CLINICAL REVIEW

Application Type	NDA Supplement
Application Number(s)	206352-S00, 21567-S35
Priority or Standard	P
Submit Date(s)	December 2, 2013
Received Date(s)	December 2, 2013
PDUFA Goal Date	June 2, 2014
Division / Office	OAP/DAVP
Reviewer Name(s)	Alan M. Shapiro, MD, Ph.D.
Review Completion Date	May 1, 2014
Established Name	Atazanavir (ATV)
(Proposed) Trade Name	Reyataz
Therapeutic Class	HIV protease inhibitor
Applicant	Bristol Myers Squibb
Formulation(s)	Powder for oral use
Dosing Regimen	Once daily
Indication(s)	Treatment of HIV in combination with other agents,
Intended Population(s)	Pediatric Patients three months and older (b) (4)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of NDA 206352-S00 for Reyataz powder and accompanying NDA supplement 21567-S35 for Reyataz capsules with modification of the proposed labeling. As recommended by the SEALD team, the proposed package insert will also be revised to correspond with current labeling guidances.

1.2 Risk Benefit Assessment

There were no new safety finding in trials AI424397 and AI424451. Therefore, the risk-benefit assessment for Reyataz powder formulation for pediatric patients ≥3 months old and weighing more than 10 kg is acceptable.

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

No REMS is needed for this NDA or the accompanying NDA supplement.

1.4 Recommendations for Postmarket Requirements (PMR) and Commitments

The Applicant has fulfilled and will be released from the March 25, 2008 PMR:

'Deferred pediatric study or studies under PREA for the treatment of HIV - 1 infection in pediatric patients ages greater than or equal to 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.'

However, a new PMR will be issued to address dosing in the 5-10 kg weight band of pediatric patients 3 months and older:

Deferred pediatric study or studies under PREA for the treatment of HIV - 1 infection in pediatric patients 3 months and older who weigh 5 kg to less than 10 kg to determine an appropriate Reyataz dose in that population.'

2 Introduction and Regulatory Background

2. Product Information

Established name: Atazanavir (ATV)
Trade Name: REYATAZ
Chemical: (3*S*,8*S*,9*S*,12*S*)-3,12-Bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6-[[4-(2-pyridinyl)phenyl]methyl]-2,5,6,10,13-pentaazatetradecanedioic acid dimethyl ester, sulfate (1:1)
Class: Antiviral agent – Protease Inhibitor
Proposed indication: Treatment of HIV-1 infection in pediatric patients three months and older more than 5 kg and less than six years of age.
Note: Usually co-administered with ritonavir (RTV) except in intolerant patients
Currently recommended Reyataz capsule dosing and regimen: For patients 6 years to less than 18 years of age:

Weight Range	Recommended Dose
15 to <20 kg	ATV/RTV 150/100mg given once daily
20 to <40 kg	ATV/RTV 200/100mg given once daily
➢ 40 kg	ATV/RTV 300/100mg given once daily

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently 28 antiretroviral drug products (see Table 1) are approved in the US for the treatment of HIV infection in pediatric patients less than 18 years of age, some in multiple formulations and fixed drug combinations. Six classes of antiretroviral agents exist. The classes are based on the mechanism of action in the HIV life cycle: nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors, integrase inhibitor and entry inhibition via CCR5 co-receptor blockade. There also are complete therapy fixed dose combinations.

Of the approved and marketed NRTI's (including combination products), only abacavir / lamivudine (Epzicom®) has no pediatric labeling. Of the approved NNRTIs, only rilpivirine (Edurant®) does not have pediatric labeling. Of the approved PIs, only indinavir (Crixivan®) does not have pediatric labeling. The fusion inhibitor enfuvirtide (Fuzeon®) has pediatric labeling. The CCR5 co-receptor antagonist HIV entry inhibitor maraviroc (Selzentry®) does not have pediatric labeling. Both HIV integrase inhibitors

raltegravir (Isentress®) and dolutegravir (Tivicay®) have pediatric labeling. Of the three fixed dose combinations providing a complete regimen, only efavirenz/ emtricitabine/ tenofovir disoproxil fumarate (Atripla®) has pediatric labeling.

Table 1: Approved HIV Antiretrovirals and Pediatric Use Labeling

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Brand Name	Generic Name	Manufacturer Name	Pediatric Use Labeling	Special Information
Combivir[1]	lamivudine and zidovudine	ViiV Healthcare	**>12 yr and ≥ 30 kg:** Tablet: 1 tablet (300 mg zidovudine/ 150 mg lamivudine) twice daily	Not recommended for children <12 yrs. due to fixed dosage form that cannot be adjusted for this population Generic formulation available
Emtriva[2]	emtricitabine (FTC)	Gilead Sciences	**0-3 months:** Solution: 3 mg/kg once daily **3 months-17 yr.** Solution: 6 mg/kg once daily **>33 kg**: Capsule: 200 mg once daily Solution: 6 mg/kg once daily	**Maximum dosage:** Solution: 240 mg/day
Epivir[3]	lamivudine (3TC)	ViiV Healthcare	**3 months-16 yr:** Solution or tablet: 4 mg/kg twice daily	**Maximum dosage:** 150 mg twice daily Generic formulation available
Epzicom[4]	abacavir and lamivudine	ViiV Healthcare	Safety and effectiveness in	Not recommended for children < 12

			pediatric patients not established	yrs. due to fixed dosage form that cannot be adjusted for this population
Retrovir[5]	zidovudine (ZDV), azidothymidine (AZT)	ViiV Healthcare	**For treatment of HIV-1 infection:** Tablet/capsule/solution: **4 - < 9kg:** 24 mg/kg/day divided two or three times daily **≥ 9 - < 30kg:** 18 mg/kg/day divided two or three times daily **≥ 30kg:** 600 mg/day divided two or three times daily **For prevention of maternal-fetal neonatal transmission** **<12 hours after birth-6 weeks:** Solution: 2 mg/kg every 6 hours until 6 weeks of age IV: 1.5 mg/kg infused over 30 minutes every 6 hours until 6 weeks of age	**Maximum dosage:** 200 mg every 8 hours Note different dosages for treatment vs. prevention of maternal-fetal transmission IV form used if neonate unable to receive oral form Generic formulation available
Trizivir[6]	abacavir, zidovudine, and lamivudine	ViiV Healthcare	Safety and efficacy not established in pediatric patients, and should not be administered to adolescents weighing < 40 kg	
Truvada[7]	tenofovir disoproxil fumarate and	Gilead Sciences	**>12 years and ≥35 kg:** 1 tablet (300 mg tenofovir /200	Not recommended for children <12 yrs. due to fixed dosage

	emtricitabine		emtricitabine) once daily	form that cannot be adjusted for this population
Videx EC[8]	didanosine (ddI)	Bristol Myers Squibb	**≥ 6 years and 20kg:** Capsule **20 - <25 kg:** 200 mg once daily **25 - <60 kg:** 250 mg once daily **>60 kg:** 400 mg once daily	**Maximum Dosage:** 400 mg once daily Videx powder for oral solution is available for children who cannot swallow tablets or weigh less than 20 kg (see below).
Videx[9]	didanosine (ddI)	Bristol Myers Squibb	Powder for oral solution: **2 weeks-8 months:** 100 mg/m2 twice daily **>8 months:** 120 mg/m2 twice daily; dosing range 90-150 mg/m2 †	**Maximum Dosage:** 400 mg per day Dosing recommendations for patients less than 2 weeks of age cannot be made because the PK in these children are too variable to determine appropriate dose. There is no data on once-daily dosing in pediatric patients. Patients with CNS disease may require higher doses. Generic formulation available
Viread[10]	tenofovir disoproxil fumarate (TDF)	Gilead Sciences	**2-12 yrs:** Oral powder/tablet: 8 mg/kg once daily **>12 yrs and 35 kg:** Tablet: 300 mg once	**Maximum dosage:** 300 mg once daily Please refer to the package insert for tablet dosing by

			daily	weight band for children who weigh > 17 kg
Zerit[11]	stavudine (d4T)	Bristol Myers Squibb	**Birth-13 days:** Tablet/oral solution: 0.5 mg/kg every 12 hours **>14 days and <30 kg:** Tablet/oral solution: 1 mg/kg every 12 hours **>30 - < 60 kg:** 30 mg every 12 hours **>60 kg:** 40 mg every 12 hours	**Maximum Dosage:** 40 mg every 12 hours Generic formulation available
Ziagen[12]	abacavir (ABC)	Glaxo Smith Kline	**3 months-16 yr:** Tablet/oral solution: 8 mg/kg twice daily	**Maximum dosage:** 300 mg twice daily Please refer to the package insert for tablet dosing by weight band for children who weigh > 14 kg

Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Brand Name	Generic Name	Manufacturer Name	Pediatric Use Labeling	Special Information
Edurant[13]	rilpivirine (RPV)	Janssen	Safety and efficacy not established in pediatric patients	
Intelence[14]	etravirine (ETV)	Janssen	**≥ 3 years and > 16 kg:** Tablets **16 - < 20 kg**: 100 mg twice daily **20 - < 25 kg**: 125 mg twice daily	**Maximum dosage:** 200 mg twice daily

			25 - < 30 kg: 150 mg twice daily **≥ 30 kg**: 200 mg twice daily	
Rescriptor[15]	delavirdine (DLV)	ViiV Healthcare	Safety and effectiveness not established in HIV-1–infected individuals <16 years	
Sustiva[16]	efavirenz (EFV)	Bristol Myers-Squibb	**>3 months and 3.5 kg** Tablet/capsule: **3.5 - < 5 kg:** 100 mg once daily **5 - <7.5 kg**: 150 mg once daily **7.5 - <15 kg**: 200 mg once daily **15 - <20 kg:** 250 mg once daily **20 - <25 kg:** 300 mg once daily **25 - <32.5 kg**: 350 once daily **32.5 - <40 kg**: 400 mg once daily **>40 kg:** 600 mg once daily	**Maximum Dosage:** 600 mg once daily For children who cannot swallow capsules, the capsule contents can be administered with a small amount of food or infant formula using the capsule sprinkle method of administration. Please refer to the package insert for instructions. Tablets should NOT be crushed. Dosing recommended at bedtime to limit CNS effects
Viramune[17]	nevirapine (NVP)	Boehringer Ingelheim	**≥ 15 days:** Oral suspension/tablet: 150 mg/m2 once daily for 14 days, then 150 mg/m2 twice daily†	**Maximum dosage:** 400 mg per day

Viramune XR[18]	Nevirapine (NVP)	Boehringer Ingelheim	**6 - < 18 years:** Tablet: **BSA 0.58-0.83 kg/m^2:** 200 mg once daily **BSA 0.84-1.16 kg/m^2:** 300 mg once daily **BSA ≥1.17 kg/m^2: 400** mg once daily†	**Maximum dosage:** 400 mg once daily All children must initiate therapy with immediate-release Viramune for the first 14 days (see above)

Protease Inhibitors (PIs)

Brand Name	Generic Name	Manufacturer Name	Pediatric Use Labeling	Special Information
Agenerase	amprenavir (APV)	GlaxoSmithKline	N/A	Product has been replaced by Lexiva (fosamprenavir), a prodrug of amprenavir. Please refer to the Lexiva section for dosage information
Aptivus[19]	tipranavir (TPV)	Boehringer Ingelheim	**2-18 yrs:** Capsule/oral solution: 14 mg/kg with 6 mg/kg RTV twice daily (or 375 mg/m2 with RTV 150 mg/m2 twice daily)†	**Maximum dosage:** 500 mg with 200mg RTV twice daily

Crixivan[20]	indinavir (IDV)	Merck	Safety and efficacy not established in pediatric patients	
Invirase[21]	saquinavir (SQV)	Hoffmann-La Roche	Safety and effectiveness in patients <16 years not established	
Kaletra[22]	lopinavir and RTV (LPV/r)	Abbott Laboratories	Patients receiving nevirapine or efavirenz with Kaletra should have their Kaletra dose increased. Dose calculation is based on the lopinavir component **14 days-6months:** 16 mg/kg twice daily **6 months-12 yrs.**: Tablet/capsule/solution: **7 - <15 kg:** 12 mg/kg twice daily (13 mg/kg with nevirapine) **15-40 kg:** 10 mg/kg twice daily (11 mg/kg with nevirapine) **>40 kg or >12 yr:** lopinavir 400 mg twice daily (533 mg with nevirapine)	**Maximum dosage:** lopinavir 400 mg twice daily for patients who are not receiving nevirapine or efavirenz. Kaletra should not be used in combination with NNRTIs in children less than 6 months of age. Refer to package insert for BSA-based dosing information.
Lexiva[23]	fosamprenavir (FPV)	ViiV Healthcare	**Protease Inhibitor-Naïve ≥ 4 Weeks OR Protease Inhibitor-Experienced ≥ 6 Months:** **<11 kg:** 45 mg/kg with 7 mg/kg	**Maximum dose:** 700 mg with 100 mg RTV twice daily Data are insufficient to

			RTV twice daily **11 kg - <15 kg:** 30 mg/kg with 3 mg/kg RTV twice daily **15 kg - <20 kg:** 23 mg/kg with 3 mg/kg RTV twice daily **≥ 20 kg** 18 mg/kg with 3 mg/kg RTV twice daily **≥ 2 years and Protease-Inhibitor Naïve:** 30 mg/kg twice daily without RTV	recommend: once-daily dosing of Lexiva alone or in combination with RTV
Norvir[24]	ritonavir (RTV)	AbbVie	**>1 month:** 350-400 mg/m2 twice daily **†** Initiate dose at 250 mg/m^2 twice daily and titrate upward every 2-3 days by 50 mg/m2 twice daily **†**	**Maximum dosage:** 600 mg twice daily Lower doses have been used to boost other protease inhibitors but the RTV doses used for boosting have not been specifically approved in children
Prezista[25]	darunavir (DRV)	Janssen	**≥ 3 yrs and 10 kg** Oral solution or tablet/capsule **Treatment naïve or experienced without DRV-associated substitutions:** **10-< 15 kg:** 35 mg/kg once daily with 7mg/kg RTV once daily **15- < 30 kg:**	DRV should not be used in children < 3 years of age due to toxicity concerns.

			600 mg with 100 mg RTV once daily **30- <40 kg:** 675 mg with 100 mg RTV once daily **>40 kg:** 800 mg with 100 mg RTV once daily **Treatment experienced with ≥1 DRV-associated substitution(s):** **10-15 kg:** 20 mg/kg twice daily with 3 mg/kg RTV twice daily **15- < 30 kg:** 375 mg with 48 mg RTV twice daily **30- <40 kg:** 450 mg with 60 mg RTV twice daily **>40 kg:** 600 mg with 100 mg RTV twice daily	
Reyataz[26]	atazanavir (ATV)	Bristol Myers Squibb	**≥ 6 yrs and 15 kg: Capsules** **15- < 20 kg:** 150 mg with 100 mg RTV once daily **20 - < 40 kg:** 200 mg with 100 mg RTV once daily **≥ 40kg:** 300 mg with 100 mg RTV once daily	**Maximum dosage:** 400 mg once daily Administration with RTV is preferred. Dose for treatment-naïve children ≥ 13 years of age and ≥ 40 kg unable to tolerate RTV: 400 mg once daily (see package insert[27] for details)

Viracept[28]	nelfinavir (NFV)	Agouron Pharmaceuticals	**2-13 yr:** Tablets/powder : 45-55 mg/kg twice daily or 25-35 mg/kg three times daily	**Maximum dosage:** 2500 mg/day 250 mg tablets are interchangeable with oral powder (625 mg tablets are not) Reliable dosing recommendations could not be determined in patients < 2 years of age

Fusion Inhibitors

Brand Name	Generic Name	Manufacturer Name	Pediatric Use Labeling	Special Information
Fuzeon[29]	enfuvirtide, T-20 (ENF)	Hoffmann-La Roche	**6-16 yr:** Subcutaneous injection: 2 mg/kg twice daily	**Maximum dosage:** 90 mg twice daily Rotate injection sites

Entry Inhibitors

Brand Name	Generic Name	Manufacturer Name	Pediatric Use Labeling	Special Information
Selzentry[30]	maraviroc (MVC)	ViiV Healthcare	Safety and efficacy not established in pediatric patients	

HIV integrase strand transfer inhibitors (INSTI)

Brand Name	Generic Name	Manufacturer Name	Pediatric Use Labeling	Special Information
Isentress[31]	raltegravir (RAL)	Merck & Co., Inc.	**≥ 4 weeks and 3-11 kg:** Oral Suspension **3 - < 4 kg:** 20 mg twice daily **4 - < 6 kg:** 30 mg twice daily **6 - < 8 kg:** 40 mg twice daily **8 - < 11 kg:** 60 mg twice daily **≥ 11 - < 25 kg:** Oral Suspension/ Chewable Tablet 6 mg/kg/dose twice daily. Please see package insert for dosage by weight band **≥ 25 kg and unable to swallow tablet:** Chewable Tablet **25 - < 28 kg:** 150 mg twice daily **28- < 40 kg:** 200 mg twice daily **≥ 40 kg:** 300 mg twice daily **6 years and ≥25 kg and able to swallow tablets:** Film coated tablet 400 mg twice daily	Oral suspension, chewable tablets and film coated tablets are not bioequivalent Maximum dose for chewable tablets: 300 mg twice daily Maximum dose for film coated tablets: 400 mg twice daily
Tivicay[32]	dolutegravir (DTG)	ViiV Healthcare	**≥ 12 years and 40 kg:** Tablets **Treatment naïve**	

			OR treatment experienced but INSTI naïve: 50 mg once daily **Treatment experienced or naïve and co-administered with efavirenz, FPV/r, TPV/r, or rifampin:** 50 mg twice daily **INSTI experienced with certain INSTI-associated resistance substitutions:** 50 mg twice daily	

Fixed Dose Combinations Providing Complete Regimen

Brand Name	Generic Name	Manufacturer Name	Pediatric Use Labeling	Special Information
Atripla[33]	efavirenz, emtricitabine, tenofovir disoproxil fumarate	Gilead Sciences	**≥ 12 years and 40 kg:** one tablet once daily	Not recommended for children <12 yrs. due to fixed dosage form that cannot be adjusted for this population
Complera[34]	emtricitabine, rilpivirine, tenofovir disoproxil fumarate	Gilead Sciences	Safety and efficacy not established in pediatric patients	
Stribild[35]	elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate	Gilead Sciences	Safety and efficacy not established in pediatric patients	

2.3 Availability of Proposed Active Ingredient in the United States

The IND for ATV was first submitted to FDA in September 1998. The initial NDA 21567 was submitted on December 20, 2002. An Advisory Committee meeting was held on May 13, 2003. The committee unanimously recommended approval of ATV for the treatment of HIV infection and ATV was approved on 6/20/2003.

2.4 Important Safety Issues With Consideration to Related Drugs

Class-related adverse events (AEs)/laboratory abnormalities and potential for significant drug-drug interaction potential are common for the approved PIs. RTV is the hallmark PI for drug-drug interactions due to its potent inhibition of CYP3A4 metabolism. The addition of RTV increases ATV exposure and may also increase the magnitude of the interaction with ATV and other agents. Traditionally, RTV-containing regimens adversely affect lipid profiles at varying degrees. While a favorable lipid profile has been observed with ATV compared to NLV, LPV-RTV, and EFV, adding RTV to ATV results in increased total and non-HDL cholesterol, and triglycerides in comparison to ATV alone[1]. As with other PIs, the ATV label includes warnings and precautions for new onset diabetes, hyperglycemia, increased bleeding episodes in patients with hemophilia and fat redistribution.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Timeline of Communications Related to ATV Powder Formulation:

Overview: ATV pediatric drug development has been ongoing since 2001. The Applicant has tested the pediatric dosing of both the approved capsule formulations and a powder formulation. Most of the pediatric data was collected in the Pediatric AIDS Clinical Trial Group (PACTG) trial 1020A. PACTG 1020A was a phase I/II 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, PK, and optimal dosage of ATV powder and capsules. Pediatric dosing for the ATV capsule formulation was first approved in March 2008. A preliminary review of the pediatric studies for the ATV powder was done with the October 2007 capsule submission which included pediatric dosing for the capsule formulation. Clinical Pharmacology noted that most of the patients receiving the powder formulation were under-dosed given the problems with bioavailability of the reconstituted powder.

Based on the PK results, the Applicant revised their pediatric powder formulation dosing to adjust for the problems in bioavailability. (b) (4)

(b) (4)

Given the need for adequate safety information in pediatric patients 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 patients using the 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 (PREA) and European regulatory requirements for the powder formulation. AI424397 enrolled pediatric patients 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 patients ages three months to less than eleven years of age to meet the EMA pediatric requirements.

In July 5, 2012, the Applicant submitted a preliminary summary of their ATV PK data for patients 5 to 25 kg in the AI424397 trial. Based on Clinical Pharmacology's review, it appeared that pediatric patients in 5-10 kg (treatment group A) were underdosed with the ATZ 150mg + RTV 80mg regimen. In the August 6, 2012 communication, DAVP recommended the Applicant increase the ATZ/RTV dose to 200/80mg for patients 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 200/80mg for patients 5-10 kg in the AI424451 trial. In the October 19, 2012 meeting package submission, the Applicant proposed requesting an exclusivity determination prior to completing dose finding for the 5-10 kg weight band.

The PK and safety results from the increased ATV dose in patients 5-10 kg weight band will be submitted at a future date with a Pediatric Written Request deadline of January 2016 .For a more detailed summary of the Timeline Relevant to ATV Pediatric Development see Appendix Section 1.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

NDA 206352 S00 and NDA 21-567 S35 was submitted in electronic common technical document format on December 2, 2013 as a complete submission. The Applicant had followed DAVP recommendations about content including a specialized safety dataset that allowed for a thorough review.

3.2 Compliance with Good Clinical Practices

Both trials AI424397 and AI424451were conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and 21CFR50. The applicant conducted site visits to ensure compliance with protocol and GCP guidelines.

3.3 Financial Disclosures

The Applicant obtained financial information for all the trial sites and no investigators had disclosable information in regard to financial interests or arrangements. The Financial Disclosure submitted by the Applicant is summarized in Appendix Section 9.3.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Per the Office of New Drug Quality Assessment (ONDQA), the applicant of this NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. The Office of compliance has made a final "Acceptable" recommendation on the facilities involved. There are labeling issues that need to be resolved prior to approval. One issue involves omitting (b) (4) to be consistent with the "Monograph Naming Policy for Salt Drug Substances in Drug Products and Compounded Preparations". A second issue is deciding on the appropriate description of the powder formulation in the label. One potential name is "Reyataz (atazanavir) oral powder. Please see ONDQA review by Yichun Sun, Ph.D.

4.2 Clinical Microbiology

In general, the resistance analysis results reported by the Applicant were consistent with independent analysis of the resistance data performed by Clinical Virology. No treatment-emergent ATV-associated substitutions (defined in the FDA label) were detected among the nine treatment failures in Trial AI424397. However four other known PI resistance-associated substitutions (L19I/R, M36M/I, H69K/R, and I72I/V) arose individually (one mutation per subject) in four subjects with virological failure. The Applicant reported that none of the subjects acquired phenotypic resistance to ATV, ATV/RTV, or any NNRTI or NRTI. In Trial AI424451, several ATV-associated resistance

substitutions arose in one subject (AI424451-14-69), including M46M/V, V82V/I, I84I/V, and L90L/M; however, the Applicant reported that these substitutions did not result in phenotypic resistance to ATV or ATV/RTV. Resistance is defined as ATV phenotypic fold-change of 1.74) as assessed by the Monogram Phenosense GT test. Additional substitutions associated with resistance to other PIs also arose in one subject each (one mutation per subject), including V11V/I, G16G/E, D30D/G, E35E/D, K45K/R, L63P/S, and I72I/T. Q61D and Q61/E/G emerged in two subjects who failed treatment with ATV/RTV. Three subjects developed M184V in the reverse transcriptase protein of their virus, and all 3 exhibited phenotypic resistance to emtricitabine (FTC) and lamivudine (3TC). In general, the resistance data sets for AI424397 and AI424451 were too small to draw any significant conclusions, and the resistance patterns were consistent with those observed in previous cohorts exposed to ATV and ATV/RTV.
Please see Clinical Virology review by Eric Donaldson, Ph.D.

4.3 Preclinical Pharmacology/Toxicology

Both ONDQA and Pharmacology/Toxicology (Pharmtox) have been evaluate the potential risk of two (b) (4) impurities, (b) (4) in atazanavir powder. The primary concern noted for both chemicals was (b) (4) which can be more severe in infant and children than in adults. The Pharmtox reviewer Mark Powley, Ph.D. reviewed the toxicological effect (b) (4) at the proposed level (b) (4) and found that the proposed level was acceptable and did not present a safety concern. There were no other Pharmtox concerns in the new NDA and accompanying supplement. Please see Pharmtox review by Mark Powley, Ph.D.

4.4 Clinical Pharmacology

Based on the information submitted to NDA 206352, the Division of Clinical Pharmacology recommends approval of the ATV powder formulation for HIV-infected pediatric patients who are 10 to < 25 kg and younger than 7 years as described in Table 2 below. For patients 7 years and older, the powder formulation can be used for those patients who cannot swallow capsules. Please see Clinical Pharmacology review by Jenny Zheng, Ph.D.

Table 2: Dosage for Pediatric Patients (10 kg to less than 25 kg) for REYATAZ Pediatric Powder with Ritonavir[a]

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

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

b Ritonavir solution.

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. ATV inhibits UDP-glucuronosyl transferase (UGT) and most patients (adult and pediatric) experience an asymptomatic elevation in indirect (unconjugated) bilirubin.

4.4.2 Pharmacodynamics

ATV has been shown to prolong the PR interval on electrocardiogram in some patients. In ATV-treated healthy volunteers and patients, abnormalities in atrioventricular (AV) conduction were asymptomatic and generally limited to first-degree AV block. In these healthy volunteers, the observed prolongation of PR interval has been found to be concentration- and dose-dependent.

4.4.3 Pharmacokinetics

Clinical Pharmacology reviewed the PK data from subjects 5 - <10 kg and found the exposures for these subjects were reduced compared to subjects in the 10 - <25 kg weight band. Based on these PK findings, Clinical Pharmacology recommended increasing the dose of ATV/RTV to 200mg/80mg from 150mg/80mg in the 5 to < 10 kg weight band; and the applicant is currently evaluating this dosing regimen in the ongoing trial, AI424451.

The PK of ATV was characterized in 33 pediatric subjects weighing 10 to < 15 kg (N=18), and 15 to < 25 kg (N=15) following administration of ATV Oral Powder with RTV liquid at doses of 150/80 mg, 200/80 mg, and 250/80 mg, respectively. See Table 3 for summary of ATV PK parameters for Groups B and C, corresponding to weight bands 10 to < 15 kg and 15 to < 25 kg, respectively.

Table 3: Summary Statistics of ATV PK Parameters

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

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

5 Sources of Clinical Data

5.1 Tables of Clinical Trials

Table 4: Pediatric Powder Formulation Trials AI424397 and AI424451

Trial	Trial Cohorts/Duration	Population	Subjects on Treatment
AI424397 PRINCE1 (Final CSR)	5- <10 kg: ATV/r 150/80mg 10- <15 kg ATV/r 200/80mg 15-<25 kg ATV/r 250/80mg Stage 1: Subjects continue on the powder formulation through the end of the 48-week period of Stage 1 and then move into Stage 2 while remaining on the powder formulation or capsule, if appropriate.	HIV-infected pediatric subjects ≥ 3 months to <5 years and 6 months of age. ARV naive or experienced without prior exposure to ATV	Weight Range / Treated (Rx) Total n: 56 5 - <10 kg: 21 10 - <15 kg: 19 15 - <25 kg: 16
AI424451 PRINCEII (Interim CSR)	5- <10 kg: ATV/r 150/80mg 10- <15 kg ATV/r 200/80mg 15-<25 kg ATV/r 250/80 Stage 1: Subjects continue on the powder formulation through the end of the 48-week period of Stage 1 and then move into Stage 2 while remaining on the powder formulation or capsule, if appropriate.	HIV-infected pediatric subjects ≥ 3 months to < 11 years and weighing ≥ 5 - < 35 kg. ARV naive or experienced without prior exposure to ATV	Weight Range / Treated (Rx) Total n: 78 5 - <10 kg: 23 10 - <15 kg: 20 15- <25 kg: 34 25 - <35 kg: 1

5.2 Review Strategy

The focus of this review is on subjects weighing 10 to <25 kg for whom ATV powder formulation will be labelled. The ATV exposure for subjects 5 - <10 kg was significantly reduced compared to subjects in 10 - <25 kg weight band and the Applicant agreed to explore an increased dose of ATV/RTV of 200 mg / 100mg in 5 to < 10 kg subjects, with results to be submitted by January of 2016. Because of the very similar trial designs and dataset construction, the efficacy and safety data for both AI424397 and AI424451 were easily pooled.

5.3 Discussion of Individual Studies/Clinical Trials

AI424397 (PRINCEI) is a prospective single arm, open-label, international, multicenter trial to evaluate the safety, antiviral activity and PK of ATV powder boosted with RTV with an optimized NRTI background therapy in HIV-infected pediatric subjects ≥ 3 months of age to less than 6 years of age. Applicant submitted a final study report for this trial.

AI424451 (PRINCEII) is a prospective single arm, open-label, international, multicenter trial to evaluate the safety, antiviral activity and PK of ATV powder boosted with RTV with an optimized NRTI background therapy in HIV-infected pediatric subjects 3 months of age to less than 11 years of age. Applicant submitted an interim study report for this trial since it is ongoing. Additional subjects in the 5 - <10 kg group are being enrolled to evaluate the increased ATV/RTV dose of 200mg/80mg.

6 Review of Efficacy

Efficacy Summary

The antiviral activity data from both AI424397 (PRINCE I) and AI424451 (PRINCE II) supports the use of the ATV powder formulation given together with RTV for pediatric patients three months and older and at least 10 kg in weight (b) (4)

The virologic snapshot data (HIV RNA < 50 copies/mL and <400 copies/mL) for subjects >10 kg from the completed Trial AI424397 (see Table 7 and Figure 1) is consistent with prior pediatric trials of ATV with an overall success of 68-71%. The interim results from AI424451 are less supportive for the 10- <15 kg weight band; however the data from this trial is incomplete and there were 50% fewer analyzed subjects in the 10 - <15 kg weight band than trial AI424397. In addition, the Applicant supplied data to show that for some of the subjects in the 10 - <15 kg weight band, there was a viral load blip (HIV RNA > 50 copies/mL and < 400 copies/mL) at 48 weeks that resolved by 60 weeks. This finding is supported by the HIV RNA <400 copies/mL data for Trial AI424451. The antiviral activity of the ATV powder formulation appeared less promising for subjects at least three month old in the 5 - <10 kg weight band with snapshot results (HIV RNA < 50 copies/mL) with overall success of 42-48%. However, the Applicant has acknowledged that subjects in the 5 - <10 kg weight band were under-dosed and has extended trial AI424451 to characterize the PK, safety and antiviral activity of an increased dose of 200mg ATV powder given concomitantly with RTV as compared to the 150mg dose in the 5 to < 10 kg weight band.

6.1 Indication

REYATAZ® (ATV sulfate) is approved for use in combination with other antiretroviral agents for the treatment of HIV-1 infection. Previously, the Applicant submitted data to support the labeling of the ATV capsule formulation (b) (4) . NDA 206352 S-000 and the accompanying NDA supplement, 21567-S035- proposed to extend the indication (b) (4) to patients at least 3 months of age weighing at least 10 kg (most patients in the US weighing 10 kg are approximately one year of age) using the ATV powder formulation given concomitantly with RTV oral solution.

6.1.1 Methods

Efficacy data from 2 trials, AI424397 and AI424451, in pediatric subjects using ATV powder/RTV liquid were reviewed. The FDA “snapshot” results for virologic response

using the success criteria of HIV RNA <50 copies/mL and < 400 copies/mL at Week 48 for Trial AI424397, and the interim results at Week 48 for Trial AI424451 were the primary focus of this reviewer's analysis. The submitted datasets and clinical study report were used for this analysis. The analysis of the antiviral activity focuses on comparing results by weight band (and the respective ATV dose) and by antiretroviral treatment experience.

This reviewer will focus on the results for subjects ≥10 kg because this is the weight band for which ATV powder is being labeled at this time. . As mentioned above, the applicant has acknowledged that the subjects weighing < 10 kg who received 150mg of ATV powder were underdosed. However for comparison purposes, the efficacy data for subjects 5 - < 10 kg are briefly discussed below.

6.1.2 Demographics

AI424397 consisted of subjects ≥10 kg who were mainly from Africa (64%), approximately 50-50 male: female and almost two-thirds treatment-naïve (see Table 5). AI424451 consisted of subjects ≥10 kg evenly split between Africa and non-African sites, mostly female (61%) and three-fifths treatment-naïve. The subjects in AI424451 tended to be older than subjects in AI424397 (median of 51 months versus 42 months).

Table 5: Patient Demographics and HIV Treatment History

	AI424397		AI424451	
	baseline weight < 10 kg (N=21)	baseline weight ≥ 10 kg (N=33)	baseline weight < 10 kg (N=19)	baseline weight ≥ 10 kg (N=41)
Age (months)				
Mean (SD)	6 (4)	41 (2)	7 (6)	54 (20)
Median	5	42	4	51
25^{TH}, 75^{TH}	3, 9	32, 52	2, 11	39, 70
Min, Max	2, 13	20, 60	2, 19	13, 84
Gender				
Male	11 (52%)	16 (48%)	9 (47%)	16 (39%)
Female	10 (48%)	17 (52%)	10 (53%)	25 (61%)
Race				
White	2 (10%)	7 (21%)	1 (5%)	19 (46%)
Black	13 (62%)	19 (58%)	16 (84%)	21 (51%)
Other	6 (29%)	7 (21%)	2 (11%)	1 (2%)
Region				
Africa	17 (81%)	21 (64%)	17 (89%)	20 (49%)
Asia	0	1 (3%)	0	0
Europe	0	0	0	7 (17%)
North America	2 (10%)	5 (15%)	1 (5%)	10 (24%)
South America	2 (10%)	6 (18%)	1 (51%)	4 (10%)
US	0	0	1 (5%)	2 (5%)
Non-US	21 (100%)	33 (100%)	18 (95%)	39 (95%)
HIV treatment history				
Treatment-naïve	13 (62%)	21 (64%)	4 (21%)	25 (61%)
Treatment-experienced	8 (38%)	12 (36%)	15 (79%)	16 (39%)

6.1.3 Subject Disposition

Given that Trial AI424451remains ongoing, comparisons to completed Trial AI42397 are of limited value, as a significant number of subjects have not completed their 48 week treatment course in AI424451. The percentage of subjects ≥ 10 kg that did not complete the 48 week treatment course was higher (24% versus 17%) for AI424451 than AI424397, a finding related to a slightly higher degree of discontinuations due to adverse events (5% versus 3%) and lack of efficacy (13% versus 9%). The data for subject disposition is summarized in Table 6 below.

Table 6: Subject Disposition

	AI424397		AI424451	
	baseline weight < 10 kg N (%)	baseline weight ≥ 10 kg N (%)	baseline weight < 10 kg N (%)	baseline weight ≥ 10 kg N (%)
Total treated	56		78	
Treated	21 (100%)	35 (100%)	23 (100%)	55 (100%)
Completed 48-wk ATV powder treatment[1]	17 (81%)	29 (83%)	12 (52%)	29 (53%)
Did not complete 48-wk ATV powder treatment	4 (19%)	6 (17%)	7 (30%)	13 (24%)
Adverse event	4 (19%)	1 (3%)	0	3 (5%)
Lack of efficacy	0	2 (6%)	3 (13%)	5 (9%)
No longer meets study criteria	0	0	1 (4%)	1 (2%)
Poor/non-compliance	0	2 (6%)	0	2 (4%)
Consent withdrawn	0	1 (3%)	1 (4%)	1 (2%)
Lost to follow-up	0	0	1 (4%)	0
Other	0	0	1 (4%)	1 (2%)
Ongoing 48-wk ATV powder treatment by 04/18/2013 (date of dataset locked for study report)	0	0	4 (17%)	13 (24%)

[1]including two subjects in AI424397 and one in AI424451 switched to ATV capsule.
N (%) = number and percentage of subjects

6.1.4 Analysis of Primary Endpoint(s)

For both AI424397 and AI424451, the 48 week virological success rate (as measured by the FDA snapshot analysis) in each study for subjects < 10kg was less than 50% with the percentage of subjects with virological failure ranging from 33% (Trial AI424397) to 47% (Trial AI424451) in this weight band (see Table 7 and Figure 1). Given that Trial AI424397 is a completed trial and Trial AI424451 is ongoing trial with interim results, both studies will be described separately. As noted previously, PK parameters were consistent with underdosing in subjects weighing 5 to < 10 kg, and in the ongoing trial A1424451, the ATV dose has been increased in that weight band.

Trial AI424397-All Subjects

The antiviral activity results from AI424397 for subjects ≥ 10 kg (see Table 7 and Figure 1) were consistent with the results obtained for other antiretroviral agents used in pediatric trials, including ATV capsules for subjects ≥ 6 years of age. The virological success (HIV RNA <50 copies/mL) at 48 weeks for subjects 10 - < 25 kg was 68-71%. For the same weight band, virological success was 74-86% when defined using the HIV RNA <400 copies/mL criterion. .

Trial AI424451-All Subjects

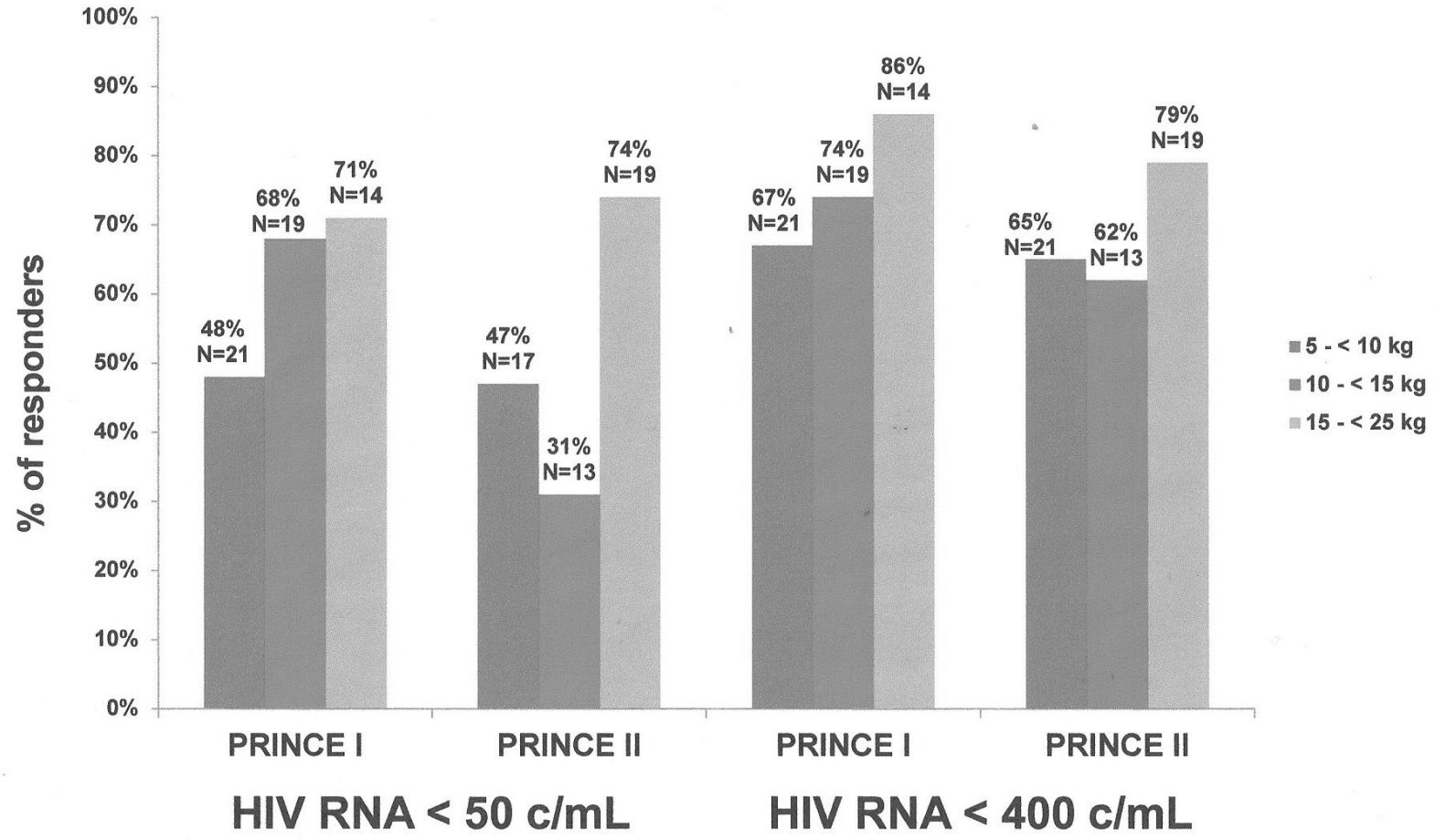
The antiviral activity results from AI424451 for subjects ≥ 10 kg were not consistent (see Table 7 and Figure 1) with prior results obtained in trials of other antiretroviral agents, including ATV dosed as capsule (in trial AI424020) or as the powder formulation (in trial AI424397). The antiviral activity for the 10 <15 kg subjects was quite low with a virological success (HIV RNA <50 copies/mL) rate of 31% which is inconsistent with the results of AI424397. Using the HIV RNA <400copies/mL cutoff, 62% of subjects were considered a virologic success which is more consistent with the results of AI424397. Given the interim nature of the data, it is too early to conclude that ATV powder did not demonstrate the expected antiviral activity in AI424451. The virological success (HIV RNA <50 copies/mL) at 48 weeks for subjects 15 - < 25 kg was 74%. For the same weight band, virological success was 79% when defined using the HIV RNA <400 copies/mL criterion. .

The 48 week virological success for all subjects (treatment-naïve and -experienced) is summarized in Table 7 and Figure 1 below.

Table 7: Snapshot Outcomes HIV RNA <50 copies/mL at Week 48 for ALL Subjects

	PRINCE I (Study AI424397)			PRINCE II (Study AI424451)		
	baseline weight 5 - < 10 kg	baseline weight 10 - <15 kg	baseline weight 15 - <25 kg	baseline weight 5 - < 10 kg	baseline weight 10 - <15 kg	baseline weight 15 - <25 kg
Number of subjects in powder cohort	21	19	14	17	13	19
Virologic success - HIV RNA <50 c/mL	10 (48%)	13 (68%)	10 (71%)	8 (47%)	4 (31%)	14 (74%)
Virologic failure[1]	7 (33%)	5 (26%)	4 (29%)	8 (47%)	7 (54%)	4 (21%)
No virologic data in analysis week window	4 (19%)	1 (5%)	0	1 (6%)	2 (15%)	1 (5%)
Discontinued due to AE or death	4 (19%)	1 (5%)	0	0	2 (15%)	1 (5%)
Discontinued due to other reason	0	0	0	1 (6%)	0	0
Missing data in window but on treatment	0	0	0	0	0	0

Figure 1: HIV Viral Load at Week 48 for AI424397 and AI424451



AI4242397 Antiviral Activity in Treatment-Naïve and Treatment-Experienced Subjects
In AI424397, antiretroviral treatment-naïve subjects did approximately the same (HIV RNA < 50 copies/mL) as antiretroviral- experienced patients (72% versus 67%). This finding was also noted when using the <400 copies/mL criteria for HIV RNA. For subjects 5 - < 10 kg, there was no significant difference between treatment-naïve versus -experienced when comparing virological success at the <50 copies/mL and the <400 copies/mL success criteria. However, the number of subjects in these subgroups was small, and any conclusions regarding these subgroup analyses are limited.

AI424451 Antiviral Activity in Treatment Naïve and Treatment Experienced Subjects

The general trend that treatment-naïve subjects do better than antiretroviral-experienced was observed in subjects 10 - < 15 kg. In subjects weighing 10 to < 15 kg, the virological success (HIV RNA <50 copies/mL) rate was 38% in treatment-naïve and 20% in treatment-experienced subjects. Similarly, 75% treatment-naïve subjects and 40% treatment-experienced subjects in this weight band were considered a virologic success using the HIV RNA < 400 copies/mL cutoff. For subjects 15 - <25 kg, antiviral activity was comparable to that reported with other antiretroviral agent, with virological success (HIV RNA <50 copies/mL) observed in 63% subjects overall. In this weight band, antiretroviral activity in treatment-naïve subjects was comparable to that in treatment-experienced subjects, with a virological success rates (HIV RNA <50 copies/mL) of 75% and 71%, respectively. Virological success in this weight band using the HIV RNA <400 copies/mL criterion was comparable in treatment-naïve and –experienced subjects, 83% and 71%, respectively. However, the number of subjects in these subgroups was small, and any conclusions regarding these subgroup analyses are limited. Numbers of subjects in the 5 - <10 kg weight band were too small to make any meaning comparisons between treatment-naïve (N=4) and treatment-experienced subjects (N=13).

The comparisons between treatment naïve and treatment experienced subjects are summarized in Tables 8 - 9 and Figures 2 - 3.

Table 8: Snapshot Outcomes at Week 48 for Treatment Naive Subjects

	PRINCE I (Study AI424397)			PRINCE II (Study AI424451)		
	baseline weight 5 - < 10 kg	baseline weight 10 - <15 kg	baseline weight 15 - <25 kg	baseline weight 5 - < 10 kg	baseline weight 10 - <15 kg	baseline weight 15 - <25 kg
Number of subjects in powder cohort	13	12	9	4	8	12
Virologic success - HIV RNA <50 c/mL	6 (46%)	9 (75%)	6 (67%)	0 (0%)	3 (38%)	9 (75%)
Virologic failure[1]	6 (46%)	2 (17%)	3 (33%)	4 (100%)	4 (50%)	2 (17%)
No virologic data in analysis week window	1 (8%)	1 (8%)	0	0	1 (13%)	1 (8%)
Discontinued due to AE or death	1 (8%)	1 (8%)	0	0	1 (13%)	1 (8%)
Discontinued due to other reason	0	0	0	0	0	0
Missing data in window but on treatment	0	0	0	0	0	0

Table 9: Snapshot Outcomes at Week 48 for Treatment Experienced Subjects

	PRINCE I (Study AI424397)			PRINCE II (Study AI424451)		
	baseline weight 5 - < 10 kg	baseline weight 10 - <15 kg	baseline weight 15 - <25 kg	baseline weight 5 - < 10 kg	baseline weight 10 - <15 kg	baseline weight 15 - <25 kg
Number of subjects in powder cohort	8	7	5	13	5	7
Virologic success - HIV RNA <50 c/mL	4 (50%)	4 (57%)	4 (80%)	8 (62%)	1 (20%)	5 (71%)
Virologic failure[1]	1 (13%)	3 (43%)	1 (20%)	4 (31%)	3 (60%)	2 (29%)
No virologic data in analysis week window	3 (38%)	0	0	1 (8%)	1 (20%)	0
Discontinued due to AE or death	3 (38%)	0	0	0	1 (20%)	0
Discontinued due to other reason	0	0	0	1 (8%)	0	0
Missing data in window but on treatment	0	0	0	0	0	0

Figure 2: HIV Viral Load at Week 48 Treatment-Naive Subjects

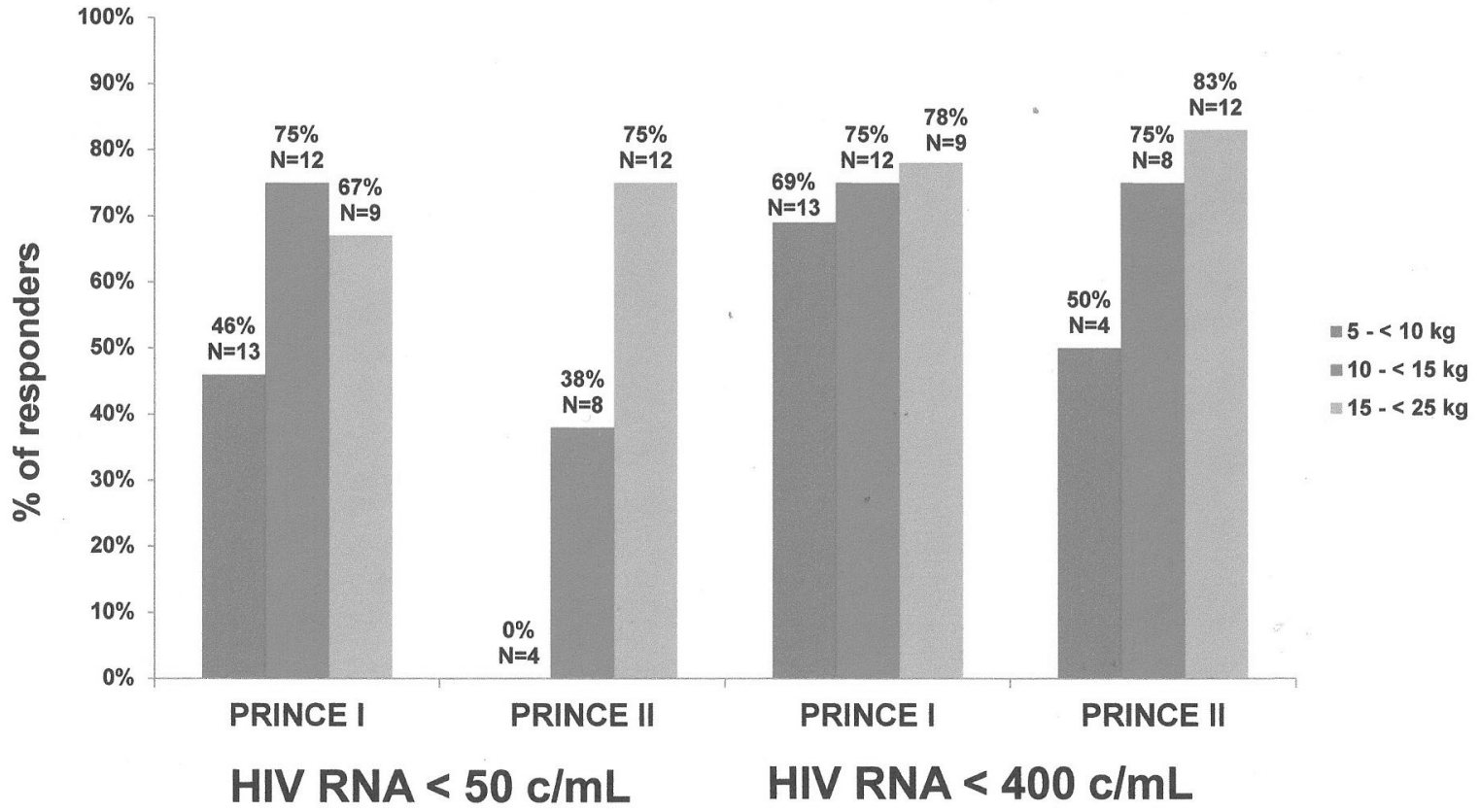
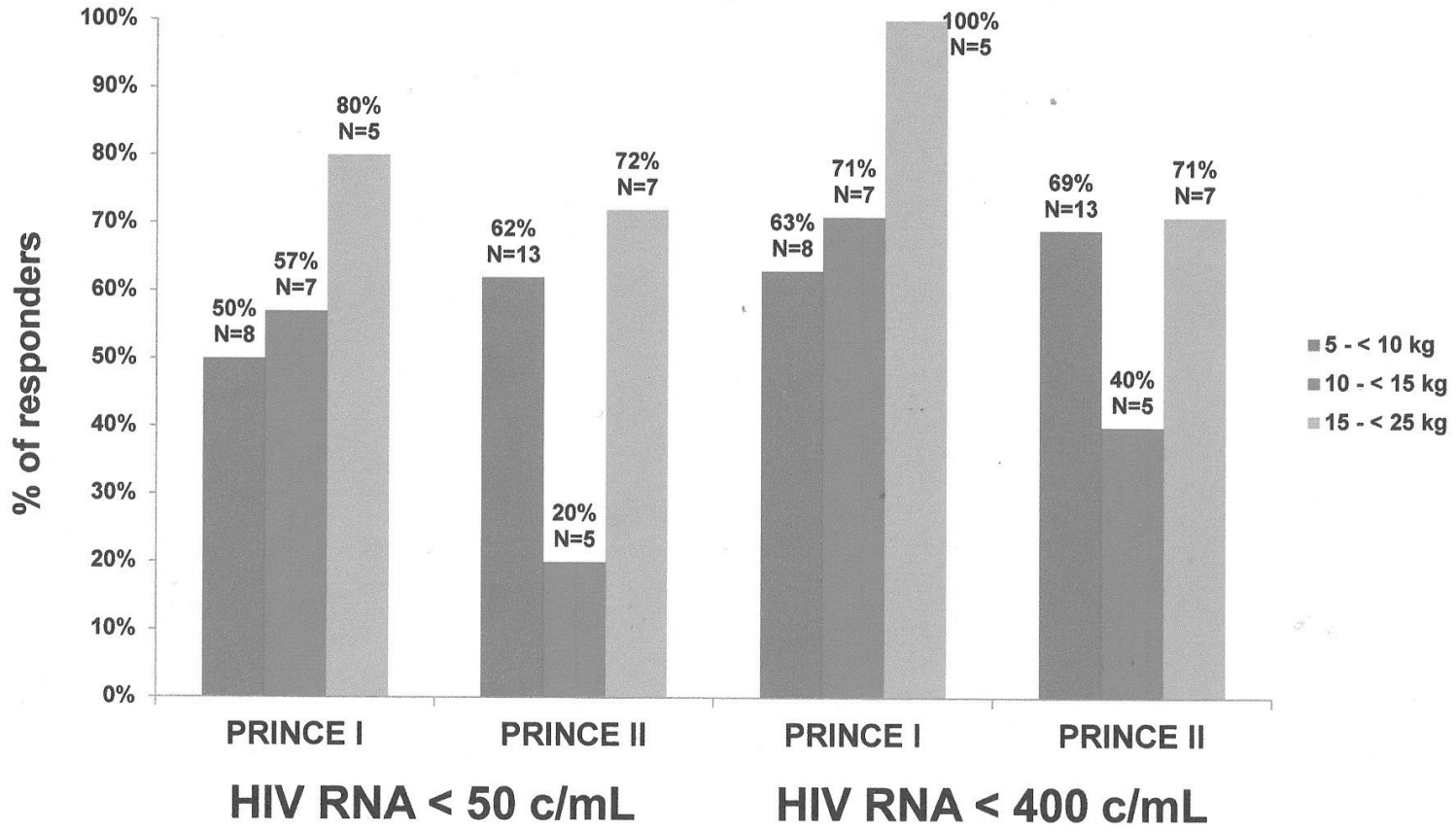


Figure 3: HIV Viral Load at Week 48 Treatment-Experienced Subjects



AI424397 Virological Response Over Time

In examining the virological response over time in subjects 10 - <25 kg, the virological success (HIV RNA <50 copies/mL) increased from 53-56% at 24 weeks to 68-71% at 48 weeks. A similar response was observed in subjects 5 - < 10 kg but the virological success (HIV RNA <50 copies/mL) was 33% at 24 weeks and increased to 48% at 48 weeks.

AI424451 Virological Response Over Time

In examining the progression of the anti-virological response in subjects 10 - <15 kg over time, unexpectedly the virological success (HIV RNA <50 copies/mL) decreased from 44% at 28 weeks to 31% at 48 weeks. The Applicant has provided data that shows that some of the subjects in this cohort had virological blips HIV RNA >50 copies/mL to <400 copies/mL that returned to <50 copies/mL on subsequent virological testing. For subjects 15 - <25 kg, the virological success (HIV RNA <50 copies/mL) increased from 56% at 24 weeks to 63% at 48 weeks which is comparable to results of other antiretrovirals in studied in pediatric subjects.

Reviewer Comment: It has been observed in pediatric subjects that it can take up to 48 weeks for some subjects to achieve virological success therefore it has been generally observed that the fraction of subjects with virological success increase over time in the first 48 weeks of treatment. Some believe that this is due to the high virological load at the beginning of treatment for many pediatric patients and the gradual improved adherence to antiretroviral therapy as caregivers become better at administering doses.

The virological response (HIV RNA <50 copies/mL) results over time (24 to 48 weeks) for trials AI424397 and AI424451 is summarized in Table 10.

Table 10: Subjects with HIV RNA <50 copies/mL at 24 and 48 weeks for ALL Subjects

	PRINCE I (Study AI424397)			PRINCE II (Study AI424451)		
	baseline weight 5 - < 10 kg	baseline weight 10 - <15 kg	baseline weight 15 - <25 kg	baseline weight 5 - < 10 kg	baseline weight 10 - <15 kg	baseline weight 15 - <25 kg
Week 24	33% (7/21)	53% (10/19)	56% (9/16)	37% (7/19)	44% (7/16)	56% (14/25)
Week 48	48% (10/21)	68% (13/19)	71% (10/14)	42% (8/19)	31% (5/16)	63% (15/24)

6.1.5 Analysis of Secondary Endpoints(s)

CD4 Count Changes from Baseline

AI424397

At Week 48, the overall mean (median) increase from baseline in CD4 cell count was 272 (319) cells/mm^3 in 10 -25 kg subjects using the Observed Approach. At Week 48, the mean (median) change from baseline in CD4 cell count using the Last Observation Carried forward approach was 225 (241) cells/mm^3 in 10 -25 kg subjects.

AI424451
At Week 48, the overall mean (median) change from baseline in CD4 cell count was 435 (289) [increase] cells/mm^3 in 10 -25 kg subjects using the Observed Approach.

Reviewer Comment: This secondary endpoint (CD4 count) is not generally useful for subjects less than six years of age because the CD4 count naturally declines from birth to six years of age and unless there is a dramatic decrease in overall count it is difficult to ascribe the change to HIV disease. CD4% is a more useful as an endpoint since the fraction of CD4 positive cells of the total T cell population generally remains constant even as the total number of T cells decline from birth to six years of age. Therefore, CD4 percentage allows one to see an improvement in immunological status (increased CD4 percentage) on antiretroviral therapy which may be masked by the natural decline in CD4 cells that occurs in all infants and young children.

The results for change from baseline in CD4 count for AI424397 and AI424451 are summarized in Table 11.

Table 11: Results for Change from Baseline in CD4 Count

CD4 count change from Baseline	AI424397 baseline weight 10 - < 25 kg (N=35)	AI424451 baseline weight 10 - < 25 kg (N=41)
Observed approach[1]		
n	**16**	**16**
mean (SE)	**272 (137)**	**435 (481)**
median	**319**	**289**
Last observation carried forward (LOCF)[2]		**not done**
n	**23**	
mean (SE)	225 (97)	
median	241	

[1]The results for Study AI424397 were obtained from Appendix 5.3A, 5.3E in final clinical study report. The results for Study AI424451 were generated by statistical reviewer based on Applicant's program.
[2]LOCF: missing values were replaced with the last on-treatment value in the previous visit window; the baseline value was carried forward if subject did not have on-treatment value

AI424397
At Week 48, using the Observed approach, the overall mean change from baseline in CD4 percent was 8% in the 10 – <25 kg subjects. The corresponding median change in the 10 - <25kg subjects was 9%.

AI424451

At Week 48, using the Observed approach, the overall mean change from baseline in CD4 percent was 9% in 10 - < 25 kg subjects. The corresponding median change in the 10 - <25kg subjects was 11%.

CD4 Percent Changes from Baseline are summarized in Table 12.

Table 12: Results for Change from Baseline in CD4 Percent

CD4 % change from Baseline	AI424397	AI424451
	baseline weight 10 - < 25 kg (N=35)	baseline weight 10 - < 25 kg (N=55)
Observed approach[1]		
n	18	19
mean (SE)	8 (1.5)	9 (8.2)
median	9	11

[1]The results for Study AI424397 were obtained from Appendix 5.3A, 5.3E in final clinical study report. The results for Study AI424451 were generated by statistical reviewer based on Applicant's program.

6.1.6 Other Endpoints

Not applicable.

6.1.7 Subpopulations

The number of subjects in the two trials was too small to analyze subgroups by race, gender, or national origin.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

No additional analyses were performed. See section 6.14 above.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No additional analyses were performed.

6.1.10 Additional Efficacy Issues/Analyses

No additional analyses were performed.

7 Review of Safety

Safety Summary

The current supplement includes the submission of pediatric data from two clinical studies: AI424397 and AI424451. AI424397 and AI424451 were conducted to primarily evaluate the PK and safety of ATV powder formulation doses derived from the PK analysis of the earlier trial AI424020 (PACTG 1020). In AI424020 it was apparent that most of the pediatric subjects dosed with the powder formulation had been under-dosed. Based on the PK analysis of that trial, new doses were selected for subjects 3 months of age to less than six years of age based on weight bands.

The safety findings for AI424397 and AI424451 are very similar to the findings from the AI424020 capsule formulation cohort (age 6 years to less than 18 years) reviewed previously, with the exception of fewer Grade 3-4 total bilirubin abnormalities (12% reported in AI424397and AI424451 overall compared to 58% in AI424020). The decreased incidence of Grade 3-4 hyperbilirubinemia may be related to the use of optimized ATV dosing in AI424397and AI424451 in comparison to the aggressive dose finding in AI424020 which resulted in some of the older subjects (> 6 years of age)

receiving supratherapeutic doses of ATV (with elevated Cmax) especially in the cohorts that received unboosted ATV.

The focus of this review will be on the subjects 10 - <25 kg of weight because subjects 5 - <10 kg in these trials were underdosed based on PK parameters.
Given the absence of new safety findings and the similarity of the safety profile between AI424020 and AI424397and AI424451, there are no outstanding safety concerns that would prevent approval of the ATV powder NDA and accompanying NDA supplement under review.

7.1 Methods

The focus of this safety summary will be subjects in the 10-25 kg weight range for which the product will be labeled. This weight range includes the two dosing groups 10 - <15 kg and 15 - <25 kg. The data for the 5 - <10 kg will be reviewed in a future submission focused on dosing for this weight band.

7.1.1 Clinical Trials Used to Evaluate Safety

Two trials AI424397 and AI424451 were primarily used to evaluate safety of the ATV powder formulation. Both trials were designed following the review of the prior trial AI424020 powder formulation subgroups. The safety data from these trials were submitted in datasets using the same format and therefore, the data from both trials were easily pooled for analysis.

Trial AI424397 is a completed Phase 3b prospective, international, single-arm, open-label, multicenter trial to evaluate the safety, efficacy, and PK of ATV oral powder boosted with RTV liquid with an optimized NRTI background regimen, in HIV-infected ARV- naïve and -experienced pediatric subjects ≥ 3 months to < 6 years of age. It includes subjects in 3 baseline weight bands: 5 - < 10 kg, 10 - < 15 kg, 15 - < 25 kg.

Trial AI424451 is an ongoing Phase 3b prospective, international, single-arm, open-label, multicenter trial to evaluate the safety, efficacy, and PK of ATV oral powder boosted with RTV with an optimized NRTI background regimen, in HIV ARV-naive and -experienced HIV-infected pediatric patients ≥ 3 months to < 11 years. It includes subjects in 5 baseline weight bands and initial ATV powder dose cohorts: 5 - < 10 kg (ATV 150mg), 5 - < 10 kg (ATV 200mg), 10 - < 15 kg, 15 - < 25 kg, 25 - < 35 kg.

Both trials included 2 stages. In AI424397, Stage 1 ended after a subject was on ATV powder for 48 weeks or when a subject reached the age of 6 years or weight ≥ 25 kg,

and then the subject entered Stage 2. In AI424451, Stage 1 ended after a subject was on ATV powder for 48 weeks or when a subject reached the age of 12 years or weight ≥ 35 kg, and then the subject entered Stage 2.

7.1.2 Categorization of Adverse Events

The investigators' adverse event terms were coded and grouped by System Organ Class (SOC) and Preferred Terms using Medical Dictionary for Regulatory Activities (MedDRA) version 16.0. The investigators determined the intensity of AEs using the Division of AIDS (DAIDS) standardized toxicity table (version 1.0, December 2004, clarification August 2009) for grading severity of pediatric adverse experiences. The Investigators used a supplemental toxicity table instead of the DAIDS toxicity table when grading skin rash, triglyceride, and cholesterol toxicities.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

This submission focuses on pooled safety data from subjects in AI424397 AND AI424451. The safety data was organized and displayed in a format as requested by DAVP. This included one record per ongoing AE with all associated visits collapsed into one record with the highest AE intensity presented along with any treatments or actions for the AE.

7.2 Adequacy of Safety Assessments

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

Overall, the median time on trial therapy was 50 weeks (range: 1 - 89 weeks) for ATV powder and 48 weeks (range: 1 - 89 weeks) for RTV oral solution. The median time on ATV powder was longer in the 10 - < 15 kg group (58 weeks) than in the 15 - < 25 kg group (48 weeks**).** This was expected, as subjects reaching a weight of 25 kg in trial AI424397 were to have switched to the ATV capsule regimen, as specified in the protocol.

7.2.2 Explorations for Dose Response

As summarized in the original review of the ATV pediatric capsule sNDA (see March 25, 2008 Clinical Review of NDA 21-567 S015) which contained safety data for both the capsule formulation and the powder formulation from Trial AI424020, 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. At that time, only the capsule formulation in patients six years and older was being considered for approval.

7.2.4 Routine Clinical Testing

Laboratory evaluations were done for the following tests:
• Hematology: hematocrit, hemoglobin, platelets, WBC and neutrophils + bands (absolute)
• Liver function tests: ALT, AST, alkaline phosphatase, total bilirubin and albumin
• Enzymes: amylase (total, total pancreatic or total salivary) and lipase (colorimetric or turbidimetric assay)
• Renal function tests: BUN/urea (BUN or urea), creatinine, creatinine clearance, and uric acid
• Electrolytes (low and high): bicarbonate (low only), calcium, chloride, potassium and sodium
• Lipids (fasting): total cholesterol, LDL cholesterol and triglycerides
• Glucose

Laboratory abnormalities were further summarized by the applicant by baseline toxicity grade (normal, grade 1 - 4, and grade 3 - 4). Laboratory test results were graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, unless specified otherwise. Hematocrit, amylase, BUN/urea and chloride were graded using modified WHO criteria. The highest toxicity grade for laboratory abnormalities in subjects on ATV powder was reported.

7.2.5 Metabolic, Clearance, and Interaction Workup

The studies submitted are Phase 3b and involve PK analysis of previously established doses. The NDA and accompanying NDA supplement did not contain any additional metabolic, clearance, and interaction studies.

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 were examined as part of the Applicant's safety analysis.

7.3 Major Safety Results

7.3.1 Deaths

No subjects died in trials AI424397 and AI424451.

7.3.2 Nonfatal Serious Adverse Events

AI424397
Six subjects (17%) weighing 10 - <25 kg treated with ATV powder had on-treatment SAEs. The only SAE reported in ≥ 2 subjects was herpes zoster (2 subjects [4%]).

In the 10 - < 15 kg group, two subjects had SAEs. One subject had bronchiectasis. Another subject, AI424397-31-47, (age 2 years) had a mild QT prolongation (QTcF of 477msec with baseline of 382 msec) on ECG that led to discontinuation of study drug. , The QT prolongation resolved on the day following discontinuation of study drug, but while atazanavir exposures were still therapeutic

In the 15 - < 25 kg group, four subjects had SAEs. Two subjects had herpes zoster, one subject had a febrile convulsion, and one subject had a transaminase increase.

Reviewer Comments: 1) The 2 year old-subject mentioned above had a one-time QT prolongation (413 msec) which resolved on the day following study drug discontinuation; however atazanavir exposures were still therapeutic at that time. Therefore, it appears that the QT prolongation observed was spurious, resolving prior to elimination of study drug exposure. 2) It should also be noted that although ATV is associated with PR prolongation, marked QT prolongation was not observed in a QT trial described in Section 12.2 of the Reyataz package insert.

AI424451
Through Week 48, 12 subjects (18%) weighing 10 - <25 kg had on-treatment SAEs. SAEs reported in two subjects or more included overdose (2 subjects- see brief narrative summaries below), ALT increased (3 subjects), and grade 3 hyperbilirubinemia (2 subjects]. Grade 3-4 increased transaminase SAEs were reported in four subjects who were followed with increased laboratory monitoring but were not hospitalized. These latter events (Grade 3-4 transaminase elevation in 4 subjects would not be considered SAEs using the regulatory definition.

Non-fatal serious adverse events in AI424397 and AI424451 are shown in Table 13:

Table 13: Non-Fatal Treatment Emergent SAEs For AI424397 and AI424451

NON- FATAL TREATMENT EMERGENT SERIOUS ADVERSE EVENTS FOR AI424397 + AI424451							
	AI424397			AI424451			AI424397 + AI424451
	10 - <15kg	15 - <25kg	OVERALL 10 - <25kg	10 - <15kg	15 - <25kg	OVERALL 10 - <25kg	COMBINED 10-<25kg
	(N=19)	(N=16)	(N= 35)	(N= 20)	(N=34)	(N= 54)	(N=89)
ANY ADVERSE EXP.	2/19 (11%)	4/16 (25%)	6/35 (17%)	6/20 (30%)	6/34 (18%)	12/54 (20%)	18/89 (20%)
BLOOD & LYMPHATICS							
LYMPHADENOPATHY				1/20 (5%)		1/54 (1.9%)	1/89 (1.1%)
THROMBOCYTOPENIA	1/19 (5.2%)		1/35 (2.9%)				1/89 (1.1%)
ULCERATIVE KERATITIS				1/20 (5%)		1/54 (1.9%)	1/89 (1.1%)
HEPATOBILLIARY DISORDER							
HYPERBILIRUBINEMIA					1/34 (2.9%)	1/54 (1.9%)	1/89 (1.1%)
INFECTIONS & INFESTATIONS							
DYSENTERY				1/20 (5%)		1/54 (1.9%)	1/89 (1.1%)
HERPES ZOSTER		2/25 (8%)	2/35 (5.7%)				2/89 (2.2%)
OTITIS MEDIA				1/20 (5%)		1/54 (1.9%)	1/89 (1.1%)
PNEUMONIA				1/20 (5%)		1/54 (1.9%)	1/89 (1.1%)
SINUSITIS				1/20 (5%)		1/54 (1.9%)	1/89 (1.1%)
TONSULITIS					1/34 (2.9%)	1/54 (1.9%)	1/89 (1.1%)
VARICELLA				1/20 (5%)		1/54 (1.9%)	1/89 (1.1%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS							
OVERDOSE					2/34 (5.9%)	2/54 (3.7%)	2/89 (2.2%)
INVESTIGATIONS							
ALANINE AMINOTRANSFERASE INCREASED				1/20 (5%)	2/34 (5.9%)	3/54 (5.6%)	3/89 (3.3%)
ASPARTATE AMINOTRANSFERASE INCREASED				1/20 (5%)		1/54 (1.9%)	1/89 (1.1%)
BLOOD BILIRUBIN INCREASED					1/34 (2.9%)	1/54 (1.9%)	1/89 (1.1%)
ECG QT PROLONGATION	1/19 (5.2%)		1/35 (2.9%)				1/89 (1.1%)
TRANSAMINASE INCREASE		1/25 (4%)	1/35 (2.9%)				1/89 (1.1%)
NERVOUS SYSTEM DISORDER							
FEBRILE CONVULSION		1/25 (4%)	1/35 (2.9%)				1/89 (1.1%)
RESPIRATORY, THORACIC & MEDIASTINAL							
BRONCHIECTASIS	1/19 (5.2%)		1/35 (2.9%)				1/89 (1.1%)

Brief Narrative Summary for Asymptomatic Overdose SAE:

Subject AI424451-6-33 was a 6-year old Black/African American female child at time of the event with no relevant medical history. From day 1 (b) (6) to day 14 ((b) (6) , the subject was given ATV twice daily (total daily dose of 500 mg) instead of 250mg ATV once daily and the adherence was noted to be 207%. When the subject came back for her regular study visit at week 2, the investigator discovered the dosing error and reported an event of moderate overdose of ATV. She did not receive treatment for this event. No action was taken with regard to the study drug. The event of overdose resolved on day 14 (b) (6) . The subject was resumed on normal dose of ATV (250 mg daily) from day 15 ((b) (6) .

Brief Narrative Summary for Overdose SAE with Subsequent Hyperbilirubinemia with Jaundice and First Degree AV Block

Subject AI424451-14-49 as a 6-year old Black/African American female child at time of the event with no relevant medical history.

From day 1 (b) (6) to day 7 (b) (6) , the subject was given atazanavir twice daily (total daily dose of 500 mg) instead of 250 mg atazanavir once daily and ritonavir twice daily (total daily dose of160 mg) instead of 80mg ritonavir once daily. On day 1 (b) (6)), the electrocardiogram (ECG) performed showed sinus arrhythmia, which was not considered clinically significant. When the subject came back for her regular study visit at week 2, the investigator discovered the dosing error and reported an event of mild overdose of study drug. On day 15 (b) (6)), the electrocardiogram performed showed “left ventricular hypertrophy”. On day 15 (b) (6)), the laboratory test results showed total bilirubin of 1.5 mg/dL (baseline: 0.2 mg/dL, reference range: normal for age (NA)-1.1 mg/dL) and direct bilirubin of 0.29 mg/dL (baseline: 0.12 mg/dL, reference range: NA-0.18 mg/dL). She was diagnosed with mild hyperbilirubinemia. She did not receive treatment for these events. No action was taken with regard to the study drug.

The event of overdose resolved on day 7 (b) (6) . The subject was resumed on normal dose of atazanavir (250 mg daily) and ritonavir (80 mg) from day 8 (b) (6)). On day 9 (b) (6) , the subject was deeply jaundiced in her sclera. Mild jaundice was reported for which treatment was not required. An ECG performed on the same day showed “left ventricular hypertrophy”. The ECG performed on day 15 ((b) (6) showed first degree AV block. The subsequent ECG performed on day 29 (b) (6) was normal. The events of jaundice and hyperbilirubinemia were considered resolved on day 57 (b) (6) with total bilirubin and direct bilirubin levels of 1.1 mg/dL and 0.18 mg/dL, respectively.

Reviewer Comment: Unconjugated hyperbilirubinemia and AV block are known ATV dose-dependent adverse reactions. ECG findings from machine readings can erroneously suggest left ventricular hypertrophy (LVH) and should be confirmed by repeat ECG. If ECG continues to suggest LVH on repeat, the finding should be confirmed by chest x-ray or echocardiogram.

7.3.3 Dropouts and/or Discontinuations

AI424397

One subject (5%) in the 10 - < 15 kg group had prolonged QT leading to discontinuation of study therapy (see description above in Section 7.32). None of the subjects in the 15 - < 25 kg group had AEs leading to discontinuation of study therapy.

AI424451
Four subjects (5%) had AEs leading to discontinuation of study therapy while on ATV powder. Two subjects in the 10 - < 15 kg group (10%) had AEs leading to discontinuation of study therapy (ALT increased/AST increased in 1 subject and vomiting in 1 subject). Only the vomiting was considered drug-related by the investigator. Subject AI424451-7-34 had elevated ALT and AST (both Grade 3) at baseline/Day 1. He did not receive any treatment, and on Day 7, he discontinued study medication due to elevated ALT and AST. Two subjects in the 15 - < 25 kg group (6%) had AEs leading to discontinuation of study therapy (ALT increased (Grade 4) and tuberculosis in 1 subject each). Only the ALT increased was considered drug-related by the investigator. Subject AI424451-6-13 had normal ALT and AST at baseline. On Day 119, she had abnormally high ALT and AST, and she continued to have increased ALT and AST throughout the trial. She received no treatment for these events. On Day 427, she discontinued study medication due to increased ALT and AST.

7.3.4 Significant Adverse Events

Grade 2 - 4 Adverse Events (AEs) for subjects 10 - < 25 kg in AI424397 and AI424451 are listed in Table 10. In AI424397 (16/35 [46%]) and AI424451 (25/54 [46%]) of subjects experienced Grade 2-4 AEs. As a category, infections made up approximately 28% of the Grade 2-4 AEs and hyperbilirubinemia (preferred term) was observed in 10% of subjects overall in both studies (AI424397 7/56 [13%] and AI424451 [6/74 8%]). Of the Grade 2-4 infection related AEs, both gastroenteritis and otitis media each occurred in greater than 5% of trial participants. From both studies there were six subjects (6.7%) with increased lipase but none of the subjects had clinical pancreatitis.

Grade 2-4 Grade 2-4 adverse events in AI424397 and AI424451 are shown in following table (Table 14):

Table 14: Grade 2-4 Adverse Events in AI424397 and AI424451

	AI424397			AI424451			AI424397 + AI424451
	10 - <15kg	15 - <25kg	Overall 10kg - <25kg	10 - <15kg	15 - <25kg	Overall 10kg - <25kg	Combined 10 - <25kg
	(N=19)	(N=16)	(N= 35)	(N=20)	(N=34)	(N= 54)	(N=89)
ANY ADVERSE EXPERIENCE	**9/19 (47%)**	**7/16 (44%)**	**16/35 (46%)**	**13/20 (65%)**	**12/34 (%)**	**25/54 (46%)**	**31/89**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1/19 (5.3%)	0	1/35 (2.9%)	3/20 (15%)	3/34 (8.8%)	6/54 (11%)	7/89 (7.9%)
ANEMIA	1/19 (5.3%)		1/35 (2.9%)			2/54 (3.7%)	3/89 (3.4%)
MEGALOBLASTIC ANEMIA				1/20 (5%)		1/54 (1.9%)	1/89 (1.1%)
LEUKOPENIA					1/34 (2.9%)	1/54 (1.9%)	1/89 (1.1%)
LYMPHADENOPATHY				1/20 (5%)		1/54 (1.9%)	1/89 (1.1%)
NEUTROPENIA					3/34 (8.8%)	3/54 (5.6%)	3/89 (3.4%)
THROMBOCYTOPENIA						2/54 (3.7%)	2/89 (2.2%)
EAR AND LABYRINTH DISORDERS				1/20 (5%)		1/54 (1.9%)	1/89 (1.1%)
EAR PAIN				1/20 (5%)		1/54 (1.9%)	1/89 (1.1%)
GASTROINTESTINAL DISORDERS	3/19 (16%)	1/16 (6.3%)	4/35 (11.4%)	2/20 (10%)		2/54 (3.7%)	6/89 (6.7%)
DENTAL CARIES	1/19 (5.3%)		1/35 (2.9%)				1/89 (1.1%)
DIARRHOEA	1/19 (5.3%)		1/35 (2.9%)				1/89 (1.1%)
GASTRITIS	1/19 (5.3%)		1/35 (2.9%)	1/20 (5%)		1/54 (1.9%)	2/89 (2.2%)
TOOTHACHE		1/16 (6.3%)	1/35 (2.9%)				1/89 (1.1%)
VOMITING	2/19 (11%)		2/35 (5.7%)	1/20 (5%)		1/54 (1.9%)	3/89 (3.4%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1/19 (5.3%)	2/16 (13%)	3/35 (8.6%)				3/89 (3.4%)
PYREXIA	1/19 (5.3%)	2/16 (13%)	3/35 (8.6%)				3/89 (3.4%)
HEPATOBILIARY DISORDERS	1/19 (5.3%)	4/16 (25%)	5/35 (14%)	2/20 (10%)	3/34 (8.8%)	5/54 (9.3%)	10/89 (11%)
HYPERBILIRUBINEMIA	1/19 (5.3%)	4/16 (25%)	5/35 (14%)	2/20 (10%)	2/34 (5.9%)	4/54 (7.4%)	9/89 (10%)
JAUNDICE					1/34 (2.9%)	1/54 (1.9%)	1/89 (1.1%)
IMMUNE SYSTEM DISORDERS					1/34 (2.9%)	1/54 (1.9%)	1/89 (1.1%)
IMMUNODEFICIENCY					1/34 (2.9%)	1/54 (1.9%)	1/89 (1.1%)

Table 14 (continued): Grade 2-4 Adverse Events in AI424397 and AI424451

	AI424397			AI424451			AI424397 + AI424451
	10 - <15kg	15 - <25kg	Overall 10kg - <25kg	10 - <15kg	15 - <25kg	Overall 10kg - <25kg	Combined 10 - <25kg
	(N=19)	(N=16)	(N= 35)	(N=20)	(N=34)	(N= 54)	(N=89)
INFECTIONS AND INFESTATIONS	6/19 (32%)	3/16 (19%)	9/35 (26%)	10/20 (50%)	6/34 (18%)	16/54 (30%)	25/89 (28%)
ACARODERMATITIS					1/34 (2.9%)	1/54 (1.9%)	1/89 (1.1%)
BRONCHITIS					1/34 (2.9%)	1/54 (1.9%)	1/89 (1.1%)
CELLULITIS				1/20 (5%)		1/54 (1.9%)	1/89 (1.1%)
EAR INFECTION	1/19 (5.3%)		1/35 (2.9%)	1/20 (5%)		1/54 (1.9%)	2/89 (2.2%)
GASTROENTERITIS		1/16 (6.3%)	1/35 (2.9%)	6/20 (30%)		6/54 (11%)	7/89 (7.9%)
HERPES SIMPLEX	1/19 (5.3%)		1/35 (2.9%)				
INFLUENZA				1/20 (5%)		1/54 (1.9%)	1/89 (1.1%)
LICE INFESTATION		1/16 (6.3%)	1/35 (2.9%)	1/20 (5%)		1/54 (1.9%)	1/89 (1.1%)
LOWER RESP. TRACT INFECTION	1/19 (5.3%)		1/35 (2.9%)	1/20 (5%)		1/54 (1.9%)	2/89 (2.2%)
LYMPH NODE TUBERCULOSIS				1/20 (5%)		1/54 (1.9%)	1/89 (1.1%)
NASOPHARYNGITIS	1/19 (5.3%)		1/35 (2.9%)	2/20 (10%)		2/54 (3.7%)	3/89 (3.4%)
OTITIS MEDIA	2/19 (11%)	2/16 (13%)	4/35 (11.4%)		2/34 (5.9%)	2/54 (3.7%)	6/89 (6.7%)
OTITIS MEDIA ACUTE	1/19 (5.3%)		1/35 (2.9%)				1/89 (1.1%)
OTITIS MEDIA CHRONIC		1/16 (6.3%)	1/35 (2.9%)				1/89 (1.1%)
PHARYNGITIS				2/30 (10%)	1/34 (2.9%)	3/54 (3.7%)	3/89 (3.4%)
PNEUMONIA	2/19 (11%)		2/35 (5.7%)	1/20 (5%)		1/54 (1.9%)	3/89 (3.4%)
PULMONARY TUBERCULOSIS				1/20 (5%)		1/54 (1.9%)	1/89 (1.1%)
RHINITIS		1/16 (6.3%)	1/35 (2.9%)				
ROTAVIRUS INFECTION				1/20 (5%)		1/54 (1.9%)	1/89 (1.1%)
SIALOADENITIS				1/20 (5%)		1/54 (1.9%)	1/89 (1.1%)
SINUSITIS		1/16 (6.3%)	1/35 (2.9%)				
TONSILLITIS	1/19 (5.3%)		1/35 (2.9%)				
TUBERCULOSIS					1/34 (2.9%)	1/54 (1.9%)	1/89 (1.1%)
UPPER RESP. TRACT INFECTION				1/20 (5%)		1/54 (1.9%)	1/89 (1.1%)
VARICELLA	1/19 (5.3%)		1/35 (2.9%)				1/89 (1.1%)

Table 14 (continued): Grade 2-4 Adverse Events in AI424397 and AI424451

	AI424397			AI424451			AI424397 + AI424451
	10 - <15kg	15 - <25kg	Overall 10kg - <25kg	10 - <15kg	15 - <25kg	Overall 10kg - <25kg	Combined 10 - <25kg
	(N=19)	(N=16)	(N= 35)	(N=20)	(N=34)	(N= 54)	(N=89)
INVESTIGATIONS	2/19 (11%)	1/16 (6.3%)	3/35 (8.6%)	3/20 (15%)	5/34 (15%)	8/54 (15%)	11/89 (12%)
ALANINE AMINOTRANSFERASE INCREASED						3/54 (5.6%)	3/89 (3.4%)
ASPARTATE AMINOTRANSFERASE DECREASED						1/54 (1.9%)	1/89 (1.1%)
ASPARTATE AMINOTRANSFERASE INCREASED						1/54 (1.9%)	1/89 (1.1%)
BLOOD ALKALINE PHOSPHATASE INCREASED						2/54 (3.7%)	2/89 (2.2%)
BLOOD BILIRUBIN INCREASED		1/16 (6.3%)	1/35 (2.9%)				2/89 (2.2%)
HEPATIC ENZYME INCREASED					1/34 (2.9%)	1/54 (1.9%)	1/89 (1.1%)
LIPASE INCREASED	2/19 (11%)		2/35 (5.7%)			4/54 (7.4%)	6/89 (6.7%)
TRANSAMINASES INCREASED						2/54 (3.7%)	4/89 (4.5%)
METABOLISM AND NUTRITION DISORDERS		1/16 (6.3%)	1/35 (2.9%)			1/54 (1.9%)	2/89 (2.2%)
MARASMUS		1/16 (6.3%)	1/35 (2.9%)				1/89 (1.1%)
HYPERCHOLESTREMIA						1/54 (1.9%)	1/89 (1.1%)

Table 14 (continued): Grade 2-4 Adverse Events in AI424397 and AI424451

	AI424397			AI424451			AI424397 + AI424451
	10 - <15kg	15 - <25kg	Overall 10kg - <25kg	10 - <15kg	15 - <25kg	Overall 10kg - <25kg	Combined 10 - <25kg
	(N=19)	(N=16)	(N= 35)	(N=20)	(N=34)	(N= 54)	(N=89)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)					1/34 (2.9%)	1/54 (1.9%)	1/89 (1.1%)
SKIN PAPILLOMA					1/34 (2.9%)	1/54 (1.9%)	1/89 (1.1%)
NERVOUS SYSTEM DISORDERS				1/20 (5%)		1/54 (1.9%)	1/89 (1.1%)
HEADACHE				1/20 (5%)		1/54 (1.9%)	1/89 (1.1%)
PSYCHIATRIC DISORDERS				1/20 (5%)		1/54 (1.9%)	1/89 (1.1%)
BRUXISM				1/20 (5%)		1/54 (1.9%)	1/89 (1.1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2/19 (11%)	1/16 (6.3%)	3/35 (8.6%)	4/20 (20%)	1/34 (2.9%)	5/54 (9.3%)	8/89 (9.0%)
ASTHMA	1/19 (5.3%)	1/16 (6.3%)	2/35 (5.7%)	2/20 (10%)		2/54 (3.7%)	2/89 (2.2%)
BRONCHOSPASM	1/19 (5.3%)		1/35 (2.9%)				1/89 (1.1%)
COUGH	1/19 (5.3%)		1/35 (2.9%)				1/89 (1.1%)
PRODUCTIVE COUGH		1/16 (6.3%)	1/35 (2.9%)				1/89 (1.1%)
RHINITIS ALLERGIC		1/16 (6.3%)	1/35 (2.9%)	3/20 (15%)	1/34 (2.9%)	4/54 (7.4%)	5/89 (5.6%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1/19 (5.3%)		1/35 (2.9%)	1/20 (5%)		1/54 (1.9%)	2/89 (2.2%)
DERMATITIS DIAPER	1/19 (5.3%)		1/35 (2.9%)				1/89 (1.1%)
PRURIGO				1/20 (5%)		1/54 (1.9%)	1/89 (1.1%)
VASCULAR DISORDERS		1/16 (6.3%)	1/35 (2.9%)				1/89 (1.1%)
HAEMATOMA		1/16 (6.3%)	1/35 (2.9%)				1/89 (1.1%)

AI424397 Grade 3 – 4 Non-SAE Adverse Events
Through Week 48, six subjects (17%) receiving ATV powder had Grade 3 - 4 AEs. Two subjects (11%) in the 10 - < 15 kg group had Grade 3 - 4 AEs (lipase increased, and anemia in one subject each [5%]). Four subjects (25%) in the 15 - < 25 kg group had Grade 3 - 4 AEs (blood bilirubin increased, chronic otitis media, and transaminases increased in one subject each [6%] and three subjects had hyperbilirubinemia [19%].

AI424451 Grade 3 - 4 Non-SAE Adverse Events: Through Week 48, seven subjects (13%) on ATV powder had Grade 3 - 4 adverse events. Three subjects (20%) in the 10 - < 15 kg group had Grade 3 - 4 AEs (blood alkaline phosphatase increased hyperbilirubinemia, rotavirus infection; in 1 subject each [5%]). Four subjects (12%) in the 15 - <25 kg group had Grade 3 - 4 AEs (one with neutropenia and hyperbilirubinemia, one with neutropenia, one with increased ALT and one with increased lipase).

Reviewer Comment: The type of Grade 3-4 AEs observed were consistent with prior pediatric studies of ATV. Unconjugated hyperbilirubinemia is a known dose-dependent side effect of ATV therapy.

Grade 3-4 adverse events in AI424397 and AI424451 are shown in following (Table 15):

Table 15: Grade 3-4 Adverse Events in AI424397 and AI424451

	AI424397			AI424451			AI424397 + AI424451
	10 - <15kg (N=19)	15 - <25kg (N=16)	Overall 10kg - <25kg (N= 35)	10 - <15kg (N=20)	15 - <25kg (N=34)	Overall 10-25kg (N= 54)	Combined 10-<25kg (N=89)
ANY ADVERSE EXPERIENCE	2/19 (11%)	4/16 (25%)	6/35 (17%)	3/20 (15%)	4/34 (12%)	7/54 (13%)	13/89 (15%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS							
ANEMIA	1/19 (5.3%)		1/35 (2.9%)				1/89 (1.1%)
NEUTROPENIA					2/34 (5.9%)	2/54 (3.7%)	2/89 (2.2%)
HEPATOBILIARY DISORDERS							
HYPERBILIRUBINAEMIA		3/16 (19%)	3/35 (8.6%)	1/20 (5%)	1/34 (2.9%)	2/54 (3.7%)	5/89 (5.6%)
INFECTIONS AND INFESTATIONS							
OTITIS MEDIA CHRONIC		1/16 (6.3%)	1/35 (2.9%)				1/89 (1.1%)
ROTAVIRUS INFECTION				1/20 (5%)		1/54 (1.9%)	1/89 (1.1%)
INVESTIGATIONS							
ALANINE AMINOTRANSFERASE INCREASED					2/34 (5.9%)	2/54 (3.7%)	2/89 (2.2%)
BLOOD ALKALINE PHOSPHATASE INCREASED				1/20 (5%)		1/54 (1.9%)	1/89 (1.1%)
BLOOD BILIRUBIN INCREASED		1/16 (6.3%)	1/35 (2.9%)				1/89 (1.1%)
LIPASE INCREASED	1/19 (5.3%)		1/35 (2.9%)		1/34 (2.9%)	1/54 (1.9%)	2/89 (2.2%)

7.3.5 Submission Specific Primary Safety Concerns

Hyperbilirubinemia and Jaundice

Twenty subjects (22%) in AI424397 and AI424451 in the 10 - < 25 kg weight groups had hyperbilirubinemia-related AEs while on ATV powder. Of these twenty subjects, two subjects (2%) had hyperbilirubinemia-related SAEs which were likely drug related (see Table 13). Fourteen subjects (16%) had Grade 2 - 4 hyperbilirubinemia- AEs considered drug-related while on ATV powder (see Table 14). Eleven subjects (12%) of the 10 - <25 kg subjects had Grade 3-4 total bilirubin (≥ 2.9 mg/dL or ≥ 49.6 micromol/L) [See Table 17].

Reviewer Comments: 1) The frequency of Grade 3-4 hyperbilirubinemia is lower than in the prior pediatric trial of the capsule formulation (12% versus 58%). However, in prior capsule studies, patients received unboosted ATV which could have resulted in higher Cmax and concomitant increased unconjugated hyperbilirubinemia. 2) The criterion for Grade 3-4 hyperbilirubinemia was also changed. Previously in the NDA submission for the capsule formulation, the criteria for Grade 3-4 hyperbilirubinemia was ≥ 3.2mg/dL.

Cardiac Abnormalities

Five subjects (5.6%) in the 10 – 25 kg weight groups had cardiac disorders while on ATV powder. In the 10 - <15kg group, one subject had QT prolongation resulting in discontinuation and another subject had tachycardia. Three subjects (8%) in the 15 - < 25 kg group had cardiac disorders (two with first degree AV block, and one with left ventricular hypertrophy).

Reviewer Comments: 1) See comment above in Section in 7.3.2 about subject with QT prolongation. 2) Prolongation of the PR interval with 1st degree AV block is a known dose-dependent side effect of ATV.

Rash

Eleven (12%) of subjects 10 – 25 kg had rash events while on ATV powder. The most common rash events were rash, allergic dermatitis, and prurigo. All were Grade 1 AEs. No Grade 2 - 4 related rash events were reported.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

While on ATV powder, 91% of subjects had AEs. The most common AEs were upper respiratory tract infection (36%), gastroenteritis (25%), and vomiting (24%). The most common AEs (≥10% in any group) are summarized in Table 16.

Table 16: Common Adverse Events

Most Common Adverse Events (at Least 10% in Any 10 - 25 kg Groups) - All Grades on ATV Powder - Treated Subjects Listed From Most to Least Frequent

System Organ Class/Preferred Term	B/L Weight 10 - <15kg (N=39)	B/L Weight 15 - <25 kg (N=50)	Combined 10 - <25kg (N=89)
TOTAL SUBJECTS WITH AN EVENT	**36 (92%)**	**45 (90%)**	**81 (91%)**
INFECTIONS AND INFESTATIONS	**32 (82%)**	**37 (74%)**	**69 (77%)**
Upper Respiratory Infection	8 (20%)	14 (28%)	22 (24%)
Gastroenteritis	10 (25%)	7 (14%)	17 (19%)
Nasopharyngitis	10 (25%)	11 (22%)	21 (23%)
Otitis Media	4 (10%)	4 (8.0%)	8 (9.0%)
Otitis Media Acute	1 (2.6%)	5 (10%)	6 (6.7%)
Acarodermatitis	0	4 (8.0%)	4 (4.5%)
Impetigo	4 (10%)	4 (8.0%)	8 (9.0%)
Pharyngitis	5 (12%)	5 (10%)	10 (11%)
Lower Respiratory Tract Infection	4 (10%)	2 (4.0%)	6 (6.7%)
Tinea Capitus	2 (5.1%)	5 (10%)	7 (7.9%)
Viral Upper Respiratory Tract Infection	4 (10%)	1 (2.0%)	5 (5.6%)
Pneumonia	3 (7.7%)	0	3 (3.4%)
Gastrointestinal Infection	17 (43%)	18 (36%)	35 (39%)
Vomiting	10 (25%)	10 (20%)	20 (22%)
Diarrhea	7 (17%)	6 (12%)	13 (14%)
RESPIRATORY THORACIC AND MEDIASTINAL DISORDERS	**14 (35%)**	**17 (34%)**	**31 (34%)**
cough	5 (12%)	12 (24%)	17 (19%)
rhinorrhea	0	4 (8%)	4 (4%)
rhinitis allergic	4 (10%)	2 (4.0%)	6 (6%)
asthma	5 (12%)	2 (4.0%)	7 (7.9%)

Table 16 (continued): Common Adverse Events

Most Common Adverse Events (at Least 10% in Any 10 - 25 kg Groups)

[Continued] - All Grades on ATV Powder - Treated Subjects

Listed From Most to Least Frequent

System Organ Class/Preferred Term	B/L Weight 10 - <15kg (N=39)	B/L Weight 15 - <25 kg (N=50)	Combined 10 - <25kg (N=89)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**10 (25%)**	**13 (26%)**	**23 (25%)**
eczema	4 (10%)	3 (6.0%)	7 (7.9%)
dermatitis diaper	1 (2.6%)	0	1 (1.1%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**10 (25%)**	**13 (26%)**	**23 (25%)**
anemia	2 (5.1%)	4 (8.0%)	6 (6%)
neutropenia	3 (7.7%)	3 (6.0%)	6 (6%)
lymphadenopathy	6 (15.4)	3 (6.0%)	9 (10%)
INVESTIGATIONS	**9 (23%)**	**11 (22%)**	**20 (22%)**
Transaminases Increased	0	1 (2.0%)	1 (1.1%)
HEPATOBILLIARY DISORDERS	**9 (23%)**	**11 (22%)**	**20 (22%)**
hyperbilirubinemia	5 (12%)	7 (14%)	12 (13.5)
jaundice	3 (7.7%)	5 (10%)	8 (9.0%)
INJURY, POISONING, AND PROCEDURAL COMPLICATIONS	**4 (10%)**	**6 (12%)**	**10 (11%)**
Arthropod bite	0	2 (4.0%)	2 (2.2%)
METABOLISM AND NUTRTION DISORDER	**5 (12%)**	**5 (10%)**	**10 (11%)**
hypercholestremia	2 (5.1%)	1 (2.0%)	3 (3.4%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**11 (28%)**	**6 (12%)**	**17 (19%)**
pyrexia	11 (28%)	5 (10%)	16 (18%)

7.4.2 Laboratory Findings Grade 3-4 Abnormalities

The most common Grade 3 - 4 laboratory abnormalities occurring in pediatric patients taking the powder formulation were increased amylase (30%), neutropenia (10%), increased ALT (10%), elevation of total bilirubin (≥ 2.6 x upper limit of normal, 10%), increased lipase (4%), and decreased hemoglobin (4%). All other Grade 3 - 4 laboratory abnormalities occurred with a frequency of < 3%.

Grade 3-4 laboratory abnormalities occurring in subjects treated with the powder formulation are summarized in Table 17 below:

Table 17: Grade 3-4 Laboratory Abnormalities

		AI424397			AI424451			AI424397 + AI424451
		10 - <15kg	15 - <25kg	Overall 10 -<25kg	10 - <15kg	15 - <25kg	Overall 10 -<25kg	Combined 10-<25kg
Lab	L/H	(N=19)	(N=16)	(N= 35)	(N= 20)	(N=34)	(N= 54)	(N=89)
Alanine Aminotransferase (ALT)	H		1/16 (6.3%)	1/35 (2.9%)	1/20 (5%)	1/34 (2.9%)	2/54 (3.7%)	3/89 (3.4%)
Aspartate Aminotransferase (AST)	H				1/20 (5%)		1/54 (1.9%)	1/89 (1.1%)
Alkaline Phosphatase (ALP)	H	1/19 (5.3%)		1/35 (2.9%)	1/20 (5%)		1/54 (1.9%)	2/89 (2.2%)
Amylase	H	5/19 (26%)	1/16 (6.3%)	6/35 (17%)	5/20 (25%)	1/34 (2.9%)	6/54 (11%)	12/89 (13%)
Bilirubin	H		4/16 (25%)	4/35 (11%)	3/20 (15%)	4/34 (12%)	7/54 (13%)	11/89 (12%)
Hemoglobin	L	3/19 (16%)		3/35 (8.6%)				3/89 (3.4%)
Hypocarbia	L	1/19 (5.3%)		1/35 (2.9%)				1/89 (1.1%)
Lipase	H		1/16 (6.3%)	1/35 (2.9%)		2/34 (5.9%)	2/54 (3.7%)	3/89 (3.4%)
Neutrophils (absolute)	L	2/19 (11%)		2/35 (5.7%)	3/20 (15%)	5/34 (15%)	8/54 (15%)	10/89 (11%)
Uric Acid	H		1/16 (6.3%)	1/35 (2.9%)				1/89 (1.1%)

Reviewer Comment: Amylase elevation without concomitant lipase elevation is very common in HIV infected pediatric patients. It is thought to be related to chronic inflammation of the parotid gland rather than of pancreatic origin.

7.4.3 Vital Signs

No trends were observed in the vital signs obtained from subjects in trials AI424397 and AI424451.

7.4.4 Electrocardiograms (ECGs)

Overall, 99% of subjects had QTc intervals (Fridericia) ≤450 msec. One subject in the 10 - < 15 kg group had a QTc interval (Fridericia) > 450 to 480 msec.
Overall, 92% of subjects had PR intervals ≤ 98th percentile for each subject's age group. Borderline values (small increase above the 98^{th} percentile for age) were observed in 1 subject in the 10 - < 15 kg group, and 7 subjects (15%) in the 15 - < 25 kg group. Two subjects (4%) in the 15 - < 25 kg group had Grade 1 first-degree AV block.

At Week 48, all subjects had QTc intervals (Fridericia) ≤450 msec and PR intervals □ 98^{th}(≤450msec) percentile.

7.6 Additional Safety Evaluations

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable since there was no systematic measurement of growth in Trials AI424397 and AI424451.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Given that ATV is a once daily drug, it is not unexpected that a patient could end up receiving twice daily dosing as most pediatric regimens involve twice daily dosing. There were two examples of overdose SAEs, as described above. Of note, both subjects had increased monitoring but were not hospitalized. These adverse events would not be considered SAEs using the regulatory definition.

7.7 Additional Submissions / Safety Issues

On February 18, the Applicant sent a 90 day safety update. There were no deaths but there were two new subjects 10 - < 15 kg with SAEs: one with mild drug induced liver injury per Applicant that did not meet Hy's criteria (narrative below) and one with severe left humerus fracture. One subject in the 15 - <25 kg group with a history of a febrile convulsion SAE developed chronic otitis media SAE which resolved after surgery for a perforated tympanic membrane. There were no discontinuations for subjects in the 10 - <25 kg weight range.

Narrative for subject with drug-related liver abnormalities:

Subject AI424397-15-36 was a 4-year-old Black/African-American female at the time of the event with relevant medical history of gastroenteritis, hepatomegaly, and splenomegaly.

On Day 29 (b) (6), the subject's laboratory test results showed total bilirubin level of 1.8 mg/mL (baseline: 0.2 mg/dL, reference range: 0-1.1 mg/mL). The subject was reported with moderate hyperbilirubinemia. On Day 61 (b) (6), the subject had severe increased lipase with lipase level of 98 U/L (baseline: 16 U/L, reference range: 4-31 U/L). She did not receive treatment for these events. On the same day, Day 61 the event of hyperbilirubinemia resolved with total bilirubin level of 0.4 mg/mL. On Day 85 (b) (6)), the event of increased lipase resolved with lipase level of 43 U/L. On Day 337 (b) (6)), the subject was noted with moderate hyperbilirubinemia with total bilirubin level of 2.7 mg/dL. The event of hyperbilirubinemia resolved on Day 421 (b) (6)) with total bilirubin level of 0.3 mg/dL.

On Day 589 (b) (6)), the subject's laboratory test results showed a lipase level of 64 U/L. She was noted with moderate increased lipase. She did not receive treatment for this event. Laboratory test results are shown in the table below.

On Day 670 (b) (6)), the subject was noted with mild gastroenteritis. She did not receive treatment for this event. On Day 671 (b) (6)), the event gastroenteritis resolved. On Day 672 (b) (6), the laboratory test results showed alanine aminotransferase (ALT) of 77 U/L (baseline: 56 U/L, reference range: 5-30 U/L), aspartate aminotransferase (AST) of 85 U/L (baseline: 59 U/L, reference range: 10-68 U/L), alkaline phosphatase (ALP) of 185 U/L (baseline: 166 U/L, reference range: 108-317 U/L), and total bilirubin of 3.2 mg/dL. The subject was reported with mild drug-induced liver injury. Both hepatitis A IgG and IgM were negative. She was asymptomatic with no clinical abnormalities. The subject did not receive treatment for these events. No action was taken with regard to the study drug. On Day 672 (b) (6), the event of

increased lipase resolved with lipase level of 35 U/L. On Day 701 ((b) (6), the event of drug-induced liver injury was considered resolved. The investigator considered the drug induced liver injury to be related to the study drug.
On Day 755 (b) (6), the subject had moderate hyperbilirubinemia with total bilirubin level of 2.5 mg/dL. On Day 785 (b) (6), the event of hyperbilirubinemia worsened to severe in intensity with total bilirubin level of 4 mg/dL. The investigator considered the hyperbilirubinemia to be related to the study drug but no treatment was required and no action was taken regarding the study drug. On Day 841 (b) (6)), the event of hyperbilirubinemia improved to mild in intensity with total bilirubin level of 2.7 mg/dL. The event of hyperbilirubinemia was ongoing at the time of this report.

8 Postmarket Experience

In a review of pediatric SAEs from July 8, 2009 to May 31, 2013, there were 17 unduplicated serious FAERS reports for ATV but no pediatric deaths were noted. There were eight liver abnormalities (one with a severe skin rash), one cardiac event, and one metabolic event which have been previously described in the product label. Hemorrhagic cystitis and gastrointestinal toxicity were two unlabeled events. SAEs also included two events of facial wasting, one event with lipoatrophy, one accident, and one report of varicella. For the serious AEs the subjects had confounding medical conditions and these subjects were on other medications that complicated the attribution of causality to ATV.

Reviewer Comment: Product labeling for safety is appropriate with Warnings for cardiac conduction abnormalities, rash, Immune Reconstitution Syndrome, hepatotoxicity, cholelithiasis, and nephroliathiasis. The review of SAEs did not yield any new unexpected SAEs or safety signals.

9 Appendices

9.1 Literature Review/References

1) Nguyen ST, Eaton SA, Bain AM, Rahman AP, Payne KD, Bedimo R, Herrington JD, Maclayton DO, Rodriguez-Barradas MC, Busti AJ. Lipid-lowering efficacy and safety after switching to atazanavir-ritonavir-based highly active antiretroviral therapy in patients with human immunodeficiency virus. Pharmacotherapy. 2008 Mar;28(3):323-30.

9.2 Timeline Relevant to ATV Pediatric Development:

August 2001: ATV was first issued a pediatric written request (PWR) for studies in children ages three months to 16 years of age. Studies were to be submitted by August 2003.

June 2003: Initial Approval of ATV Capsule formulation (400mg without RTV boosting) for adult patients. Note: The Pediatric Rule was on legal hold at time of approval (prior to the PREA legislation).

August 2003: Amendment to PWR for a time extension for submission of pediatric studies to Oct 31, 2006.

July 2004: Supplemental NDA (sNDA) for new adult dosing regimen approved: 300mg ATV coadministered with 100mg RTV. PREA requirement for pediatric patients less than 3 months of age waived for safety concerns related to hyperbilirubinemia and potential for kernicterus. PREA requirements for pediatric patients three months to 18 years were deferred. The deadline for report submission was October 31, 2006.

December 2006: Resubmitted PWR (Prior PWR expired). Studies were to be submitted by December 15, 2008.

March 2008: sNDA with pediatric dosing for capsule formulation approved. Applicant was granted a partial PREA deferral for pediatric patients ≥ 3 months to 6 years of age to determine safe and appropriate dosing of ATV. In addition, there was an additional PREA requirement to address the incomplete safety information in the ATV capsule sNDA:

> "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."

These studies were to be submitted by December 15, 2010.

May 2008: PWR extension for submission of remaining pediatric studies to December 15, 2009.

November and December 2008: Pre-NDA meeting package submissions for pediatric ATV powder formulation in advance for February 2009 meeting (note: these submissions are not in EDR but are described in MO review dated 02/20/2009).

DAVP Response Dated February 23, 2009 (excerpt from Clinical comment #3)

"…We anticipate that data from approximately 30 subjects, ages three months to less than six years, who receive the recommended ATV powder dose coadministered with RTV for at least 24 weeks will be needed to support the safety of this formulation. However, depending on the PK, safety, and virologic data that are obtained, it is possible that more subjects would be necessary. As previously mentioned, having data from only one subject who has received the recommended powder dose for at least 24 weeks is unlikely to be considered adequate. From the information we have received to date, we do not believe the data from your ATV capsule cohorts can substitute for your apparent lack of safety data from your ATV powder cohorts…"

July 2009: Based on discussions from February 2009 meeting, Applicant proposed a post-marketing commitment protocol (PRINCE trial) with 200 enrolled patients/ 100 treated: 50 patients (ages 3 months to less than 6 years) treated with powder formulation and 50 patients (ages 6 to 18 years) treated with the capsule formulation.

Reviewer Comment: The proposal to treat 50 patients treated with the capsule formulation was to address the March 2008 PREA requirement for additional safety data.

November 2009: Excerpt from DAVP communication to the Applicant regarding the powder formulation:

A. Pediatric Powder Supplement
"Based on our review, you will need at least 20 additional pediatric patients ages six months to less than six years to support the safety of the powder formulation. These 20+ patients taken together with the patients three to six months of age plus the four patients appropriately dosed with ATV powder and RTV will make

> up a safety cohort of at least 30 patients to support the approval of the ATV powder formulation."

April 2009: PWR extension to December 15, 2011.

March 4, 2010: DAVP communication to Applicant regarding powder formulation tolerability and adherence:

> "In regard to your proposed powder formulation protocol, we request that tolerability and adherence to your reconstituted powder formulation and liquid ritonavir be studied in detail and be submitted in your final study report. Consistent dosing of patients three months to six years of age is a challenge especially when administering liquid ritonavir."

October 2011: Approval of NDA for revision of pediatric capsule dosing. PREA Language for the patients ≥3 months to <6 years of age:

> "We are deferring submission of your pediatric study for ages ≥ 3 months to < 6 years for this application because the product is ready for approval in patients ≥ 6 to < 18 years of age and ATV powder for oral solution is currently under study in the ≥ 3 months to < 6 year age group."

November 2011: PWR extension to December 15, 2013.

June 29, 2012 Type C Meeting to discuss re-formulated ATV powder formulation with aspartame reduced from 10% to 4.2%. DAVP agreed with Applicant's plan to reformulate ATV Powder.

July 5, 2012: Applicant submitted a preliminary summary of their ATV PK data for patients 5 to 25 kg in the AI424397 trial. Based on Clinical Pharmacology's review, it appeared that pediatric patients in 5-10 kg (treatment group A) were underdosed with the ATZ 150mg + RTV 80mg.

August 6, 2012: DAVP recommended that the Applicant increase the ATZ/RTV dose to 200/80mg for patients weighing 5-10 kg in the AI424451 trial. The Applicant responded in their Type B meeting request of August 6, 2012 they planned to study the increased dose of ATV/RTV 200/80mg for patients 5-10 kg in the AI424451 trial.

October 19, 2012: In the meeting package, the Applicant proposed requesting an exclusivity determination prior to completing dose finding for the 5-10 kg weight band.

November 19, 2012: Pre-NDA meeting: The applicant accepts DAVP advice to defer submission of their request for pediatric exclusivity till they complete their studies of ATV powder formulation in the 5 to less than 10 kg weight band.

9.3 Labeling Recommendations

Pediatric Specific:

1) DAVP concurs with the Applicant's proposed dosing powder formulation for the 10 to less than 25 kg weight band:

POWDER FORMULATION

Body Weight	Daily Dosage of REYATAZ Powder	Daily Dosage of Ritonavir Oral Solution
10 kg to less than 15 kg and ≥ 3mos of age	200 mg (4 packets)'	80mg
15 kg to less than 25 kg	250 mg (5 packets)'	80mg

2) DAVP recommends that Applicant propose dosing for the powder formulation for pediatric patients ≥25 kg and adults who cannot take capsule formulation.

3) DAVP recommends that Applicant modify Section 6.2 Clinical Trial Experience in Pediatric Patients subsection for the powder formulation to only include safety data for the subjects 10 kg to less than 25 kg and omit the safety data for the (b) (6) for now. The information (b) (6) can be included when the Applicant submits the updated data (b) (6)

4) DAVP is modifying Section 2.4 Dosage and Administration of REYATAZ Powder to clarify the amount of food or liquid needed to assist in administering ATV powder. In addition, the professional instructions in this section and in Dosage and Administration of REYATAZ Pediatric Powder will be optimized to ensure caregivers can properly administer the ATV dose correctly.

5) DAVP is modifying Clinical Studies Section 14.3 Pediatric Patients: Pediatric Studies with Powder for clarity and so there is an agreement between Biometrics and the Applicant on presentation of the antiviral activity results.

General:

The SEALD team has made recommendations to make extensive changes to ATV label to conform to the latest labeling regulations and guidances including the draft Indications and Usage Guidance. SEALD's recommendations involve parsing the label to include the most relevant and prescriber friendly information into the label.

9.4 FINANCIAL DISCLOSURE

Clinical Investigator Financial Disclosure Review Template

Application Number: 206352-S00, 21567-S35

Submission Date(s): December 2, 2013

Applicant: Bristol Myers Squibb

Product: Reyataz (atazanavir)

Reviewer: Alan M. Shapiro

Date of Review: April 28, 2014

Covered Clinical Study: AI423020, AI424397, AI424451, and AI424466

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: AI424020: 285 investigators, AI424397: 73 investigators, AI424451: 93 investigators, AI424466: 7 investigators (Note: Some of the investigators are listed more than once since they were involved in multiple studies)		
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)): **Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study:** N/A **Significant payments of other sorts:** N/A **Proprietary interest in the product tested held by investigator:** N/A **Significant equity interest held by investigator in sponsor of covered study:** N/A		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ **N/A**
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant) **N/A**
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant) **N/A**

Reviewer Comment: Per the Applicant's Form 3454 statement and Financial Interests and Arrangement List of Investigators and Sub-Investigators for studies: AI424020, AI424397, AI424451, and AI 424466. From the review of the lists, the Applicant was able to obtain financial disclosures from all the investigators and sub-investigators. None of the investigators had any disclosable information.

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
05/09/2014

MARY E SINGER
05/09/2014
I concur with Dr. Shapiro's review and recommendations.