnea	1 (14)

7.3.5 Submission Specific Primary Safety Concerns

The safety profile of ATV was taken into consideration for this detailed review of specific safety concerns such as hyperbilirubinemia/jaundice, rash, hepatotoxicity, hyperglycemia, nephrolithiasis, and fat redistribution. Overall, no new safety signals or unexpected toxicities were observed in the 96 week safety data.

Jaundice/Hyperbilirubinemia/Ocular Icterus

Overall, in pediatric subjects treated with ATV capsule (both unboosted (N=63) and boosted (with RTV) (N=41) jaundice and ocular icterus were observed in 15-16% of patients. In the ATV Capsule Low Weight Cohort (N=7), mild jaundice was observed in 43% (N=3) of patients. Although the proportion of subjects with jaundice was higher in the subset, because the number of subjects is small, no definitive conclusions can be drawn regarding relative frequency of jaundice.

Grade 2-4 Treatment Emergent Hyperbilirubinemia

The overall incidence of treatment-emergent Grade 3-4 hyperbilirubinemia in pediatric subjects in Study AI424020 dosed with ATV capsules (ATV alone + ATV-RTV) was 52-67% (see Table 14) In comparison, in adults treated with ATV-RTV in Study AI424-045, 49% of subjects had treatment emergent Grade 3-4 hyperbilirubinemia..

Treatment-emergent Grade 3-4 unconjugated (indirect) hyperbilirubinemia, a known dose-dependent toxicity of ATV, was observed in 51-57% of pediatric subjects dosed with ATV capsules (ATV alone + ATV-RTV) in Study AI424020. Grade 3-4 treatment-emergent direct hyperbilirubinemia was observed in 13% (7/56) of subjects treated with ATV alone and 22% (9/41) of subjects treated with ATV-RTV. One ATV-treated subject, who had a prior history of interstitial lung disease, cor pulmonale, congestive heart failure, and hepatomegaly but with normal total bilirubin of 0.2 at enrollment, experienced Grade 4 treatment-emergent direct hyperbilirubinemia. Both ATV and RTV are labeled for hepatotoxicity mainly in patients with underlying liver disease.

Table 14: Grade 3-4 Treatment Emergent Hyperbilirubinemia: All ATV Capsule Cohort

Laboratory Abnormality	ATV (N=63)	ATV-RTV (N=42)	Total (N=105)
Total Bilirubin (>ULN 1.2mg/dL)	33 (52%)	28 (67%)	61 (58%)
Unconjugated Bilirubin (>ULN 1.2 mg/dL)	31 (51%)*	24 (57%)	55 (52%)
Conjugated Bilirubin (>ULN 0.3mg/dL)	7 (13%)**	9 (22%)***	13 (13.4%)#

* Two ATV patients had missing indirect bilirubin samples (31/61)
** Six ATV patients had abnormal direct bilirubin at baseline and one patient had a missing sample (7/56)
*** One patient had abnormal direct bilirubin at baseline (9/41)
# 13/97 =4.1%

For the ATV-RTV Capsule Low Weight cohort, the frequency of treatment emergent Grade 3-4 total hyperbilirubinemia and indirect hyperbilirubinemia was similar to the entire ATV capsule cohort (see Table 15). The frequency of treatment emergent Grade 3-4 direct hyperbilirubemia was similar to ATV capsule subjects receiving coadministered ritonavir (ATV-RTV).

Table 15: Grade 3-4 Treatment Emergent Hyperbilirubinemia: ATV Capsule Low Weight Cohort

Laboratory Abnormality	ATV-RTV (N=7)
Total Bilirubin (>ULN 1.2mg/dL)	4 (57%)
Unconjugated (indirect) Bilirubin (>ULN 1.2 mg/dL)	3 (43%)
Conjugated (direct) Bilirubin (>ULN 0.3mg/dL)	2 (29%)

7.4 Safety Summary

Study AI424020 is a pharmacokinetic and safety study of ATV which established dosing for pediatric subjects six years and older for the capsule formulation which was approved in March of 2008. At the time of approval, the number of subjects dosed at or above the approved dosing was smaller than the regulatory norm for a pediatric product, and a post-marketing commitment to increase the number of subjects dosed with atazanavir for safety was requested. Prior to starting the safety study in with the capsule formulation, the Applicant wanted to streamline dosing (i.e., have one dosing regimen for both ARV-naïve and ARV-experienced patients with the use of 100mg RTV) and to extend ATV-RTV dosing to ARV- experienced subjects who weighed between 15 and 25 kg.

In addition to modeling and simulation of previously submitted data, this submission included safety data for subjects who had been dosed up to 96 weeks and greater. The Applicant did not identify any new safety concerns, and none were identified by this reviewer. The atazanavir safety profile in adults and pediatric patients (ages 6 to < 18 years old) is well-characterized, and is currently described in approved labeling. Atazanavir has been associated with hyperbilirubinemia and PR prolongation on ECG, both of which were specifically assessed in this study. The seven subjects in the ATV-RTV capsule Low Weight Cohort had a similar adverse event profile as that observed in the rest of the cohort.

There were no additional deaths since the prior supplement and only one additional toxicity-related discontinuation. The additional 96 week data reinforces the known safety profile for atazanavir, with the main concerns still being indirect hyperbilirubinemia and PR interval prolongation, both of which are dose-dependent.

Hyperbilirubinemia:
In the ATV Capsule Cohort, the majority of subjects had Grade 2-4 AEs of hyperbilirubinemia. Fifteen percent of subjects had Grade 2-4 AEs of jaundice and/or ocular icterus. In the ATV/RTV Capsule Low Weight Cohort that received the proposed recommended dose, all 7 subjects had Grade 2-4 AEs of hyperbilirubinemia. While on the newly proposed dosing regimen, 4 of 7 subjects had Grade 2-4 AEs of hyperbilirubinemia; while no Grade 2-4 AEs of jaundice or ocular icterus were reported.

P-R interval Prolongation:

Atazanavir has been associated with Type 1 AV block in a dose-dependent fashion in both adult and pediatric patients. In the pediatric ATV Capsule Cohort in study AI424020, 5/105 (5%) subjects had Grade 2-4 AEs in the MedDRA system organ class of Cardiac Disorders. One subject had first degree AV block, one subject had both first and second degree AV block, one subject had had second degree AV block alone, one subject had bradycardia, one subject had cardiomyopathy, and one subject had congestive heart failure. In the current submission, 10 subjects reportedly had SAEs in the MedDRA system organ class of Cardiac Disorders; however, 5 of these events were previously

submitted (2007), but were categorized differently before. (See Section 7.3.2 Nonfatal Serious Adverse Events (SAEs) and the March 25, 2008 Clinical Review for additional details).

None of the 7 subjects in the ATV/RTV Capsule Recommended Dose Cohort had Grade 2-4 Cardiac Disorder AEs.

Reviewer Comment: The safety data from the small (N=7) Capsule ATV-RTV Low Weight Cohort suggests that the Applicant's proposed ATV-RTV dosing regimen for subjects 15-25kg has a similar AE profile to that observed previously in adult and pediatric patients. Additional data from the Applicant's planned PMC safety study will help to further define the safety of the Applicant's streamlined dosing regimen.

8 Appendix

8.1 Labeling Recommendations: Applicant's proposed changes to Proposed Package Insert and Patient Package Insert

(b) (4)

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALAN M SHAPIRO
10/04/2011

MARY E SINGER
10/05/2011
Agree with review and recommendations for approval of this supplement.