Amended Clinical Review: Table 11 Revised from Original Clinical Review

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-567
Submission Code	015
Letter Date	September 27, 2007
Stamp Date	September 26, 2007
PDUFA Goal Date	March 26, 2008
Reviewer Name	Alan M. Shapiro, M.D., Ph.D.
Review Completion Date	March 25, 2008
Established Name	Reyataz
(Proposed) Trade Name	
Therapeutic Class	HIV Protease Inhibitor
Applicant	Bristol-Myers Squibb Company (BMS)
Priority Designation	P
Formulation	Capsule
Dosing Regimen	ATV 150 to 300mg Daily plus RTV 80-100mg Daily based on weight
Indication	Treatment of HIV-1 infection
Intended Population	Pediatric Patients Ages Six to Less than 18 years

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of Reyataz® (atazanavir, ATV) capsule for use in HIV-1 infected pediatric patients ages six years to less than 18 years.

The Applicant proposes ATV in combination with low dose ritonavir (RTV) for treatment-experienced subjects and treatment-naive patients younger than 13 years of age and ATV alone for treatment-naive patients 13 years and older. This application includes one dose ranging / pharmacokinetic, safety and viral activity trial (Pediatric AIDS Clinical Trials Group (PACTG) 1020A also known as AI424020) in treatment-experienced subjects and treatment-naive patients from 3 months to less than 18 years of age. This study evaluated the approved capsule formulation and [redacted] powder formulation. This NDA review focused on patients (6 to less than 18 years of age) receiving the capsule formulation. In this study, the ATV with RTV (groups 5-8) were started later than the ATV alone (groups 1-4) and therefore efficacy comparisons can be primarily made at the 24 week timepoint because an insufficient number of patients receiving ATV-RTV reached 48 weeks.

The Applicant submitted adequate data characterizing the pharmacokinetics of Reyataz Capsules in pediatric patients six to less than 18 years of age to establish dosing of ATV plus RTV based on weight. The data demonstrate comparable exposures (e.g., AUC) and antiviral activity (proportion with HIV RNA <50 c/mL and increases in CD4 cell counts) in pediatric patients compared to adult patients. The safety profile of ATV capsules with and without RTV was comparable to what is observed in adults. However, rash and vomiting occurred more frequently in pediatric patients compared to adults (14% versus 7% and 8% versus 3-4%, respectively).

Of note, in this capsule cohort 33 patients received ATV-RTV at or above the recommended dose for at least 24 weeks. This limited safety database only allows the identification of adverse reactions that occur at a frequency of 10% or more with 95% confidence. However, in this submission pharmacokinetic (PK), safety, and antiviral activity data were available for pediatric patients treated with the powder formulation of ATV. [redacted]. In the powder cohorts approximately 40 patients received ATV-RTV for approximately 24 weeks. Of these 40 ATV powder-RTV patients, 33 with equivalent ATV exposure to the pediatric study patients treated with ATV-RTV were selected to supplement the safety database. The safety profile of the additional 33 patients who were mainly three months to less than seven years of age were similar to the capsule patients and many of the differences between the two treatment groups could be explained by age related differences in adverse events. Together the capsule and powder treatment groups make up a larger safety database of 66 patients with 24 weeks of

therapy which is similar to fosamprenavir which had a total of 68 pediatric patients with two different formulations treated for at least 24 weeks.

Based on clinical and pharmacokinetic (PK) analysis and extrapolation of efficacy from adults (see Section 1.2), ATV taken concomitantly with RTV is the recommended regimen for all pediatric patients both antiretroviral treatment-naive and -experienced. For adolescent patients 13 years and older weighing at least 39kg, ATV alone is an option for those patients intolerant of RTV. For treatment-experienced patients weighing 15 to less than 25 kg., the ATV Cmin for this group was higher than observed at 400 mg ATV in adult patients but lower than observed at ATV/RTV 300/100 mg in adult patients. Therefore, dosing of treatment-experienced patients weighing less than 25 kg could not be supported. The data submitted supports a dose of ATV 200 to 300mg plus RTV 100mg based on weight for treatment-experienced patients 25kg and greater. The recommended dosing in labeling will result in doses that are generally lower than what many patients received in the clinical trial; but based on Clinical Pharmacology analysis, the PK parameters of the recommended dosing regimen will result in acceptable exposures.

1.2 Risk Benefit Analysis

Review of the safety data submitted in this supplement did not identify any new or unexpected toxicities for ATV in pediatric patients. As expected, approximately half of the pediatric patients treated with the capsule formulation had hyperbilirubinemia. Increases in mean PR interval were observed in patients receiving ATV and ATV –RTV but only 2% of patients had a Grade 2-4 asymptomatic atrioventricular (AV) block. The safety profile of ATV capsules with and without RTV was comparable to what is observed in adults. However, rash and vomiting occurred more frequently in pediatric patients compared to adults (14% versus 7% and 8% versus 3-4%, respectively). The activity results (proportion of patients with HIV RNA < 400 and < 50 copies/mL and increases in CD4 cell counts) were consistent with the findings in adults. Therefore, the observed toxicities did not outweigh the clear benefit of ATV/RTV as a treatment option for pediatric patients.

The extrapolation of efficacy for antiretroviral drugs like atazanavir are based on the presumption that the course of HIV disease and the effects of the drug are sufficiently similar in adults and pediatric patients (21 CFR 201.57 (f)(9)(iv), Sec. 505B 21 USC 355c)[1]. DAVP agrees that HIV disease in pediatric patients is similar but not identical to adult HIV disease (Domachowske, JB; Pediatric Human Immunodeficiency Virus Infection; October 1996; Clin. Microbiol. Rev. 9(4) 448-468), although the route of transmission may be different. Vertical transmission from mother to child is the predominant means of infection for children less than

[1] TITLE IV—PEDIATRIC RESEARCH EQUITY ACT OF 2007 ‘‘(B) SIMILAR COURSE OF DISEASE OR SIMILAR EFFECT OF DRUG OR BIOLOGICAL PRODUCT.— (i) IN GENERAL.—If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, the Secretary may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies. (ii) EXTRAPOLATION BETWEEN AGE GROUPS.—A study may not be needed in each pediatric age group if data from one age group can be extrapolated to another age group. (iii) INFORMATION ON EXTRAPOLATION.—A brief documentation of the scientific data supporting the conclusion under clauses (i) and (ii) shall be included in any pertinent reviews for the application under section 505 of this Act or section 351 of the Public Health Service Act (42 U.S.C. 262).

12 years of age in contrast to adolescent and adult patients in whom sexual contact or injection drug use are the primary modes of transmission. The pathophysiology of immune system destruction by HIV is similar in adult and pediatric patients. Consequently, infectious complications of pediatric HIV disease consist of both severe manifestations of common pediatric infections and also opportunistic infections like those seen in adults.

In pediatric patients and adults, treatment of HIV disease is monitored by the same two surrogate markers, CD4 count and HIV RNA load. Antiretroviral drugs including nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) have been shown to lower HIV RNA, improve CD4 count (or percentage) and improve general clinical outcome in all ages and treatment recommendations are very similar across all ages (see Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. February 28, 2008 1-134. Available at http://aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf. for a review of studies and references).

1.3 Recommendations for Risk Evaluation and Mitigation Strategies

Reyataz capsules have been marketed in the US since June 2003 with a patient package insert. No serious new post-marketing concerns have emerged. As such, no new risk management activity is required. However, review of post-marketing AERS reports revealed at least three cases of toxic skin eruptions related to ATV use. Therefore, this information was added to product labeling.

1.4 Recommendations on Post Marketing Activities/Phase 4 Commitments

The Applicant has three outstanding Phase-4 commitments:

Table 1: Outstanding Phase-4 Commitments

Date of Study Commitment	Description of Commitment	Status
June 20, 2003	4. Conduct a drug-drug interaction study to explore dosing recommendations for the coadministration of atazanavir and nevirapine and of atazanavir/ritonavir and nevirapine.	Submitted (part of pending submission)
	1. A pediatric study or studies under PREA for the treatment of HIV infection in pediatric patients ages greater than or equal to 3 months to 18 years to determine safe and appropriate dosing.	Delayed (partial response with the current submission)

In the current submission, the Applicant has requested a partial pediatric deferral of this requirement specific to pediatric patients who are three months or older to less than six years of age. A partial waiver of PREA requirements for pediatric patients younger than three months due to potential issue of neonatal and/or infant hyperbilirubinemia was previously granted.

The clinical review team recommends granting the partial deferral . From a preliminary review of the data from patients who received the powder formulation , the review team is concerned that the Applicant will not have the safety data for a minimum of 100 patients treated at or above the recommended ATV dose for 24 weeks. Therefore, the review team is recommending the following PREA requirement:

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.

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2 Introduction and Regulatory Background

2.1 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 6 years to less than 18 years of age
Dose and regimen: For treatment-naive patients 6 years to less than 18 years of age:

Weight Range	Recommended Dose
15 to <25kg	ATV/RTV 150/80mg given once daily
25 to <32kg	ATV/RTV 200/100mg given once daily
32 to <39kg	ATV/RTV 250/100mg given once daily
>39kg	ATV/RTV 300/100mg given once daily or ATV 400 mg given once daily for patients intolerant to RTV

For treatment-experienced patients 6 years to less than 18 years of age:

25 to <32kg	ATV/RTV 200/100mg given once daily
32 to <39kg	ATV/RTV 250/100mg given once daily
>39kg	ATV/RTV 300/100mg given once daily

Dosage forms: 100, 150, 200, and 300mg capsules

ATV also known as Reyataz® is an azapeptide HIV-1 protease inhibitor that selectively inhibits the virus-specific processing of viral Gag and Gag-Pol polyproteins in HIV-1 infected cells, thus preventing formation of mature infectious virions. The mechanism of action of ATV is similar to other PIs used in the treatment of HIV infection. ATV was developed by Bristol-Myers Squibb (BMS). Currently ATV 400 mg given orally once daily is indicated for the treatment of HIV infection in combination with other antiretroviral agents for treatment-naive patients. ATV/RTV 300/100 mg given orally once daily is indicated for the treatment of HIV infection in combination with other antiretroviral agents for treatment-experienced patients and for treatment-naive patients receiving concomitant tenofovir, efavirenz, or pH lowering medications. Traditional approval was granted in June 2003 on the basis of analyses of plasma HIV RNA levels and CD4 cell counts from controlled studies of 48 weeks duration or longer in antiretroviral-naive patients and a controlled study of 24 weeks duration in antiretroviral-treatment-experienced patients.

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently 20 antiretroviral drug products (see Table 2) 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: NRTIs, NNRTIs, PIs, fusion inhibitors, integrase inhibitor and entry inhibition via CCR5 co-receptor blockade.

Reviewer Comment: According to CDER regulations, the pediatric age group is defined as being 16 years and younger. In clinical practice, the upper limit of pediatric patients can vary from 18 to 21 years. For the purpose of this review, pediatric patients are defined as 18 years of age or younger.

Currently 9 NRTI's (including combination products) are approved and marketed in the US with pediatric labeling : lamivudine / zidovudine fixed dose combination (Combivir®), emtricitabine (Emtriva®), lamivudine (Epivir®), zalcitabine (Hivid®), zidovudine (Retrovir®), abacavir / zidovudine / lamivudine fixed dose combination (Trizivir®), stavudine (Zerit®) and abacavir (Ziagen®). The approved NNRTIs with pediatric labeling include delavirdine (Rescriptor®), efavirenz (Sustiva®) and nevirapine (Viramune®). The PI class with pediatric labeling is comprised of the following agents:

amprenavir (Agenerase®), saquinavir (Invirase®), lopinavir/ritonavir fixed dose combination (Kaletra®), fosamprenavir (Lexiva®), ritonavir (Norvir®) and nelfinavir (Viracept®). There are three additional classes of antiretrovirals currently with one approved agent each that are labeled for pediatric patients 16 years and older:

enfuvirtide (Fuzeon®), a GP41 fusion inhibitor
maraviroc (Selzentry®), a CCR5 co-receptor antagonist HIV entry inhibitor
raltegravir (Isentress®), a HIV integrase inhibitor

As part of atazanavir's pediatric development program, the Applicant was issued a pediatric written request in August 2001.

Table 2: Drugs Used in the Treatment of Pediatric HIV Infection < 18 years of Age

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)			
Brand Name	**Generic Name(s)**	**Manufacturer Name**	**Pediatric Use Labeling**
Combivir	lamivudine (LMV) and zidovudine (ZDV),	GlaxoSmithKline	≥12 years
Emtriva	emtricitabine, FTC	Gilead Sciences	0-3 months and above
Epivir	lamivudine, 3TC, LMV	GlaxoSmithKline	≥3 months
Hivid	zalcitabine, ddC, dideoxycytidine	Hoffmann-La Roche	≥13 years
Retrovir	zidovudine, ZDV, azidothymidine, AZT	GlaxoSmithKline	≥ 6 weeks
Trizivir	abacavir (ABC), zidovudine (ZDV), and lamivudine (LMV)	GlaxoSmithKline	Adolescents > 40kg
Videx	didanosine, ddI, dideoxyinosine	Bristol Myers-Squibb	≥ 2 weeks
Zerit	stavudine, d4T	Bristol Myers-Squibb	Birth-13 days and above
Ziagen	abacavir, ABC	GlaxoSmithKline	≥ 3 months
Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)			
Brand Name	**Generic Name**	**Manufacturer Name**	**Pediatric Use Labeling**
Rescriptor	delavirdine, DLV	Pfizer	≥ 16 years
Sustiva	efavirenz, EFV	Bristol Myers-Squibb	≥3 years
Viramune	nevirapine, NVP, BI-RG-587	Boehringer Ingelheim	≥ 2 months

Protease Inhibitors (PIs)			
Brand Name	**Generic Name(s)**	**Manufacturer Name**	**Pediatric Use Labeling**
Agenerase	amprenavir, APV	GlaxoSmithKline	≥ 4 years
Invirase	saquinavir mesylate, SQV	Hoffmann-La Roche	≥16 years
Kaletra	lopinavir and ritonavir, LPV/RTV	Abbott Laboratories	≥ 6 months
Lexiva	Fosamprenavir Calcium, FOS	GlaxoSmithKline	≥ 2 years
Norvir	ritonavir, ABT-538, RTV	Abbott Laboratories	>1 month
Viracept	nelfinavir mesylate, NFV	Agouron Pharmaceuticals	≥2 years
Fusion Inhibitors			
Brand Name	**Generic Name**	**Manufacturer Name**	**Pediatric Use Labeling**
Fuzeon	enfuvirtide, ENF, T-20	Hoffmann-La Roche & Trimeris	≥ 16 years
CCR5 Co-receptor Antagonist –HIV entry inhibitor			
Brand Name	**Generic Name(s)**	**Manufacturer Name**	**Pediatric Use Labeling**
Selzentry	maraviroc, MVC	Pfizer	≥ 16 years
HIV Integrase Inhibitor			
Brand Name	**Generic Name**	**Manufacturer Name**	**Pediatric Use Labeling**
Isentress	raltegravir, RAL	Merck and Co.	≥ 16 years

2.3 Availability of Proposed Active Ingredient in the United States

The IND for ATV was first submitted to FDA in September 1998. The initial NDA 21-567 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.

Table 3: Labeling Changes Since Marketing Approval:

Date	Supplement #	Labeling Change
03/2004	001	Prior approval supplemental NDA for studies that support coadministration of ATV-RTV and tenofovir (TDF)
07/2004	002	Efficacy supplement to add a new dosing regime of ATV-RTV 300/100mg
10/2004	004	Changes Being Effected (CBE) supplemental NDA for the Carcinogenesis, Mutagenesis, and Impairment of Fertility section of the label
07/2005	005	CBE supplemental NDA to provide new labeling text addressing drug-drug interactions between atazanavir (with or without ritonavir) and fluticasone and trazodone
01/2006	007	Prior approval supplement to provide *in vitro* inhibition data and clinical drug-drug interaction information regarding coadministration of ATV and/or ATV-RTV with proton pump inhibitors, H2 receptor antagonists, methadone, rifampin, enteric-coated didanosine and tenofovir
08/2006	008	CBE supplemental NDA with new labeling text for the ADVERSE REACTIONS section, which include updating post-marketing safety information
08/2006	011	CBE supplemental NDA with new labeling text for the CLINICAL PHARMACOLOGY: Microbiology section, as requested in FDA communication dated May 19, 2006
10/2006	009	Prior approval supplement for a new dosage form a new 300 mg Reyataz® (atazanavir sulfate) Capsule
03/2007	012	Prior approval supplemental NDA with revisions to the PRECAUTIONS section of the US package insert to include statements of cases of nephrolithiasis reported during post-marketing surveillance in HIV-infected patients receiving atazanavir therapy
12/2007	014	Prior approval supplemental NDA to provide clinical drug-drug interaction information regarding the administration of ATV and/or ATV-RTV with food, proton pump inhibitors, H2 receptor antagonists, acetaminophen, fluconazole, and in patients with renal impairment
02/2008	018	CBE supplemental NDA with updates to the WARNINGS (Drug Interactions with rosuvastatin and Cardiac Conduction Abnormalities), ADVERSE REACTIONS (Postmarketing Experience for cardiac and gallbladder events) and PATIENT INFORMATION (Possible side effects of REYATAZ, REYATAZ with other medicines and REYATAZ disposal statement)

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. Because of the known drug-drug interactions between RTV (and therefore ATV-RTV) and other drugs metabolized via the CYP3A4 isoenzyme, additional interaction studies may be warranted for ATV when given with RTV. Few interaction studies were conducted with ATV and RTV. The addition of RTV 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 was seen with ATV compared to NLV, LPV-RTV, and EFV, we postulated the addition of RTV may result in increases in lipids similar to other ARVs. 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

This supplement is a partial response to the ATV pediatric written request originally issued on 08/02/ 2001 and amended on 8/25/2003 and 12/04/2006 and the PREA commitment of 07/06/2004.

Timeline of Atazanavir Pediatric Capsule Supplement Pre-Submission Activity:

August 2, 2001 Original Pediatric Written Request (PWR) issued for multiple-dose pharmacokinetic, safety and activity study of atazanavir in combination with other antiretroviral agents in HIV-infected pediatric patients 3months to 16 years of age.

July 9, 2002 Applicant submits protocol (AI424020, PACTG 1020-A) to IND 56,897. Study to be conducted under IND 60,878 held by National Institute of Allergy and Infectious Diseases.

August 25, 2003 PWR timeframe extended to October 31, 2006

July 6, 2004 PREA Commitment in the approval letter for the ATV-RTV 300/100mg new dosage regime which waived the pediatric study requirement for patients younger than three months of age and deferred pediatric studies for patients three months of age to 18 years. PREA Commitment: A pediatric study or studies under PREA for the treatment of HIV infection in pediatric patients ages ≥ 3 months to 18 years to determine safe and appropriate dosing.

December 4, 2006 PWR amended to utilize the updated HIV PWR template for patients 3 months to 18 years of age.

Highlights of major changes:
1) Safety of atazanavir must be studied in an adequate number of pediatric patients to characterize adverse events across the age range. A minimum of 100 patients with at least 24 weeks of safety is required.

2) Minimum number of patients for PK studies were listed:
3 months to < 6 months: 6
6months to <2 years: 6
2 years to < 6 years: 12
6 years to < 12 years: 8
12 years to 18 years: 6

3) Safety and tolerability
HIV-infected pediatric patients should be followed for safety for a minimum of 24 weeks at the recommended dose. In addition, please also submit plans for long-term safety in HIV-infected pediatric patients who have received atazanavir.

Reviewer Comment: The Applicant submitted 24 week safety data for 33 patients who received the capsule formulation at the recommended dose for weight or higher of ATV-RTV. The safety evaluation was supplemented by an additional 33 patients who received [redacted] *powder formulation and ATV-RTV*

4) Resistance
Collect and submit information regarding the resistance profile (genotypic and phenotypic) of clinical isolates at baseline and during treatment from pediatric patients receiving atazanavir, particularly from those who experience loss of virologic response.

5)Extension of Time Frame:
PWR timeframe extended to December 15, 2008

March 28, 2007 Type B meeting/Teleconference to discuss the requirements of the capsule pediatric supplement. Also discussed was the need to enroll additional patients three to six months of age to meet the requirements of the atazanavir PWR. BMS notified the review team that it planned to submit a supplemental NDA for the capsule formulation in September of 2007.

[redacted]

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

NDA 21-567 S015 was submitted in electronic common technical document format on September 27, 2007. The initial submission did not include all of the pharmacokinetic datasets and an additional submission was sent on October 5, 2007 with the missing datasets. The submitted interim study report contained all the information collected for patients three months of age to 21 years of age who received either the capsule or powder formulations. The Applicant only briefly addressed and summarized the information for the labeling cohort which consisted of patients six to less than 18 years of age who received the capsule formulation. Additional data summaries for this labeling cohort were subsequently requested by the review team. The lack of a thorough focused summary (tables and descriptive narrative) required additional efforts by the review team to appropriately review the labeling supplement.

3.2 Compliance with Good Clinical Practices

The informed consent for the study was designed by the Division of AIDS PACTG for the submitted protocol PACTG 1020-A. This protocol adequately explained the risks of Study BMS-232632.

Two clinical site inspections were conducted by Division of Scientific Investigations (DSI) in Puerto Rico (site #5031) and in South Africa (site #8031). These sites were selected since they had the largest number of patients enrolled. The inspections of the Puerto Rico and South African sites revealed no significant problems that would adversely impact data acceptability. However, at the Puerto Rico site, DSI did look into the lack of adverse event intensity information in the Applicant's datasets which was identified by the review team. They found the grading of events by intensity was not required by the protocol. No data entry was done on site. Data entry was done by [redacted]
Also one irregularity was noted. Subject 500956 did not have the onset date of an event (respiratory) listed.

Please see DSI's clinical site review for additional details.

Reviewer Comment: The adverse event dataset was examined to look for other missing onset dates. We found many adverse event records did not include the onset date. This issue was discussed with the PACTG. Following discussions with BMS and PACTG, we better understood the construction of the adverse event dataset. The first time an adverse event was noted at a patient visit the onset date was coded. However on subsequent visits, if the event was ongoing no date was recorded. To understand the progression of an adverse event, all the reports (dataset records or line listings) for a single patient were sequentially arranged and to determine onset, continuation and resolution of each event.

DSI also investigated the handling and processing of pharmacokinetic and other analytical samples from three study sit [redacted] (Site 7301), [redacted] (Site 8051) and the [redacted] (Site 8052). The inspection also examined the ATV and RTV analyses conducted at [redacted]

DSI found that the accuracy of analyte concentrations in subject samples from some of [redacted] runs was not assured. Also some of [redacted] runs did not meet quality control acceptance criteria and DSI recommended these [redacted] runs should have been rejected.
Please see DSI's Bioanalytic Inspection Report for additional details.

Reviewer Comment: The Clinical Pharmacology reviewer reanalyzed the PK data excluding the identified [redacted] run and concluded the proposed dosing recommendations are not affected by the excluded data.

3.3 Financial Disclosures

At the March 28, 2007, Type B teleconference, the Applicant asked for clarification on their requirement to file form 3454 and/or 3455 since the PACTG which conducted the study did not collect financial disclosure forms under 21 CFR Part 54 of the appropriate personnel at each participating site. At that time, the Applicant inquired about the possibility of a waiver of the financial disclosure requirement. The Applicant was informed a waiver could not be granted. They were also informed that the submission should not be delayed for obtaining the financial disclosures. In the current submission, the Applicant files a form 3454 with a table of all the investigators and sub-investigators. More than half of the investigators were listed as having no disclosable information. For approximately 100 subinvestigators, we do not know if these investigators had disclosable income. The Applicant stated the following in regard to the missing financial information:
"The financial disclosures for these investigators have been submitted and exist in the database, however, information on if the investigator had disclosable income is currently unknown. The disclosable information is not available at this time as the IMPAACT financial database upgrade is in progress. However, IMPAACT -SOP No NET 1003-01 is in place to review any disclosed conflict of interest and determine necessary steps if a conflict is confirmed."

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

For this submission, the previously approved capsule formulation was used and there were no new Chemistry Manufacturing and Controls issues.

4.2 Clinical Microbiology

The clinical microbiology team reviewed this submission. Limited resistance data was submitted. The available resistance data appears consistent with the adult experience regarding development of resistance is patients who experience virologic failure and the impact of baseline resistance and outcome. The microbiology team recommended minor changes to update the USPI Microbiology Section and for consistency with other recently approved ARV labels. The team did not recommend adding any new resistance information to the label.

Please see Dr. Lisa Naeger's Clinical Microbiology Review for additional information.

4.3 Preclinical Pharmacology/Toxicology

No new chemistry and manufacturing data, pharmacotoxiciology data or pharmacokinetic data were submitted with this sNDA. Please refer to the reviews of the original NDA and prior supplements for background.

4.4 Clinical Pharmacology

Summary of Clinical Pharmacology's Findings

This submission was submitted to establish pediatric dosing for the capsule formulation in pediatric patients six to less than 18 years of age. The primary major objectives for the Applicant's study were:

- To determine the PK profile and dosing schedule of the capsule formulation for atazanavir ATV and ATV-RTV in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) in human immunodeficiency virus (HIV)-infected in pediatric subjects
- To determine the PK profile and dosing schedule for the powder formulation of ATV and ATV-RTV in combination with two NRTIs in HIV-infected in pediatric subjects
- To determine the safety and tolerability of ATV and ATV-RTV in combination with two NRTIs in HIV-infected in pediatric subjects

Please see the Clinical Pharmacology Review by Dr. Jenny Zheng for additional details. This submission used an aggressive dose finding algorithm described below to assure most pediatric patients receive exposures comparable to adults. This dose finding study resulted in many patients receiving doses per body surface area (BSA) higher than the recommended adult dose. One of the concerns the review team had was some of the pediatric patients receiving comparable dosing to adults may have an elevated Cmax which could result in additional toxicity.

The Clinical Pharmacology team analyzed the PK data from the Applicant's submission and compared the exposures in children with the exposures observed in adults receiving either 400mg ATV alone or ATV-RTV 300/100 mg. In their analysis of ATV-RTV treatment PK results, the Clinical Pharmacology review team evaluated the exposures obtained to ensure the recommended dosing regime would provide treatment-naive pediatric patients with exposures between the PK values obtained for adults treated with ATV alone and those treated with ATV-RTV. For ATV-RTV dosing of treatment-experienced pediatric patients, the PK criteria was to ensure most patients attain an exposure that approximated or exceeded that with ATV-RTV 300/100mg in adults. The other criteria Clinical Pharmacology used in establishing a pediatric dose was to avoid exceeding the adult doses of 400mg ATV alone and ATV-RTV 300/100mg unless necessary to obtain minimum exposures due to increased clearance in pediatric patients. The Clinical Pharmacology team did not find any evidence of increased clearance in pediatric patients; therefore, doses exceeding the recommended adult doses were not necessary. Based on the results from the Applicant's submission, the Clinical Pharmacology team could not support dosing recommendations for treatment-experienced pediatric patients weighing less than 25kg. For treatment-experienced pediatric patients weighing more than 25kg, the Applicant's recommended dosing of ATV-RTV (up to an adult maximum of 300/100mg) was acceptable. For treatment-naive patients, the clinical pharmacology team was more comfortable with using the Applicant's recommended weight band dosing for patients weighing at least 15kg.

For treatment-naive adolescent pediatric patients 13years old and weighing at least 39kg, the preferred dosing regimen is ATV-RTV 300/100 mg. However, the review team concluded 400mg ATV alone is an option for adolescent treatment-naive patients 13 years and older weighing at least 39kg who were intolerant of RTV.

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

Atazanavir has been shown to prolong the PR interval of the 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 (see Section 7.4.5 for pediatric cardiac safety findings). In these healthy volunteers, the observed prolongation of PR interval has been found to be concentration- and dose-dependent. Drug-drug interactions studies with atazanavir have been done to examine the effects on PR interval. Atazanavir in combination with diltiazem increased diltiazem plasma concentration by 2-fold with an additive effect on the PR interval. In a pharmacokinetic study between atazanavir 400 mg once daily and atenolol 50 mg once daily, no clinically significant additive effect of atazanavir and atenolol on the PR interval was observed. Dose adjustment of atenolol is not required when used in combination with atazanavir. Pharmacokinetic studies between atazanavir and other drugs that prolong the PR interval including beta blockers [other than atenolol], verapamil, and digoxin have not been performed. An additive effect of atazanavir and these drugs cannot be excluded; therefore, caution should be exercised when atazanavir is given concurrently with these drugs, especially those that are metabolized by CYP3A (e.g., verapamil). Please refer to section 7.4.5 for the PR interval and cardiac-related adverse event evaluation.

4.4.3 Pharmacokinetics

The PACTG used an intensive dose finding algorithm to ensure most patients received a dose comparable to the adult exposure. This was first done with ATV alone (Groups 1-4) and then for ATV with RTV boosting (Groups 5-8) for both the powder formulation (only PK and safety reviewed for this submission) and the capsule formulation (see Table 4). Given the central importance of the dose finding study to this submission, an overview of the dose ranging study will be presented in this section. Additional details regarding the pharmacokinetic evaluation will be discussed in Dr. Zheng's Clinical Pharmacology review.

Methodology: The PACTG conducted a multicenter, open-label study conducted in the US and South Africa to determine the safety, PK and optimal dose of ATV powder and capsules, administered with or without RTV, in pediatric subjects aged 91 days to 21 years infected with HIV. Eligible subjects were assigned to treatment groups, stratified by age, ATV formulation, concomitant administration of RTV:

Table 4: Definition of Treatment Groups

Stratification and Regimens Used

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

Five subjects were to be enrolled in each group to receive the starting dose of ATV in the appropriate formulation and with or without RTV. If prospectively defined dose acceptance criteria, based upon intensive PK assessments made at Week 1 and safety data collected through Week 4, were not met, the ATV starting dose was either decreased or increased in the same

group of 5 subjects (see (Figures 1 and 2). If dose acceptance criteria were met, an additional 5 subjects were enrolled at the same dose and the regimen evaluated once more with 10 total subjects. If still satisfying the dose acceptance criteria after 10 subjects, the group fully enrolled at that dosing cohort and treatment in Step 1 continued until 96 weeks after the last subject was enrolled in the respective study part (Part A: ATV alone; Part B: ATV with RTV).

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

Figure 1

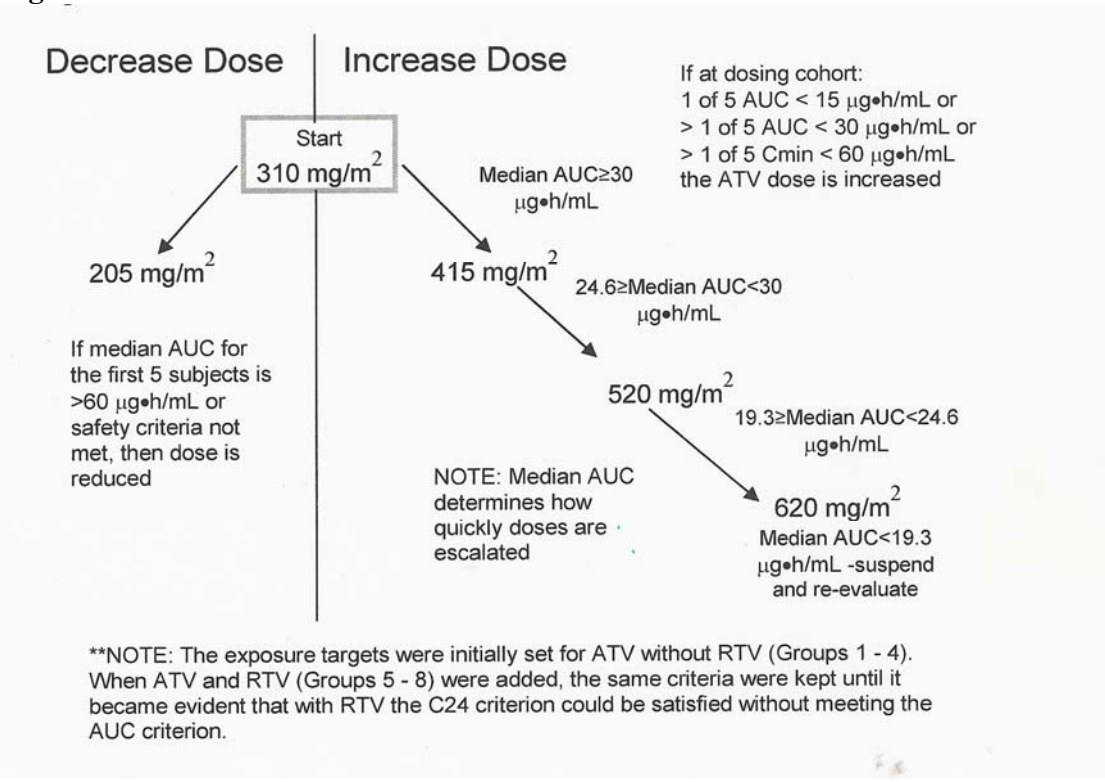
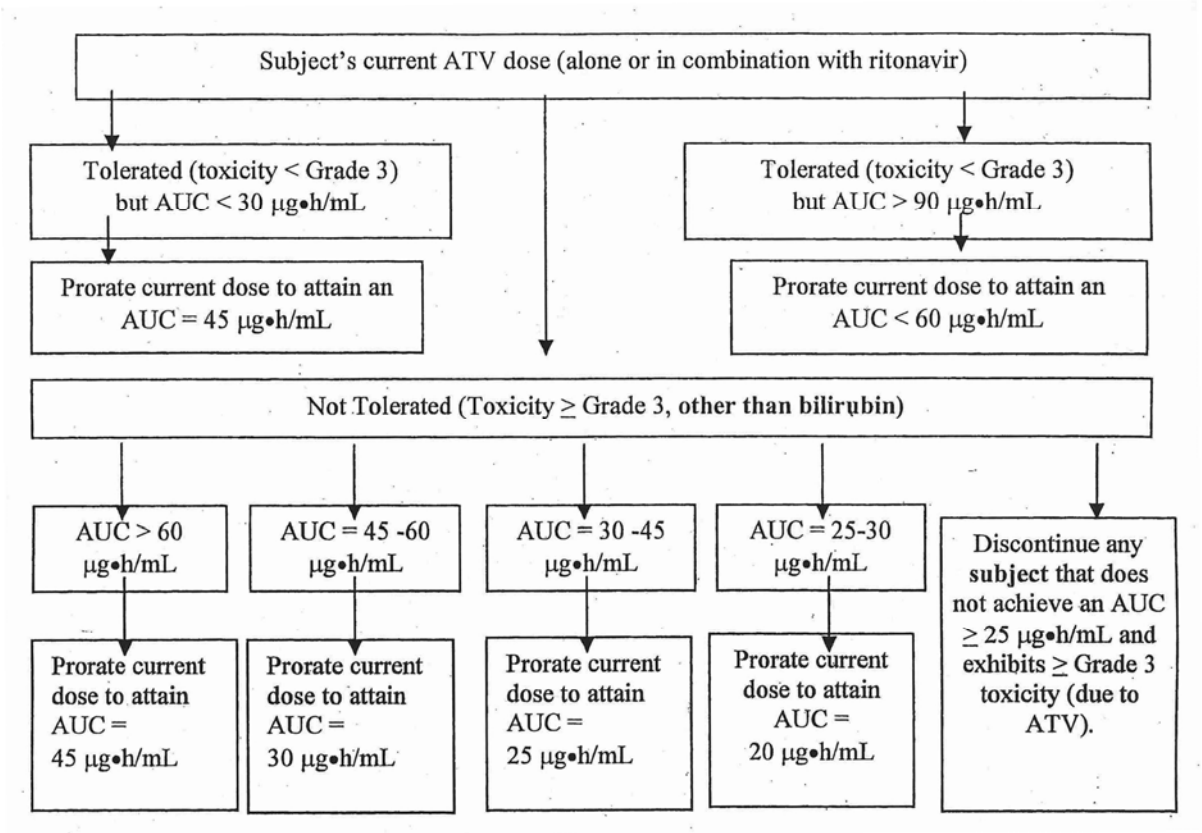


Figure 2



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

Pharmacokinetic Results:
Based on the PACTG's dose ranging study, the Applicant proposed the following dosing recommendations for use in pediatric patients six years to less than 18 years of age receiving the capsule formulation:

Applicant's Original Dosing Recommendation:

- Therapy-naive and therapy-experienced patients from 15 kg to less than 20 kg: REYATAZ 8.5 mg/kg with ritonavir 4 mg/kg once daily taken with food (see *Table 1*).

- Therapy-naive (less than 13 years or 20 kg to less than 39 kg) and therapy-experienced patients (at least 20 kg): REYATAZ 7 mg/kg with ritonavir 4 mg/kg once daily taken with food not to exceed the recommended adult dose of REYATAZ 300 mg and ritonavir 100 mg (see *Table 5*).

- Therapy-naive patients at least 13 years of age and at least 39 kg may use REYATAZ 400 mg without ritonavir once daily taken with food.

Recommended dosages for REYATAZ in combination with ritonavir based on weight as described above are shown in the Table below.

Pediatric Dose (6 to less than 18 years of age) for REYATAZ Capsules with ritonavir

Body Weight[a]		REYATAZ dose	ritonavir dose
(kg)	(lbs)	(mg)[b]	(mg)
15 to less than 20	33 to less than 44	150	64[c]
20 to less than 25	44 to less than 55	150	80[c]
32 to less than 39	70 to less than 86	250	100[d]
at least 39	at least 86	300	100[d]

[a] There are no data in pediatric patients at least 6 years of age and less than 15 kg.

[b] Doses of REYATAZ can be achieved using a combination of commercially available capsule strengths.

[c] Ritonavir liquid.

[d] Ritonavir capsule or liquid.

Review Team Findings (see Dr. Zheng's Clinical Pharmacology Review for more details): The Clinical Pharmacology Team's pharmacokinetic analysis was discussed with the review team. Overall, the review team agreed with the Applicant's dosing recommendations with the following exceptions:

1. ATV-RTV is the recommended regimen for all pediatric patients both treatment-naive and experienced.
2. For adolescent patients 13 years and older weighing at least 39 kg, ATV alone is an option only for those patients intolerant of RTV.

3. For antiretroviral experienced patients weighing 15 to less than 25 kg., the ATV Cmin for this group was higher than observed at 400 mg ATV in adult patients but lower than observed at 300mg ATV/100 mg RTV in adult patients. Therefore, dosing of antiretroviral experienced patient weighing less than 25 kg is not supported.

4. Simplification of the ritonavir dosing for treatment-naive patients weighing 15 to less than 25kg to 80mg for all patients in this weight range.

The intensive dose finding in the study resulted in many patients during the trial exceeding the recommended dose per weight and the review team had concerns about the degree of patient exposure at the recommended dose. Based on the analysis of the four ATV-RTV dosing cohorts: treatment-naive ages six to less than 13 years, treatment-experienced ages six to less than 13 years, treatment-naive ages 13 to less than 18 years, treatment-experienced ages13 to less than 18 years, [see Tables 6-11 below], the review team determined a total of 40 patients received the recommended dose per weight or higher. Of these 40 patients, only 33 patients received ATV-RTV for approximately 24 weeks. Note two of the 33 patients received ATV-RTV for 23.1 weeks of therapy when the datalock occurred on 02/28/2007 (see Table 11). Of the seven patients treated with ATV-RTV for less than 24 weeks, six patients discontinued from therapy prior to 24 weeks and one patient was on therapy for 11 weeks at the time of the datalock.

To supplement the safety data from the capsule cohort, the review team examined the PK and safety data from the patients receiving powder ATV-RTV (Treatment Groups 5 and 6). Forty patients primarily ages three months to six years of age from treatment groups 5 and 6 were on therapy for approximately 24 weeks or greater. Thirty-three patients had an equivalent exposure to adolescent patients receiving ATV capsule-RTV (Group 8). The exposure limit was obtained by taking a 90% confidence interval for the AUC_{tau} and the C_{min} values for Group 8. To be considered an equivalent exposure, the ATV powder-RTV patients must have both a minimum AUC_{tau} of 25.9 μg*h/mL and a minimum C_{min} of 409 ng/mL (see Table 12). Using the ATV-RTV capsule and powder data, the safety database is increased to 66 patients who received ATV-RTV for approximately 24 weeks or greater. The comparison of the capsule and the powder ATV-RTV safety cohorts is discussed in Section 7.

The review team also examined the exposure of treatment-naive adolescent (13 to less than 18 years) patients who weighed 39kg or more to dose of 400mg or higher of ATV. The dose of 400mg ATV alone is recommended for treatment-naive ritonavir intolerant adolescent patients 13 years and older who are at least 39kg. A total of eight patients received doses of ATV alone that were 600mg or greater (see Table 5).

Tables 5-9 Pharmacokinetic Data for Group4: Naive Patients and Groups 7 & 8: Naive and Experienced

Table 5

Doses Received Group 4 (13 to < 18 years) ATV Naive >39 Kilograms

Patient #	PID	DOSE	DOSE_BSA
1	370221	1000	630
2	670618	800	480
3	710217	800	460
		600	320
5	800015	1000	640
6	800016	1000	590
7	800304	700	500
8	800318	1000	620

Median Dose 900 mg
Median Dose_BSA 545 mg/M^2

Note: 400mg dose is equivalent to 310 mg/M^2
but PK parameters for adult 400mg dose
is between 310 and 520 mg/M^2

Table 6

Doses Received Group 7 (6 to < 13 years) ATV-RTV Naïve

Patient #	PID	WEIGHT	DOSE	DOSE_BSA (rounded to nearest 10)	Ritonavir Dose (mg)
1	800280	17.4	150	210	100
		19.3	150	200	100
		22.3	150	180	100
2	801001	17.5	150	210	100
3	800316	17.6	150	210	100
4	800323	21.2	150	180	100
		21.6	150	180	100
5	800328	21.1	150	180	100
		22.8	250	290	100
6	800041	21.3	150	180	100
7	800285	21.5	150	190	100
		22.1	250	300	100
		22.5	400	480	100
		25.9	400	430	100
8	800272	25.7	200	210	100
9	800313	26.4	200	200	100
10	450398	28.8	200	190	100
		33.1	200	180	100
		35	200	170	100
11	374204	32.7	200	170	100
		33.9	250	220	100
12	800319	33	250	230	100
13	460642	52.5	300	210	100

Median Dose_BSA was 200mg/M^2

Note: 300mg ATV (+100mg RTV) dose is equivalent to 205 mg/M^2
and the adult PK parameters for this dose overlap the pediatric values

Table 7

Doses Received Group 7 (6 to < 13 years) ATV-RTV Experienced

Patient #	PID	WEIGHT	DOSE	Dose_BSA rounded to nearest 10	Ritonavir Dose (mg)
1	506046	27.8	300	300	100
		29.1	100	100	100
2	450366	29.8	300	280	100
		32.7	300	260	100
3	440162	30.9	200	190	100
		32.1	200	180	100
4	670176	32.7	200	190	100
		33.1	200	190	100
		33.6	250	230	100
5	509480	33.4	250	220	100
		39	150	120	100
6	650606	33.8	250	220	100
		36.7	250	210	100
7	400535	34.3	250	220	100
		46.2	250	180	100
		48.4	400	280	100
8	506990	35.3	400	350	100
9	360822	50.1	200	140	100
		50.2	300	210	100
10	290170	54.1	400	270	100
		58.3	500	320	100
		60.5	300	190	100
11	400193	55	500	330	100
		57.7	500	320	100
12	460404	64.2	500	310	100
		70.3	500	290	100
		70.9	300	180	100
13	690595	72.9	400	220	100

Median Dose_BSA: 220mg/M^2

Note: 300mg ATV (+100mg RTV) dose is equivalent to 205 mg/M^2
and the adult PK parameters for this dose overlap the pediatric values

Table 8: Doses Received Group 8 (13 to < 18 years) ATV-RTV Naïve

Patient #	PID	WEIGHT	DOSE	Dose_BSA rounded to nearest 10	Ritonavir Dose (mg)
1	140367	90.7	400	190	100
2	506510	91.9	400	190	100
		92.7	200	100	100
3	401129	94.5	400	190	100
4	470282	118.6	500	220	100
		121.9	500	220	100

Median Dose_BSA 190 mg/M^2

Note: 300mg ATV (+100mg RTV) dose is equivalent to 205 mg/M^2
and the adult PK parameters for this dose overlap the pediatric values

Table 9

Doses Received Group 8 (13 to < 18 years) ATV-RTV Experienced

Patient #	PID	WEIGHT	DOSE	Dose_BSA rounded to nearest 10	Ritonavir Dose (mg)
1	660229	37.5	250	200	100
2	500956	48.2	400	280	100
		58.2	400	250	100
3	509951	50.5	200	130	100
		52.4	300	190	100
4	800028	55.8	300	190	100
5	410179	55.8	300	200	100
		57.9	400	260	100
6	470090	62.9	500	300	100
7	470289	82.7	400	210	100
8	470009	74.1	600	310	100
		75.4	600	310	100
9	500016	82	400	210	100
		82	600	310	100
		83.3	300	150	100
		83.5	600	320	100
10	440045	89.6	400	190	100
		90.5	200	90	100
		92.3	200	90	100

Median Dose_BSA 210 mg/M^2

Note: 300mg ATV (+100mg RTV) dose is equivalent to 205 mg/M^2
and the adult PK parameters for this dose overlap the pediatric values

Table 10: ATV-RTV Patients that Received at Least One Dose At or Above Recommended Dose for Weight

	At least one dose at the recommended dose for weight	Above (no doses were at the one recommended for weight)	TOTAL	Comment
Group 7 naïve	13	0	13	
Group 7 experienced	8	5	13	One patient in the safety dataset was not included in the PK dataset (see note below)
Group 8 naïve	0	4	4	One patient had doses above and below that recommended for weight
Group 8 experienced	5	5	10	One patient had doses above and below that recommended for weight
TOTAL	26	14	40	The ATV-RTV subset in the baseline dataset included 41 patients

Note: PID 850034 NOT INCLUDED IN PK DATASET-started study one month prior to datalock. [Age 12.3 Weight 41kg Group 7 (experienced) ATV 205mg/M^2] Patient had AEs recorded

Table 11:

ATV-RTV Patients Receiving Doses at or Above the Recommended Dose for Weight Broken Down by Weight Groups						
	Patients 6 to less than 13 years of age					
Weight Group	Treatment-Naive Patients (#)		Treatment Experienced Patients		TOTAL (#)	
	number on therapy <24 wks	number on therapy ≥24 wks	number on therapy <24 wks	number on therapy ≥24 wks	number on therapy <24 wks	number on therapy ≥24 wks
15 - < 25kg	1*	6	0	0	1*	6
25 – < 32 kg	0	3	0	3	0	6
32 - < 39kg	0	2	1	4	1	6
> 39 kg	0	1	3	2	3	3
SUBTOTAL	1*	12	4	9	5	21
	~~Patients 6 to less than 13 years of age~~ Patients 13 to less than 18 years of age[#]					
32 - < 39kg	0	0	0	1	0	1
> 39 kg	0	4	2	7	2	11
SUBTOTAL	0	4	2	8	2	12
TOTAL	1*	16	6	17	7	33

* One patient was on therapy for 11 weeks when datalock (2/28/2007) occurred.

[#] Revision to table from original review. Table sub-heading was mis-labeled as "Patients 6 to less than 13 years of age".

Table 12: Safety Cohort of Pediatric Patients 3 Months to 13 Years of Age Treated with Powder ATV (310mg/m^2) Plus RTV with Cmin and AUC Values Equivalent to Capsule Patients Treated with Appropriate Dosing of ATV-RTV

PID	Age Group	Cmin (ng/mL)	AUCTAU (ug *h/mL)	weeks on therapy (Last dose - first dose)	therapy to database lock (Datalock-start date)
360801	Group 6:: 2 -13 years of age	1134	52.2	33	154.9
400805	Group 6:: 2 -13 years of age	1280	56.0	on therapy at datalock	89.3
401059	Group 6:: 2 -13 years of age	478	52.0	on therapy at datalock	94.7
450397	Group 5:: 3 months - 2 years of age	1436	89.0	on therapy at datalock	138.3
450453	Group 5:: 3 months - 2 years of age	560	79.4	on therapy at datalock	158.3
460965	Group 6:: 2 -13 years of age	956	50.3	on therapy at datalock	155
461086	Group 6:: 2 -13 years of age	521	40.6	on therapy at datalock	149
461183	Group 6:: 2 -13 years of age	521	53.6	on therapy at datalock	51.1
660252	Group 6:: 2 -13 years of age	1510	101.7	on therapy at datalock	99
670456	Group 6:: 2 -13 years of age	940	51.2	on therapy at datalock	140.3
670483	Group 6:: 2 -13 years of age	1143	77.0	on therapy at datalock	36
670634	Group 5:: 3 months - 2 years of age	701	49.2	on therapy at datalock	162.1
690414	Group 6:: 2 -13 years of age	1760	68.3	on therapy at datalock	137.3
690606	Group 6:: 2 -13 years of age	1256	60.1	on therapy at datalock	156.1
690745	Group 5:: 3 months - 2 years of age	929	89.5	on therapy at datalock	166.3
690790	Group 5:: 3 months - 2 years of age	787	53.3	on therapy at datalock	55.1
720222	Group 6:: 2 -13 years of age	2131	67.6	on therapy at datalock	158
800003	Group 6:: 2 -13 years of age	787	33.4	on therapy at datalock	104.3
800023	Group 5:: 3 months - 2 years of age	530	56.0	on therapy at datalock	105.3
800034	Group 6:: 2 -13 years of age	561	41.1	on therapy at datalock	30.3
800036	Group 6:: 2 -13 years of age	1875	83.6	on therapy at datalock	28.3

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

One clinical study AI424020 (or PACTG 1020-A - IND 56,987) conducted under IND 60,878 was submitted for review.

5.2 Review Strategy

The clinical review is based on the evaluation of NDA 21-567 S015 which includes study reports for AI424020. This review predominately focused on the subset of pediatric patients six to less than 18 years of age and received the capsule formulation. Safety data from patients receiving the powder formulation of ATV with RTV was also evaluated. The safety and efficacy analyses conducted by BMS were confirmed by independent FDA analyses of the data. Dr. Hammerstrom (Biometrics reviewer) performed the efficacy analyses for the HIV RNA and CD4 endpoints. For this review the study design, patient demographics, adverse events, laboratory data, efficacy and virology results were reviewed in detail. JMP Statistical Discovery software was used to evaluate the efficacy and safety data. Minor differences in the efficacy, rates of AEs and laboratory abnormalities were noted between the reviewer's analyses and those presented by BMS. The differences had no impact on the overall conclusions.

Overview of Materials Consulted in Review: The efficacy and safety data from study AI424020 were submitted electronically following the common technical document format. Narratives for all serious adverse events (SAEs), deaths, and premature discontinuations were provided in the interim study report as a pdf file.

5.3 Discussion of Individual Studies

Study AI424020:
Phase 1/2, Open-label, Pharmacokinetic and Safety Study of a Novel Protease Inhibitor (BMS-232632, Atazanavir, ATV, Reyataz™) in Combination Regimens in Antiretroviral Therapy (ART)-Naïve and Experienced HIV-infected Infants, Children and Adolescents

STUDY PERIOD: Study Initiation Date: 16-Nov-2000
Study Completion Date: Ongoing
Database lock for this Report: 28-Feb-2007

CLINICAL PHASE: 1/2

OBJECTIVES:

Primary Objectives:

- To determine the pharmacokinetic (PK) profile and dosing schedule of the capsule formulation for atazanavir (ATV) and atazanavir/ritonavir (ATV/RTV) in combination with two nucleoside reverse
- transcriptase inhibitors (NRTIs) in human immunodeficiency virus (HIV)-infected in pediatric subjects
- To determine the PK profile and dosing schedule for the powder formulation of ATV and ATV/RTV in combination with two NRTIs in HIV-infected in pediatric subjects
- To determine the safety and tolerability of ATV and ATV/RTV in combination with two NRTIs in HIV-infected in pediatric subjects

Secondary Objectives:

- To assess the antiretroviral activity of ATV and ATV/RTV containing regimens as measured by viral load response when given to protease inhibitor (PI) treatment-experienced and naive study subjects
- To assess the development of virologic resistance as measured by genotypic and phenotypic assays during treatment with ATV and ATV/RTV

METHODOLOGY: This was a multicenter, open-label study conducted in the US and South Africa to determine the safety, PK and optimal dose of ATV powder and capsules, administered with or without RTV, in pediatric subjects aged 91 days to 21 years infected with HIV. Eligible subjects were assigned to treatment groups, stratified by age, ATV formulation, concomitant administration of RTV:

NUMBER OF SUBJECTS (Planned and Analyzed): Of the 183 enrolled patients, 182 patients (99%) were treated (powder and capsule formulations): 85 with ATV alone and 97 with ATV/RTV. Of the 182 enrolled patients, 104 patients received the capsule formulation: 63 with ATV alone and 41 with ATV/RTV. The patients were enrolled in the following treatment groups 1-8 (see Table 13 below). Groups 1-2 (powder formulation) were closed to accrual early because the patients in these Groups could not meet the required PK parameters for continued dosing.

Table 13

Table 3.1: Stratification and Regimens Used

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

ATV - atazanavir, RTV - ritonavir

The protocol considered Adolescents as > 13 yrs to 21 yrs; subgroup tables for this report used the following categories: Adolescents >13 yrs to ≤ 18 yrs and Adults >18 yrs.

Source: Protocol in Appendix 1.1

APPLICANT'S PRIMARY ASSESSMENT CONDUCTED AT WEEK 24.

CRITERIA FOR EVALUATION:

PK: The primary PK parameters were AUC(TAU) (referred as AUC 0-24 in the protocol), and Cmin(trough concentration), Clearance (CL/F), elimination half-life (T-half), peak concentration (Cmax), and time to peak concentration (Tmax) were secondary PK parameters.

Safety: Safety endpoints include the frequency of adverse events (AEs), serious adverse events (SAEs), deaths, discontinuation due to AEs, laboratory abnormalities, and electrocardiograms. The percentages for deaths and SAEs were calculated using all enrolled subjects; the percentages in all other safety tables used all treated subjects. SAEs were required to be reported based on the PACTG 1020-A protocol definition that follows reporting requirements as defined in the current U.S Division of AIDS Serious Adverse Experience Reporting Manual. All Grade 3 and 4 laboratory abnormalities suspected to be an adverse drug reaction were mandated to be reported as an SAE.

Efficacy: The efficacy focuses on results for the efficacy cohort who started study therapy no later than 31-Aug-2006; these subjects would have had the opportunity to reach the Week 24 visit by the time of the 28-Feb-2007 database lock. Subjects who started study therapy by 31-Aug-2006 and discontinued before Week 24 were included in the efficacy cohort. Efficacy parameters included the following:

- Virologic response: virologic one log suppression (VOLS), Virologic response (VR) and virologic response - observed cases (VR-OC), and time to loss of virologic response (TLOVR)
- Virologic suppression: HIV RNA change from baseline • Immunologic response: CD4 and CD8 absolute counts and percents

The protocol was initially developed to evaluate ATV without RTV (Step 1, Part A), because at this time, ATV was still an investigational drug in adults and ritonavir (RTV) use for pharmacologic enhancement of ATV exposures was not yet characterized. The study was later modified to include regimens of ATV with low-dose RTV in separate groups of subjects (Step 1, Part B). The confirmed dose of ATV or ATV given in combination with RTV for each dosing cohort was selected in this study based on prospectively defined safety and PK criteria.

After confirmation of the dose, subjects were treated with ATV or ATV/RTV for up to 96 weeks after the last subject was enrolled to evaluate the long-term safety and efficacy. Subjects enrolled at sites in South Africa were eligible to continue treatment beyond this time (Step 2) until ATV [redacted] capsules are approved and available in this country. As of 28-Feb-2007, no subject enrolled at a site in South Africa had completed 96 weeks of therapy and entered Step 2; therefore the Applicant did not include information on Step 2 in the interim study report.

The demographics for patients six to less than 18 years of age who received the capsule are listed below (see Tables 14-16). Enrollment was balanced between males and females and the majority of the patients were from in North America. More then half of the ATV and ATV-RTV patients were antiretroviral treatment experienced.

Table 14: Demographics for Capsule Patients Ages 6 to Less Than 18 years

		ATV	ATV-RTV	TOTAL
		(N=63)	(N=41)	(N=104)
Age (Years)				
MEAN (SE)		11.93 (0.43)	11.70 (0.55)	11.84 (0.34)
MEDIAN		13.07	11.06	11.76
MIN, MAX		6.29, 17.62	6.36, 17.69	6.29, 17.69
Gender: N (%)				
FEMALE		33 (52)	21 (51)	54 (52)
MALE		30 (48)	20 (49%)	50 (48)
Race Group: N (%)				
BLACK/MIXED		37 (59)	28 (68)	65 (62)
OTHER		15 (23)	5 (12)	20 (19)
WHITE		11 (17)	8 (20)	19 (18)
ASIAN		0	0	0
Region: N (%)				
NORTH AMERICA		42 (67)	30 (73)	72 (69)
AFRICA		21 (33)	11 (27)	32 (31)

Table 15: ARV Experience of Patients 6 to less than 18 years Receiving Capsule Formulation

	ATV (n=63)	**ATV-RTV (n=41)**	**TOTAL (n=104)**
ARV naïve	27 (43%)	17 (41%)	44 (42%)
ARV experienced	36 (57%)	24 (59%)	60 (58%)

Table 16

ARV Experience Per Treatment Group

Treatment Group	Ages	Treatment	ARV Naïve	ARV Experienced	Total Number of Patients
3	6 to less than13 years	ATV	12	19	31
4	13 to less than 18 years	ATV	15	17	32
7	6 to less than13 years	ATV-RTV	13	14	27
8	13 to less than 18 years	ATV-RTV	4	10	14

6 Review of Efficacy

6.1 Efficacy Summary

For efficacy analyses FDA uses the intent to treat (ITT) population. The analyses conducted were the proportion of patients achieving HIV RNA < 400 and < 50 copies/mL at Week 24. Additionally, the proportion of patients achieving HIV RNA < 400 and < 50 copies/mL using the time to loss of virologic response (TLOVR) algorithm was also evaluated. This analysis is consistent with guidance for industry and is used for traditional approval for trials with 48 weeks or longer. The TLOVR analysis is also calculated through 24 weeks; however, some patients may not have had adequate time to achieve HIV RNA < 50 (or < 400) copies/mL and calculation may not be optimal for shorter term data. Both analyses are presented below. The label contains the proportion of patients achieving HIV RNA < 400 and < 50 copies/mL at Week 24. This analysis is included in other ARVs labels for studies with 24 week results.

For the ITT analysis, an efficacy cohort of 99 patients was used. In this efficacy cohort, the overall proportions of antiretroviral-naive and -experienced patients with HIV RNA <400 copies/mL at week 24 were 68% (28/41) and 33% (19/58), respectively. The overall proportions of antiretroviral-naive and -experienced patients with HIV RNA <50 copies/mL at week 24 were 59% (24/41) and 24% (14/58), respectively. These results are comparable to the HIV RNA results for treatment-naive adults treated with ATV alone and for treatment-experienced treated with ATV-RTV. Tables 20-21 describe the TOLVR results for HIV RNA < 400 and < 50 copies/mL in treatment-naïve and treatment-experienced patients.

CD4 cell counts were obtained at 20 and 32 weeks of therapy. . The median increase from baseline in absolute CD4 count at 20 weeks of therapy was 171 cells/mm^3 in antiretroviral-naive patients and 116 cells/mm^3 in antiretroviral-experienced patients (see Table 22). Overall the efficacy results seen in pediatric patients were similar to the results in adults

6.2 Indication

Reyataz (atazanavir sulfate) is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. The Applicant is proposing to extend this indication to pediatric patients six to less than 18 years of age for the capsule formulation.

6.2.1 Methods

Efficacy was analyzed using the Applicant's HIV RNA and CD4 result datasets. Discontinuations were followed by the Applicant's STAT (status) dataset and by the efficacy flags in the HIV and CD4 datasets. The efficacy analyses were based on the ITT population and included the proportion of patients achieving HIV RNA < 400 and < 50 copies/mL at week 24. The analysis was also conducted using the TLOVR algorithm. The CD4 cell count analyses were based on the as treated population and included those patients completing at 20 weeks of treatment.

6.2.2 Demographics (related to efficacy)

For both the ATV and ATV-RTV treatment groups, the treatment-experienced patients had a lower baseline HIV RNA and higher baseline CD4 count compared to the treatment naive patients (see Table 17-18). In regard to baseline HIV RNA, the ATV treatment groups (Group 3 and 4) had a median $\log_{10}$ (HIV RNA copies/mL) of 4.70 for treatment-naive patients and 4.42 for treatment-experienced patients. The ATV-RTV treatment groups (Groups 7 and 8) had a median $\log_{10}$ (HIV RNA HIV RNA copies/mL) of 4.84 for treatment-naive patients and 4.05 for treatment-experienced patients. In regard to baseline CD4 cell count, the ATV treatment groups (Group 3 and 4) had a median CD4 count (cells/mm^3) of 278 for treatment-naive patients and 404 for treatment-experienced patients. The ATV-RTV treatment groups (Groups 7 and 8) had a median CD4 count (cells/mm^3) of 422 for treatment-naive patients and 468 for treatment-experienced patients.

Table 17

Baseline Disease Characterisitics: HIV Viral Load & CD4 Count by Treatment Group and Experience

Treatment Group/ Naïve vs. Experienced	Ages	Treatment	Median HIV RNA Level (log 10 c/mL)	Median CD4 Cell Count (cells/mm^3)	Median CD4 Percentage
3	6 to less than13 years	ATV			
ARV Naïve			4.76	340	14
ARVExperienced			4.48	463	25
4	13 to less than 18 years	ATV			
ARV Naïve			4.70	261	16
ARV Experienced			4.42	342	15
Groups 3,4 combined	6 to less than18 years	ATV			
ARV Naïve			4.70	278	15
ARV Experienced			4.44	404	21
7	6 to less than13 years	ATV-RTV			
ARV Naïve			4.92	445	12
ARVExperienced			4.02	516	26
8	13 to less than 18 years	ATV-RTV			
ARV Naïve			4.28	198	16
ARV Experienced			4.12	410	22
Groups 7,8 combined	6 to less than18 years	ATV-RTV			
ARV Naïve			4.84	422	14
ARV Experienced			4.05	468	26

Table 18: Baseline Immune Suppression Based on CD4 Count*

Treatment Group/ Naïve vs. Experienced	Ages	<50 N (%)	50-<200 N (%)	200 - <350 N (%)	350 - <500 N (%)	≥ 500 N (%)	Unknown N (%)
3 (ATV)	6 to less than13 years						
ARV Naïve		0	3 (25)	3 (25)	2 (17)	4 (33)	
ARVExperienced		1 (5)	0	3 (16)	6 (32)	9 (47)	
4 (ATV)	13 to less than 18 years						
ARV Naïve		0	5 (33)	6 (40)	4 (27)	0	
ARV Experienced		3 (18)	3 (18)	2 (12)	6 (36)	2 (12)	1 (6)
Groups 3,4 combined	6 to less than 18 years						
(ATV)							
ARV Naïve		0	8 (30)	9 (33)	6 (22)	4 (15)	
ARV Experienced		4 (11)	3 (8)	5 (14)	12 (33)	11 (31)	1 (3)
7	6 to less than13 years						
ARV Naïve		2 (15)	2 (15)	0	4 (31)	5 (38)	
ARVExperienced		0	1 (7)	0	5 (36)	8 (57)	
8	13 to less than 18 years						
ARV Naïve		1 (25)	1 (25)	1 (25)	1 (25)	0	
ARV Experienced		0	2 (20)	1 (10)	6 (60)	1 (10)	
Groups 7,8 combined	6 to less than 18 years						
(ATV-RTV)							
ARV Naïve		3 (18)	3 (18)	1 (6)	5 (29)	5 (29)	
ARV Experienced		0	3 (12)	1 (4)	11 (46)	9 (38)	

*** CD4 count or CD4 percentage are acceptable means of gauging immune suppression in pediatric patients > 5 years**

6.2.3 Patient Disposition

A total of 104 HIV-infected pediatric patients were enrolled and received at least one dose of ATV or ATV-RTV capsules. Of the 104 enrolled patients, 19 were discontinued prior to the 24 week visit. Of those 19, 11 were discontinued due to toxicity and two were discontinued due to clinical events or disease progression (see Table 19). Roughly the same fraction (17-20%) of ATV and ATV-RTV discontinued prior to Week 24. After Week 24 , direct comparisons between the ATV and ATV-RTV treatment groups are not made because the ATV-RTV treatment groups were started later and only 50% ATV-RTV groups (~20 patients) were treated for at least 48 weeks as compared to 67% of the ATV groups (~40 patients).

Table 19

Subject Disposition (Enrollment through Treatment)

	ATV	ATV-RTV	TOTAL
ENROLLED	**63**	**41**	**104**
TREATED	**63**	**41**	**104**
DISCONTINUED PRIOR TO WEEK 24 VISIT	**11**	**8**	**19**
Clinical Events or Progression	2	0	2
Protocol Compliance	2	2	4
Requests Treatment Discontinuation	1	1	2
Toxicity	6	5	11
DISCONTINUED AFTER 24 WEEK VISIT AND PRIOR TO 48 WEEK VISIT	**8**	**1**	**9**
Clinical Events or Progression	3	0	3
Disallowed Medications	1	0	1
Protocol Compliance	2	1	3
Toxicity	2	0	2
DISCONTINUED AFTER 48 WEEK VISIT	**15**	**5**	**20**
Clinical Events or Progression	3	0	3
Disallowed Medications	1	0	1
Protocol Compliance	5	4	9
Requests Treatment Discontinuation	3	1	4
Toxicity	1	0	1
Other Reasons	2	0	2
CONTINUING ON TREATMENT	**29**	**27**	**56**

Source: Derived from STAT (Patient Status) dataset submitted by Applicant

6.2.4 Analysis of Primary Efficacy Endpoint(s)

The secondary objectives for this study include:

- To assess the antiretroviral activity of ATV and ATV/RTV containing regimens as measured by viral load response when given to protease inhibitor (PI) treatment-experienced and naive study subjects
- To assess the development of virologic resistance as measured by genotypic and phenotypic assays during treatment with ATV and ATV/RTV

Comparisons of antiretroviral activity of ATV and ATV-RTV regimens for treatment-naive and –experienced patients were done by both ITT analysis at 24 weeks and by TLOVR.

Tables 20- 21 provide the overall antiviral activity results for the 99 patients (out of 104 patients enrolled) that were used for the efficacy analysis.

Using the HIV RNA <400 copies/mL endpoint at 24 weeks for treatment-naive patients, 19/26 (73%) of the ATV treated and 12/15 (80%) of the ATV-RTV treated patients achieved a virological response. For treatment-experienced patients with HIV RNA <400 copies/mL at 24 weeks, 10/36 (28%) of the ATV treated and 10/22 (45%) of the ATV-RTV treated patients achieved a virological response. Overall for both treatment-naive and -experienced at the HIV RNA <400 copies/mL endpoint at 24 weeks, 29/62 (47%) of ATV treated and 22/37 (59%) of the ATV-RTV patients achieved a virological response.

Using the HIV RNA <50 copies/mL endpoint at 24 weeks for treatment-naive patients, 14/26 (54%) of the ATV treated and 11/15 (73%) of the ATV-RTV treated patients achieved a virological response. For treatment-experienced patients with HIV RNA <50 copies/mL at 24 weeks, 7/36 (19%) of the ATV treated and 8/22 (36%) of the ATV-RTV treated patients achieved a virological response. Overall for both treatment-naive and -experienced at the HIV RNA <50 copies/mL endpoint at 24 weeks, 21/62 (34%) of ATV treated and 19/37 (51%) of the ATV-RTV patients achieved a virological response. Analyzing the virological response by age groups, the younger patients six to less than 13 years of age (Groups 3,7) had a larger virological response overall than the older patients 13 to less than 18 years of age, 28/54 (52%) versus 12/45 (27%). This held true for young versus older comparisons within the following subsets: treatment-naive ATV treated patients, treatment-naive ATV-RTV patients, treatment-experienced ATV patients and treatment-experienced ATV-RTV patients. In general, as a trend, patients treated with ATV-RTV did better than patients treated with ATV alone but for some comparisons the numbers were small and not statistically significant.

For the purpose of labeling, the snapshot ITT analysis of the 99 patient efficacy cohort was used. In this cohort, the overall proportions of antiretroviral-naive and -experienced patients with HIV RNA <400 copies/mL at week 24 were 68% (28/41) and 33% (19/58), respectively. The overall proportions of antiretroviral-naive and -experienced patients with HIV RNA <50 copies/mL at week 24 were 59% (24/41) and 24% (14/58), respectively. These results are comparable to the HIV RNA results for treatment-naive adults treated with ATV alone and for treatment-experienced treated with ATV-RTV.

Reviewer Comments: The Applicant originally proposed to include a description of the virological results (HIV RNA < 400 and <50) of observed cases but the review team believed that an ITT analysis was more appropriate. Labeling was changed to include ITT analysis.

Table 20: Efficacy outcomes based on number of treatment sucesses at 24 weeks:

HIV RNA <400 (TLOVR Analysis)

Comparison / Groups	Treatment	Age Range	HIV RNA < 400 Naïve (%)	HIV RNA < 400 Experienced (%)	HIV RNA < 400 TOTAL (%)
ATV vs. ATV-RTV					
Groups 3,4	ATV	6 to < 18 years	19/26 (73)	10/36 (28)	29/62 (47)
Groups 7,8	ATV-RTV	6 to < 18 years	12/15 (80)	10/22 (45)	22/37 (59)
6 - <13 years vs. 13 - <18 years					
Groups 3,7	ATV and ATV-RTV	6 to < 13 years	19/23 (83)	15/31 (48)	34/54 (63)
Groups 4,8	ATV and ATV-RTV	13 to < 18 years	12/18 (67)	5/27 (19)	17/45 (38)
Groups Individually					
3	ATV	6 to < 13 years	10/12 (83)	8/19 (42)	18/31 (58)
4	ATV	13 to < 18 years	9/14 (64)	2/17 (12)	11/31 (35)
7	ATV-RTV	6 to < 13 years	9/11 (82)	7/12 (58)	16/23 (70)
8	ATV-RTV	13 to < 18 years	3/4 (75)	3/10 (30)	6/14 (43)

Note: TLOVR analysis represents 99 out of the 104 patients enrolled treated with the capsule formulation from six to less than 18 years of age. Five of the 104 patients were enrolled less than 28 weeks from the datalock for this interim submission and were excluded from the TLOVR analysis.

Table 21: HIV RNA <50 (TLOVR Analysis)

Comparison / Groups	Treatment	Age Range	HIV RNA < 50 Naïve (%)	HIV RNA < 50 Experienced (%)	HIV RNA < 50 TOTAL (%)
ATV vs. ATV-RTV					
Groups 3,4	ATV	6 to < 18 years	14/26 (54)	7/36 (19)	21/62 (34)
Groups 7,8	ATV-RTV	6 to < 18 years	11/15 (73)	8/22 (36)	19/37 (51)
6 - <13 years vs. 13 - <18 years					
Groups 3,7	ATV and ATV-RTV	6 to < 13 years	17/23 (74)	11/31 (35)	28/54 (52)
Groups 4,8	ATV and ATV-RTV	13 to < 18 years	8/18 (44)	4/27 (15)	12/45 (27)
Groups Individually					
3	ATV	6 to < 13 years	8/12 (67)	6/19 (32)	14/31 (45)
4	ATV	13 to < 18 years	6/14 (43)	1/17 (6)	7/31 (23)
7	ATV-RTV	6 to < 13 years	9/11 (82)	5/12 (42)	14/23 (61)
8	ATV-RTV	13 to < 18 years	2/4 (50)	3/10 (30)	5/14 (36)

Note: TLOVR analysis represents 99 out of the 104 patients enrolled treated with the capsule formulation from six to less than 18 years of age. Five of the 104 patients were enrolled less than 28 weeks from the datalock for this interim submission and were excluded from the TLOVR analysis.

The efficacy analysis included changes in HIV RNA over 24 weeks and changes in CD4 count over 20 weeks both from baseline. An observed case analysis was done for both efficacy endpoints (see Table 22). At 24 weeks, treatment-naive patients treated either with ATV or ATV-RTV had similar $\log_{10}$ median decreases in HIV RNA, -2.7 versus -2.9, respectively. Treatment experienced patients treated with ATV-RTV had a greater $\log_{10}$ median decreases in HIV RNA at 24 weeks than patients treated with ATV alone, -1.7 versus – 0.7, respectively. However the confidence interval for these treatment-experienced patient groups overlapped. Treatment-naive patients treated with either ATV or ATV-RTV had similar median increases in CD4 counts (cells/mm^3), 171 versus 152, respectively. Treatment experienced patients treated with ATV-RTV had a greater median increase in CD4 counts (cells/mm^3) than patients treated with ATV alone, 216 versus 100, respectively. Overall treatment-naive patients had a greater median increase in CD4 counts (cells/mm^3) on therapy (ATV and ATV-RTV) then treatment experienced patients, 171 versus 116, respectively.

Reviewer Comments: Although the numbers for each comparison subset is small, the treatment response (virological response with HIV RNA <50 and CD4 count increases) in pediatric patients was similar to adults. Antiretroviral treatment-experienced patients had a greater treatment response with ATV-RTV as compared to ATV alone. This likely reflected the higher ATV exposures received with coadministration of RTV. Also treatment-naive patients had a greater treatment response then treatment-experienced patients.

Table 22a:

Efficacy outcomes based on changes in HIV RNA and CD4 count from baseline around 24 weeks of therapy (Completer Analysis)

	ATV			ATV-RTV		
Efficacy Parameter	**Naïve**	**Experienced**	**TOTAL**	**Naïve**	**Experienced**	**TOTAL**
Δ HIV-RNA 24 weeks (median)	-2.7 $\log_{10}$	-0.70 $\log_{10}$	-1.6 $\log_{10}$	-2.9 $\log_{10}$	-1.7 $\log_{10}$	-2.1 $\log_{10}$
(25th - 75th percentile)	(-3.0, -2.0)	(-2.3, -0.27)	(-2.8, -0.49)	(-3.3, -1.9)	(-2.4, -0.39)	(-2.7, -0.94)
(N=)	N=18	N=30	N=48	N=12	N=15	N=27
Δ CD4+ 20 weeks (median)	+171/mm^3	+100/mm^3	+143/mm^3	+152/mm^3	+216/mm^3	+186/mm^3
(25th - 75th percentile)	(+98,+284)	(-25, +228)	(=+20 +246)	(+60, +272)	(+36, +273)	(+55, +267)
(N=)	N=23	N=27*	N=50*	N=14	N=16	N=30

Note: CD4 counts were not collected at the 24th week so the Δ CD4+ results from 20 weeks are used

* One patient who completed 20 weeks of therapy did not have a baseline CD4 count obtained and was excluded from the analysis

Table 22b:
Capsule patients (Groups 3,4,7,8) 6 to less than 18 years of age

Efficacy Parameter	**Naïve**	**Experienced**
Δ CD4+ 20 weeks (median)	+171/mm^3	+116/mm^3
(25th - 75th percentile)	(+92,+274)	(+16, +240)
(N=) [##]	N=37	N=43*

* One patient who completed 20 weeks of therapy did not have a baseline CD4 count obtained and was excluded from the analysis

7 Review of Safety

Summary of Safety Results and Conclusions

The safety analysis predominately focused on patients six to less than 18 years of age who received the capsule formulation. However, as discussed earlier, patients treated with ATV powder-RTV with equivalent ATV exposure to patients treated with ATV capsule-RTV were included this safety review to increase the size of the safety database to support dosing of ATV capsule-RTV in pediatric patients. To fully explore the safety of ATV powder-RTV dosing, all 47 patients receiving ATV powder-RTV not just the 33 patients with equivalent exposure and duration of approximately 24 weeks or greater was analyzed. In the analysis of the powder formulation, the results for the two age cohorts: three months to two years (Group 5) and greater than two years to 13 years (Group 6) are displayed separately and jointly. Most of the patients in Group 6 are from two to six years of age.

Overall the adverse event profile in pediatric patients was similar to adults. No new or unexpected toxicities were observed. Two deaths reported for the capsule cohort after therapy was discontinued and the deaths were not considered treatment related by the investigator. The

third death occurred in a 23 month old male treated with the ATV powder formulation who had a complicated past medical history including encephalitis, hepatosplenomegaly, and porphyria treated with the powder formulation who died of hemorrhagic pneumonia and renal failure. The investigator could not rule out ATV role in the third patient's renal failure. Sixteen ATV capsule treated patients discontinued due to toxicity. There was a single toxicity related discontinuation in ATV powder treated patients due to a patient death. Most of the discontinuations related to toxicity in the capsule patients were due to cardiac AEs or elevated bilirubin. Fifty-three patients (51%) in the ATV capsule group developed serious adverse events (SAEs) which were predominantly due to elevated bilirubin (45 patients) and cardiac disorders (5 patients). In the ATV-powder group, 14 patients (30%) developed an SAE and 11 (23%) were due to elevated bilirubin.

The most common Grade 2–4 adverse events (≥5%, regardless of causality) reported in the study of patients treated with the capsule formulation were cough (22%), fever (18%), rash (14%), jaundice/scleral icterus (14%), diarrhea (10%), vomiting (9%), headache (6%), and rhinorrhea (6%). Both rash and vomiting occurred almost twice as frequently then adults. Cough and fever which are frequently infection related were seen at a much higher frequency than adults. The most common Grade 3–4 laboratory abnormality was elevation of total bilirubin (≥ 3.2 mg/dL) which occurred in 49% of pediatric patients. All other Grade 3–4 laboratory abnormalities occurred with a frequency of less than 3%.

Reviewer Comment: The Applicants common pediatric Grade 2-4 AEs frequencies were within 1-2% of the review team's number (difference of 1-2 patients) so the Applicant's number will be used in the updated product label.

The safety data from the capsule and powder formulation cohorts are complimentary and few differences in the frequency of certain adverse events were seen. The powder formulation patients had a lower frequency of Grade 3-4 hyperbilirubinemia (28% vs. 49%) , first degree AV block (13% vs. 29%) and Grade 2-4 rash (2% vs. 14%). Both the capsule and powder formulations had similar frequencies of Grade 2-4 vomiting and diarrhea. However the powder formulation had a higher frequency of Grade 1 rash (57% vs. 37%) and Grade 3-4 neutropenia (26% vs. 7%). Of note, the powder formulations also had a higher frequency of overall Grade 1-4 rash (57% vs. 44%). The subset of 33 ATV powder-RTV patients used to supplement the safety database (equivalent ATV exposure for approximately 24 weeks or more) had a lower frequency of Grade 3-4 hyperbilirubinemia (21%) and a similar frequency of first degree AV block (12%) compared to all 47 patients receiving ATV powder-RTV.

7.1.1.1

7.2 Methods

The interim study report for AI424020, included a summary of adverse events, laboratory, and ECG findings and SAS datasets for the entire study population 3 months to 21 years of age who

received either the powder or capsule formulation with and without ritonavir. The Applicant only initially provided minimal breakdown of the capsule formulation cohort for patient six years to less than 18 years of age. Most of the safety information for this formulation/age cohort was derived through manipulation of the datasets. Evaluation of the adverse event dataset was challenging since pre-existing diagnoses, treatment-emergent diagnoses and symptoms were intermixed and individual record review was needed to identify treatment emergent symptoms and diagnoses. Many records consisted of sequential reports of ongoing symptoms and diagnoses but lacked the onset date contained in an earlier record. The review of this supplement required the alignment of patient records by visit for each symptom or diagnosis to track its start, progression, and termination. Also of concern was the lack of intensity information for treatment-emergent diagnoses capable of being graded by the Division of AIDS Table for Grading the Severity of Adult and Pediatric AEs, December 2004. The PACTG utilized the April 1994 version of the chart which did not grade diagnoses and therefore many of the infectious treatment-emergent diagnoses were not graded. However, even with the 1994 version of the AE chart, it would be possible to grade the mood alteration of the two patients with the treatment-emergent diagnosis of depression.

The lack of assignment of causality to almost all of recorded AEs was another serious deficiency of the AE dataset. Only 245 (1%) of the AE records out of a total of 20,638 entries had a coding for relationship to study drug. This lack of causality information complicated the interpretation of AEs and as a result the findings from the AE database primarily have to be reported as adverse events rather than adverse reactions.

In addition to the problems with the adverse event database, the grading of the laboratory abnormalities was not consistent. The toxicity grading for each laboratory abnormality was left to the discretion of each investigator and there was no consistent standard for setting the upper limit of normal (ULN) for laboratory values and subsequently grading them. For instance, the same laboratory values could be graded differently by different sites. Therefore all the laboratory results had to be reanalyzed for toxicity grading using a set of normal values for age and sex. In the submission, the Applicant references a set of normal laboratory values from the 2005 Harriet Lane Manual. These laboratory normal values were used in the clinical review team's analysis. Another explanation for the difference in toxicity grading of abnormal laboratory values is that the cut-off for Grades 3-4 changed for some laboratory tests between the April 1994 and December 2004 DAIDS toxicity charts. For example, abnormalities previously assigned a Grade-2 (such as total bilirubin 2.6 X the upper limit of normal (ULN)) by the April 1994 DAIDS toxicity charts are now considered a Grade-3 by the December 2004 DAIDS toxicity charts. For this review, the December 2004 Division of AIDS Toxicity Table was used to Grade abnormal laboratory values. This change of grading scale frequently resulted in different number of patients with Grade 3-4 laboratory abnormalities between the review team and the Applicant.

As mentioned above, the adverse event dataset provided by BMS lacked intensity information for many of the treatment-emergent diagnoses. This made the determination of the frequency of Grade 2-4 treatment-emergent diagnoses in the trial difficult.

The Applicant provided a dataset of adverse events that included pre-existing diagnoses, treatment emergent diagnoses, and treatment emergent symptoms (see Appendix Tables A1, A2 & A3). The studies which were conducted by the PACTG graded primarily treatment emergent symptoms and a few treatment emergent diagnoses. The PACTG used the April 1994 Division of AIDS Toxicity Table for Grading of Pediatric (>3 months) Adverse Experience to grade symptoms and laboratory values. This toxicity table focused on symptoms rather than diagnoses. The later versions of the Division of AIDS Toxicity Tables including the most recent 2004 table do grade both symptoms and diagnoses. As a consequence of this, many treatment-emergent diagnoses capable of being graded especially those involving infections were not graded. Even with the 1994 Division of AIDS toxicity table, assigning a toxicity grade the patient with the diagnosis of depression was possible.

To compensate for the lack of intensity information for treatment emergent diagnoses, all identified diagnoses were conservatively considered Grade 2 or above. This was especially helpful for infectious related diagnoses because the use of any systemic therapy would classify the diagnosis as Grade-2 or above. If additional details were available in the adverse event record to identify the diagnosis as Grade-1 such as type-1 AV block, then the diagnosis was consider a Grade 1 event for the safety analysis. During the review, the applicant provided pre-existing diagnoses chart and status coding for each adverse event (e.g. new, brief onset and termination, ongoing and terminating). The additional information allowed the review team to clarify whether a recorded diagnosis was pre-existing.

The Applicant also provided an interim study report which described the results for the entire treatment cohort including patients ages three months to 21 years of age that received the powder and capsule formulation. In this interim report, few tables and summary text regarding the labeling subset of patients 6 years to less than 18 years of age that received the capsule formulation were included. Subsequently, at the review team's request, tables summarizing AEs and laboratory abnormalities (including ECGs) for the labeling cohort were provided on January 4, 2008. In the original and subsequent submissions, the Applicant defined treatment emergent AEs and laboratory abnormalities as those events occurring on therapy or up to 56 days after the end of therapy.

Following the review of the PK data and establishment of a pediatric dosing regime, the review team discerned only 33 pediatric patients received the recommended dose or higher for at least 24 weeks. This number of pediatric patients in this safety cohort was relatively small compared to other protease inhibitors such as fosamprenavir which had 68 pediatric patient exposed for 24 weeks in the study submitted in partial response to Lexiva's pediatric written request. Of note, in contrast to atazanavir, fosamprenavir's pediatric approval was for a larger pediatric population consisting of patients two to 18 years of age. To supplement the database, the review team utilized the PK and safety data for the ATV powder formulation [redacted] which was submitted with the current supplement. Forty patients received ATV powder – RTV for approximately 24 weeks or greater. Of these 40 patients, 33 have equivalent exposure to the adolescent patients who received ATV-RTV in Group 8 (13 to less than 18 years of age). Adding the powder formulation safety cohort increases the safety database to 68 patients for this submission.

These two safety cohorts differ mainly by age. The majority of the pediatric patients treated with ATV powder–RTV are from three months of age to six years of age. The safety findings which will be discussed in detail in Section 7 of this review identified some safety differences between the capsule and powder formulations that could be age related but a lower ATV exposure for the powder group could not be ruled out. These differences included a lower frequency of hyperbilirubinemia and PR interval changes in the younger patients receiving the powder formulation as compared to the older patients receiving the capsule formulation. It is possible despite selecting ATV powder-RTV patients with a minimum C_{min} and AUC_{tau} to approximate exposures of patients treated with ATV capsule-RTV, the actual clinically relevant exposure was less; and therefore, the frequency of adverse events and abnormal laboratory values was also lower.

7.2.1 Adequacy of Data

The adequacy issues with the datasets were discussed in the Section 7-Summary of Safety and Section 7.2 Methods

7.3 Adequacy of Safety Assessments

The adequacy of safety assessments of the datasets were discussed in the Section 7-Summary of Safety and Section 7.2 Methods

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

Please see discussion in 4.43 Pharmacokinetics regarding the overall exposure at appropriate doses and duration of the exposure.

7.3.1.1 Demographics

Please see Section 5.3 Discussion of Individual Studies for an explanation of the demographics of the study. A cohort of ATV powder-RTV patients was used to supplement the safety dataset. These patients consisted of two treatment groups: three months to two years of age (Group 5) and two years one day to 13 years of age (Group 6). For both powder treatment groups, the median age was 2.7 years (range 0.3- 12 years), the gender distribution was 43% female and 57% male and the patients were 64% antiretroviral treatment-naive and 36% antiretroviral treatment-experienced.

7.3.2 Explorations for Dose Response

The size of the dosing cohorts in this study was too small to make any conclusions about dose-response of adverse events such as hyperbilirubinemia and PR interval increase.

7.3.2.1 Extent of exposure (dose/duration)

Please see Section 4.4.3 Pharmacokinetics for a discussion of the extent of exposure.

7.3.3 Routine Clinical Testing

The Applicant's laboratory monitoring was adequate for the study however it would have been advantageous to obtain the CD4 cell counts at the time the HIV RNA at 24 weeks was obtained to examine degree of immune suppression at the time of measuring virological response.

7.3.4

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

In this study, cholesterol, triglycerides, and glucose were followed to monitor for protease inhibitor class adverse effects. As part of the clinical examinations, the presence or absence of fat redistribution was assessed.

7.4 Major Safety Results

7.4.1 Deaths (see Applicant's summaries in Section 9.3 following Table A3)

Three deaths were reported among the 183 patients ages 3 months to 18 years of age enrolled and received either the powder or capsule formulation (see Table 23). In the safety cohort for patients ages six to less than 18 years and received the capsule formulation, two deaths were reported. Both deaths occurred more than 56 days after the end of therapy and were not considered related to ATV therapy by the investigators. The third death was in a 23 month old patient with a complicated past medical history treated with the ATV powder formulation who decompensated while on therapy and died of pneumonia and renal failure. A brief summary of these three deaths are provided in this section. The complete summary for these deaths can be found in the appendix of this review.

One of the two deaths in capsule patients was due to acute respiratory distress syndrome and sepsis in a 16 year old male and the death occurred 239 days after stopping ATV therapy for first degree heart block. Of note, this patient was non-compliant with HIV therapy and had a CD4 cell count less than 50 cells/mm^3. The second capsule patient death was due to decompensated

congestive heart failure in a 13 year old female with a prior history of HIV cardiomyopathy. After 74 days of ATV therapy, the patient developed worsening cardiomyopathy which was considered an SAE and ATV was discontinued. The post-ATV therapy clinical course was significant for worsening heart failure, pneumococcal bacteremia, and suspected *Pneumocystis jiroveci* pneumonia (PCP). A second SAE of congestive heart failure was reported 136 days after stopping ATV therapy which resulted in the patient's death.

In ATV powder-RTV treated patients there was one death. A 23 month old male with a complicated prior medical history of being a floppy infant, hypotonia, cerebral palsy and encephalitis, epilepsy with convulsion, pulmonary tuberculosis, lymphadenopathy, porphyria, hepatomegaly and splenomegaly, acrodermatitis and rash, cough, nasal congestion initiated therapy with atazanavir 150 mg daily on Day 1. On Day 98, the patient experienced SAE's of hemorrhagic pneumonia and acute renal failure. These were judged by the investigator to be fatal. The pneumonia was judged by the investigator to be unrelated to the study medication. The investigator was unable to judge the relationship of the renal failure to the study medication.

Table 23: Deaths in Enrolled Patients (includes one powder formulation patient)

Deaths - Enrolled Subjects

SUBJECT	GENDER, AGE RACE REGION	FIRST DATE OF DOSING LAST DOSE DATE DEATH DATE	STUDY DAYS TO DEATH	TREATMENT REGIMEN	SOURCE OF INFORMATION	CAUSE OF DEATH/ ASSOCIATED DIAGNOSES
AI424020-450087	MALE, 16 RACE NOT AVAILABLE (RAC ETH = HISPANIC/LATINO) NORTH AMERICA		351	ATV	DEATH FORM	NON HIV DISEASE-ARDS,ADULT RESP DISTRESS SYN.
					AE/SAE FORM	ACUTE RESPIRATORY DISTRESS SYNDROME
					AE/SAE FORM	SEPSIS
AI424020-500311	FEMALE, 13 RACE NOT AVAILABLE (RAC ETH = HISPANIC/LATINO) NORTH AMERICA		207	ATV	DEATH FORM	HIV INFECTION OR HIV RELATED DIAGNOSES-CONGESTIVE HEART FAILURE
					AE/SAE FORM	CARDIAC FAILURE CONGESTIVE
					AE/SAE FORM	CARDIOMYOPATHY
AI424020-800288	MALE, 1 BLACK AFRICAN AFRICA		101	ATV/RTV	DEATH FORM	OTHER-PNEUMONIA
					AE/SAE FORM	PNEUMONIA
					AE/SAE FORM	RENAL FAILURE
					STATUS FORM	

** = Did not start therapy
Age = Years at enrollment
# = More than 56 days past the date of last dose
Source: AI424020 CSR Table 8.6.1A.

7.4.2 Nonfatal Serious Adverse Events (SAEs)

Capsule Formulation:
Fifty-three patients (51%) experienced SAEs (see Table 24a). Most of the reported SAEs were due to elevated bilirubin levels (45 patients (43%)). The cases of elevated bilirubin levels

occurred at similar frequencies in the ATV (40%) and ATV-RTV (49%) treatment subgroups. Cardiac disorders including atrioventricular block were the next most common SAE occurring at 5% and were primarily reported in patients treated with ATV alone. The patient with HIV cardiomyopathy who died (summarized in 7.3.1 and with full clinical description in the appendix) developed two SAEs (cardiomyopathy and congestive heart failure). The remaining non-cardiac, non-hyperbilirubinemia SAEs occurred at a frequency of less than or equal to 2%.

Powder Formulation:
Fourteen patients (30%) experienced SAEs (see Table 24b). Most of the reported SAEs were due to elevated bilirubin levels (11 patients(23%)). Of note, the 23 month old patient who died had SAEs reports of pneumonia and renal failure. The remaining non-hyperbilirubinemia SAEs had a frequency of less than or equal to 2%.

Table 24a: Serious Adverse Events In Capsule Patients

SYSTEM ORGAN CLASS PREFERRED TERM	**ATV (N = 63)**	**ATV/RTV (N = 41)**	**TOTAL (N = 104)**
Any Adverse Experience	**31 (49)**	**22 (54)**	**53 (51)**
Cardiac Disorders	**5 (8)**	**0**	**5 (5)**
Atrioventricular block	3 (5)	0	3 (3)
Congestive Heart Failure#	2 (3)	0	2 (2)
Cardiomyopathy#	1 (2)	0	1 (1)
Gastrointestinal Disorders	**1 (2)**	**1 (2)**	**2 (2)**
Pancreatitis	1 (2)	0	1 (1)
Stomatitis	0	1 (2)	1 (1)
General Disorders	**0**	**1 (2)**	**1 (1)**
Pyrexia	0	1 (2)	1 (1)
Hepatobiliary Disorders	**0**	**1 (2)**	**0**
Jaundice	0	1 (2)	1
Infections and Infestations	**1 (2)**	**0**	**1 (1)**
Pneumonia	1 (2)	0	1 (1)
Investigations	**27 (43)**	**21 (51)**	**48 (46)**
Blood bilirubin increased	25 (40)	20 (49)	45 (43)
Blood creatinine increased	0	1 (2)	1 (1)
Blood glucose increased	0	1 (2)	1 (1)
Blood Sodium decreased	1	0	1 (1)
Cardiac Function Test Abnormal	2	0	2 (2)
ECG abnormal	1	0	1 (1)
Gamma-glutamyl transferase increased	1	0	1 (1)
Liver function test abnormal	1	1	2 (2)
Skin and subcutaneous tissue disorder	**0**	**1 (2)**	**1 (1)**
Dermatitis allergic	0	1 (2)	1 (1)

Same patient with two cardiac preferred terms. This patient subsequently died.

Table 24b Serious Adverse Events in Powder ATV-RTV Patients

SYSTEM ORGAN CLASS PREFERRED TERM	Group 5 (3 mos to < 2 yrs.) (N = 21)	Group 6 (2 to < 13 yrs) (N = 26)	TOTAL (N = 47)
Any Adverse Experience	**7 (33)**	**7 (27)**	**14 (30)**
Infections and Infestations	**1 (5)**	**1 (4)**	**2 (4)**
Anogenital Warts	0	1 (4)	1 (2)
Pneumonia	1 (5)#	0	1 (2)
Investigations	**5 (24)**	**6 (23)**	**11 (23)**
Blood bilirubin increased	4 (19)	6 (23)	11 (23)
Blood Sodium decreased	1 (5)	0	1 (2)
Gamma-glutamyl transferase increased	2 (10)	0	2 (4)
Liver function test abnormal	1 (5)	0	1 (2)
Renal and Urinary Disorder	1 (5)	**0**	**1 (2)**
Renal Failure	1 (5) #	0	1 (2)
Respiratory, Thoracic, and Mediastinal Disorders	1 (5)	0	1 (2)
Respiratory Disorder	1 (5)	0	1 (2)

Same patient with pneumonia and renal failure who died

7.4.3 Dropouts and/or Discontinuations

Capsule Formulation:
A total of 56 patients discontinued study, of which 16 discontinuations were due toxicity (see Table 25a). Two discontinuations coded as "protocol compliance" and "other reasons" were considered toxicity related. The "protocol compliance" discontinuation patient was diagnosed with depression which could have played a role in the patient's actions. Depression is listed as a potential adverse reaction in adults. The second patient who discontinued for "other reasons" was unable to reach a desired AUC without bilirubin toxicity. Six of the 16 discontinuations were for cardiac related reasons (all on ATV alone): three with heart block/increased PR interval AEs, two with worsening cardiac condition AE, and one with a QTcB prolongation. Another six had toxicity related discontinuations (three for ATV and three for ATV-RTV) due to elevated bilirubin and/or jaundice. Two patients treated with ATV-RTV were discontinued for rash (one was described as an "allergic rash"). One patient was discontinued for pancreatitis and another was discontinued for increased liver enzymes and elevated glucose.

Powder Formulation:
A total of five patients discontinued study, one discontinuation was due to toxicity (see Table 25b). The discontinued patient died of renal failure and pneumonia (see clinical summary in Appendix).

Table 25a: TOXICITY RELATED TREATMENT DISCONTINUATIONS

Patient ID	Treatment Group and Dosing Cohort of ATV	ARV Experience	Weeks on Therapy	Type of Discontinuation	Brief Summary of Discontinuation (additional information from AE dataset)
800011	Group 3 -520 mg/m2	Naïve	31	Toxicity	PROTOCOL DEFINED ENDPOINT QTCB INTERVAL GREATER THAN 470 MSEC
800262	Group 3 -520 mg/m2	Naïve	89	Toxicity	PROLONGED PR INTERVAL AND LOW RESTING HEART RATE
450377	Group 3 - 415 mg/m2	Experienced	98	Other Reasons	NEVER REACHED AUC WITHOUT TOTAL BILIRUBIN TOXICITY
440028	Group 4 - 620 mg/m2	Experienced	1.4	Toxicity	SUBJECT/PHYSCIAN REQUESTS DISCONTINUATION (SAE with increased bilirubin and heart block)
730012	Group 4 - 620 mg/m2	Experienced	1.4	Toxicity	PT DECIDED TO DISCONTINUE STUDY MEDS, CONCERNS OF RE-OCCURRING JAUNDICE.
800304	Group 4 - 620 mg/m2	Naïve	9.4	Toxicity	HYPER BILIRUBINAEMIA (GRADE 3)
500311	Group 4 - 620 mg/m2	Experienced	11	Toxicity	WORSENING OF CARDIOMYOPATHY
400031	Group 4 - 520 mg/m2	Experienced	11	Toxicity	PANCREATITIS
450087	Group 4 - 520 mg/m2	Experienced	16	Toxicity	1ST DEGREE HEART BLOCK, MILD
710217	Group 4 - 620 mg/m2	Naïve	25	Protocol Compliance	PT RAN AWAY FROM HOME AGAIN. UNABLE TO CONTACT PT (treatment emergent depression diagnosed)
800301	Group 4 - 620 mg/m2	Naïve	44	Toxicity	NOT IN BEST INTEREST FOR SUBJECT TO CONTINUE - CARDIAC CONDITION WORSE
690595	Group 7 - 205 mg/m2 + RTV	Experienced	1.4	Toxicity	SUBJECT REACHED PROTOCOL DEFINED TOXICITY END POINT ALLERGIC RASH.
360822	Group 7 - 205 mg/m2 + RTV	Experienced	20	Toxicity	PT HAD AN ELEVATED BILI X 2 WHERE DRUG HAD TO BE DISCONTINUED. PER PROTOCOL PT. HAD TO
506990	Group 7 - 310 mg/m2 + RTV	Experienced	3.7	Toxicity	GUARDIAN REQUESTED TO TAKE PATIENT OFF STUDY DUE TO ADVERS EVENT (RASH).
509951	Group 8 - 205 mg/m2 + RTV	Experienced	12	Toxicity	SUBJECT AND FATHER DO NOT WANT TO RECHALLENGE FOLLOWING THE SECOND GRADE 3 BILIRUBIN TOXICITY.
470090	Group 8 - 310 mg/m2 + RTV	Experienced	17	Toxicity	SUBJECT CONTINUES TO HAVE GRADE 3 TOXICITIES: ELEVATED LIVER ENZYMES AND GLUCOSE DURING RECHALLENGE PERIOD.

Table 25b: TOXICITY RELATED TREATMENT DISCONTINUATIONS

Patient ID	Treatment Group and Dosing Cohort of ATV	ARV Experience	Weeks on Therapy	Type of Discontinuation	Brief Summary of Discontinuation (additional information from AE
800288	Group 5 - Powder 310 mg/m2 + RTV	Naïve	14	Death	Died of renal failure and pneumonia

Note: Only one out of five study discontinuations due to toxicity (death). Two discontinuations due to medicine intolerance, one due to moving out of the country, and one due to parent withdrawal in patient with minor lab abnormalities.

7.4.4

7.4.5 Submission Specific Primary Safety Concerns

The adult safety profile of ATV was taken into consideration for this detailed review for specific safety concerns in children and includes, hyperbilirubinemia/jaundice, cardiac conduction abnormalities, rash, hyperglycemia, nephrolithiasis and fat redistribution.

Hyperbilirubinemia/Jaundice

Adult patients taking atazanavir experience asymptomatic elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl transferase (UGT). This hyperbilirubinemia is reversible upon discontinuation of atazanavir. From clinical trials, the incidence of Grade 3-4 hyperbilirubinemia in treatment-naive patients treated with ATV alone was 35-47% and 49% for treatment-experienced patients treated with ATV-RTV. In these clinical trials, clinical reports of Grade 2-4 clinical jaundice in treatment-naive patients treated with ATV alone was 7% and 9% for treatment-experienced patients treated with ATV-RTV.

Capsule Formulation:
In pediatric patients treated with the capsule formulation, hyperbilirubinemia was also noted in approximately half of the patients receiving either ATV (46%) or ATV/RTV(54%) [see Table 27a]. This finding in children is similar to adults. Clinical reports of Grade 2-4 jaundice and/or ocular icterus occurred in 14% of patients [see Table 26a]. For patients, receiving ATV alone, no correlation between the dose of ATV per m^2 and the incidence of Grade 3-4 hyperbilirubinemia [see Table 28] was observed. The patients receiving ATV 310 mg/m^2 with RTV had a higher degree of Grade 3-4 hyperbilirubinemia (8/10 (80%)) than those patients receiving ATV 210 mg/m^2 (14/31 (45%)). Overall, antiretroviral experienced patients (ARV+) had a higher degree of Grade 3-4 hyberbilirubinemia than antiretroviral naive patients (ARV-) 35/60 (58%) versus 16/44 (36%) [see Table 29a]. This difference in bilirubin elevations was also observed in patients receiving ATV with or without RTV (sees Table 29).

These findings were confirmed when the results of the indirect bilirubin were examined. Conjugated (or direct) hyperbilirubinemia in general has not been associated with ATV use [see Table 27a]. Depending on which upper limit of normal is used for conjugated bilirubin (0.3 or 0.4), there is a small incidence of Grade 3-4 abnormalities (12-14% for ATV or ATV-RTV) for the cutoff of 0.3 or isolated incidence of Grade 3 to 4 abnormalities (n=1 for ATV) for a cutoff of 0.4.

Reviewer Comment: The increased incidence of hyperbilirubinemia for the ATV 310mg/m^2 + RTV as compared the lower ATV dose of 205mg/m^2 + RTV supports the Applicant's recommended dose of 205mg/m^2 + RTV given this toxicity concerns.

Powder formulation
No Grade 2-4 reports of jaundice were observed in patients receiving ATV powder-RTV [see Table 26b]. Overall the frequency of Grade 3-4 hyperbilirubinemia is lower in patients receiving the ATV powder-RTV (28%) as compared to patients receiving the capsule formulation

(49%)[see Tables 27a & b). This finding was also confirmed when the indirect bilirubin results were analyzed. The frequency of Grade 3-4 conjugated hyperbilirubinemia was the same (13%) for both the capsule and powder treatment cohorts. The increased frequency of Grade 3-4 total hyperbilirubinemia in antiretroviral treatment-experienced patients (47%) as compared to antiretroviral treatment-naive patients (17%) was also observed in the ATV powder-RTV treatment cohort [see Table 29b].

Reviewer Comment: The reason for the absence of Grade 2-4 jaundice and lower frequency of Grade 3-4 hyperbilirubinemia in ATV powder-RTV patients is not apparent. An age-related difference in the metabolism of bilirubin and/or of ATV is one possible explanation.

Table 26a: Grade 2-4 Jaundice AEs in Pediatric Patients in Capsule Cohort

	ATV (N=63)	ATV-RTV (N=41)	TOTAL (N=104)
Jaundice and ocular icterus	10 (16%)	5 (12%)	15 (14%)

Table 26b: Grade 2-4 Jaundice AEs in Pediatric Patients in the ATV Powder-RTV Cohort

	Group 5 [3 mos. to ≤ 2 yrs.] (N=21)	Group 6 [2 to <13 yrs.] (N=26)	TOTAL (N=47)
Jaundice and ocular icterus	0	0	0

Table 27a: Grade 3-4 Hyperbilirubinemia in Capsule Treatment Cohort

		ATV	ATV-RTV	TOTAL
Lab Test	BASELINE	Grade 3-4	Grade 3-4	Grade 3-4
Total Bilirubin (ULN 1.2mg/dL)	ALL	29/63 (46%)	22/41 (54%)	51/104 (49%)
	NORMAL	28/62 (44%)	22/41 (54%)	50/103 (49%)
	ABNORMAL	1/1	0/0	1/1 (100%)
	MISSING	0/0	0/0	0/0
Indirect Bilirubin (ULN 1.2mg/dL)	ALL	26/63 (41%)	20/41 (49%)	46/104 (44%)
	NORMAL	26/61 (43%)	20/41 (49%)	46/102 (45%)
	ABNORMAL	0/0	0/0	0/0
	MISSING	0/2	0/2	0/2

Direct Bilirubin (ULN 0.3mg/dL)	ALL	9/63 (14%)	5/41 (12%)	14/104 (13%)
	NORMAL	7/60 (12%)	5/40 (12%)	12/100 (12%)
	ABNORMAL	2/2 (100%)	0/1	2/3 (67%)
	MISSING	0/1	0/0	0/1

Table 27b: Grade 3-4 Hyperbilirubinemia in Powder ATV-RTV Treatment Cohort

		Group 5 [3 mos. to ≤ 2 yrs.]	Group 6 [2 to <13 yrs.]	TOTAL
Lab Test	BASELINE	Grade 3-4	Grade 3-4	Grade 3-4
Total Bilirubin (ULN 1.2mg/dL)	ALL	5/21 (24%)	8/26 (31%)	13/47 (28%)
	NORMAL	5/20 (25)	8/26 (31)	13/46 (28%)
	ABNORMAL	0/1	0/0	0/1
	MISSING	0	0	0
Indirect Bilirubin (ULN 1.2mg/dL)	ALL	4/21 (19%)	7/26 (27%)	11/47 (23%)
	NORMAL	4/21 (19%)	7/25 (28%)	11/46 (24%)
	ABNORMAL	0	0	0
	MISSING	0	0/1	0/1
Direct Bilirubin (ULN 0.3mg/dL)	ALL	4/21 (19%)	2/26 (8%)	6/47 (13%)
	NORMAL	4/21 (19%)	2/26 (8%)	6/47 (13%)
	ABNORMAL	0	0	0
	MISSING	0	0	0

Table 28: Grade 3-4 Total Bilirubin By Treatment Group in Capsule Cohort

		Number of treated subjects w/ Gr3-4 Abnormalities out of the total treated at a given dose (mg/M^2) in each treatment group (%)					
		Dose (mg/M^2)					
Treatment Group	Age Group/ Treatment	205	310	415	520	620	All Doses
3	6 to <13 years ATV		1/5 (20%)	4/5 (80%)	9/21 (43%)		14/31 (45%)
4	13 to < 18 years ATV		2/4 (50%)		1/5 (20%)	12/23 (52%)	15/32 (47%)
TOTAL FOR ATV all ages			3/9 (33%)	4/5 (80%)	10/26 (38%)	12/23 (52%)	29/63 (46%)
7	6 to <13 years ATV/RTV	8/21 (38%)	5/6 (83%)				13/27 (48%)
8	6 to <13 years ATV/RTV	6/10 (60%)	3/4 (75%)				9/14 (64%)
TOTAL FOR ATV/RTV all ages		14/31 (45%)	8/10 (80%)				22/41 (54%)

Table 29a: Grade 3-4 Total Bilirubin By Antiretroviral Treatment Experience and Treatment in Capsule Treatment Cohort

	Antiretroviral Treatment Experience (ARV – or ARV+)		
Treatment	ARV -	ARV+	Total
ATV	10/27 (37%)	19/36 (53%)	29/63 (46%)
ATV/RTV	6/17 (35%)	16/24 (66%)	22/41 (54%)
Total	16/44 (36%)	35/60 (58%)	51/104 (49)

Table 29b: Grade 3-4 Total Bilirubin in Patients by Antiretroviral Treatment Experience in Powder ATV-RTV Treatment Cohort

	Antiretroviral Treatment Experience (ARV – or ARV+)		
Treatment	ARV -	ARV+	Total
Group 5	2/14 (14%)	3/7 (43%)	5/21 (24%)
Group 6	3/16 (19%)	5/10 (50%)	8/26 (31%)
Total	5/30 (17%)	8/17 (47%)	13/47 (28)

PR Interval Prolongation and Other Cardiac AEs

Atazanavir has been shown to prolong the PR interval of the electrocardiogram in some adult patients. In healthy volunteers and in patients, abnormalities in atrioventricular (AV) conduction were asymptomatic and generally limited to first-degree AV block. There have been rare reports of second-degree AV block and other conduction abnormalities and no reports of third-degree AV block. In adult clinical trials, asymptomatic first-degree AV block was observed in 5.9% of atazanavir-treated patients (n=920), 5.2% of lopinavir/ritonavir-treated patients (n=252), 10.4% of nelfinavir-treated patients (n=48), and 3.0% of efavirenz-treated patients (n=329). In Study AI424-045, asymptomatic first-degree AV block was observed in 5% (6/118) of atazanavir/ritonavir-treated adult patients and 5% (6/116) of lopinavir/ritonavir-treated patients who had on-study electrocardiogram measurements.

In the submitted clinical trial, ECGs were done to monitor PR interval and QTc changes. For reference, Table 30 derived from Gajewski, K; Cardiology; Chapter 6 in The Harriet Lane Handbook 17th Edition; 2005 was provided.

Capsule formulation

In pediatric patients ages six years to less than 18 years receiving the capsule formulation (see Table 31a), two (3%) ATV treated patients had a prolonged PR interval compared to no patients in ATV-RTV group. The ATV group had almost a two-fold higher frequency of patients with borderline PR intervals as compared to patients treated with ATV-RTV, 30% versus 17%, respectively. A similar finding was seen in the patients with first degree AV block (see Table 32a). Thirty-two percent of ATV treated patients experienced first degree AV block compared to 24% of the ATV-RTV treated patients. At least one of the treated patients had a 2nd degree AV block (see Table 32). To further characterize PR interval changes, the mean change in PR interval was analyzed after one week of ATV (see Table 33). The largest mean change from baseline was observed at the two-three hour post-dose measurement (7.2 – 28 msec). Overall the ATV treated groups had a mean change of 22 msec versus 9.7 msec for the ATV-RTV treated groups. Therefore, the labeled warning for cardiac conduction abnormalities including PR interval prolongation observed in adults is also applicable to pediatric patients. Pediatric providers must also be aware of the related drug-drug interaction information.

Reviewer Comment: The more prominent PR interval changes and first degree AV block were observed in the ATV groups as compared to the ATV-RTV groups may reflect the fact that more ATV patients received higher than recommended adult doses of ATV then the ATV-RTV patients.

Powder formulation

Patients treated with ATV powder-RTV had a similar frequency of borderline PR intervals as compared to the ATV capsule-RTV patients, 13% versus 17%, respectively (see Tables 31a & b). The frequency of first degree AV block was lower in the ATV powder-RTV patients (13%) as compared to the ATV capsule-RTV patients (24%) (see Tables 32a & b). Second degree AV block was not reported in ATV powder-RTV patients.

Reviewer Comment: The lower frequency of first degree AV block in ATV powder-RTV patients may either reflect changes in heart physiology with age or differences in ATV metabolism with age.

Table 30:

Normal PR Interval in Children

Age	PR Interval (msec) Mean (normal range)
1- <6 months	110 (80-130)
6months - 3 years	120 (100-140)
4-5 years	130 (110-150)
6-8 years	140 (120 - 160)
9-11 years	140 (120 - 170)
12- 16 years	150 (120 - 170)
> 16 years	150 (120 - 200)

Gajewski, K; Cardiology; Chapter 6 in The Harriet Lane Handbook 17th Edition; 2005

Table 31a:

PR Intervals of Capsule Treated Patients

PR Interval: N (%)#	ATV (N = 63)	ATV/RTV (N = 41)	TOTAL (N = 104)
≤ 98th Percentile	41 (67)	34 (83)	75 (74)
Borderline	18 (30)	7 (17)	25 (25)
Prolonged	2 (3)	0	2 (2)
Missing	2	0	2

#Percentage (%) is based on fraction of actual measurements taken (e.g. ATV borderline PR is 18/61 or 30%)

Table 31b: PR Interval of Powder Treated Patients

PR Interval N (%)	Group 5 (N=21)	Group 6 (N=26)	TOTAL (N=47)
<= 98th percentile	18 (86)	23 (88)	41 (87)
Borderline	3 (14)	3 (12)	6 (13)
Prolonged	0	0	0
MISSING	0	0	0

Table 32a:

Capsule Patients with AV Block

	ATV (N = 63)	ATV/RTV (N = 41)	TOTAL (N = 104)
First Degree	20 (32)	10 (24)	30 (29)
Second Degree AV Block	1 (2)	1 (2)*	2 (2)

* Diagnosis of 2nd degree AV block subsequently downgraded to first degree AV and second degree AV block type I Mobitz during sleep (consider a normal pediatric variant)

Table 32b:

ATV Powder-RTV Patients with AV Block

	Group 5 (N=21)	Group 6 (N=26)	TOTAL (N=47)
First Degree	3 (14)	3 (12)	6 (13)
Second Degree AV Block	0	0	0

Table 33

PR Interval Changes (msec) Following ATV Dosing at One Week

		ATV			ATV-RTV		
	Summary Statistic	Naïve	Experienced	TOTAL	Naïve	Experienced	TOTAL
Baseline	N	24	16	40	17	24	41
	Mean (range)	138 (111, 161)	141 (96, 200)	140 (96, 200)	141 (101, 180)	141 (111, 198)	141 (101, 198)
1 week trough	N	23	15	38	17	24	41
	Mean (range)	142 (110, 181)	154 (122, 192)	147 (110, 192)	142 (112,198)	149 (122, 216)	146 (112, 216)
	Mean Change	3.9	12	7.0	1.3	8.5	5.5
1 week 2-3 hr post dose	N	22	15	37	17	24	41
	Mean (range)	156 (120, 213)	170 (124, 277)	162 (120, 277)	148 (107, 190)	152 (121, 227)	150 (107, 227)
	Mean Change	18	28	22	7.2	12	9.7
1 week 4-6 hr post dose	N	22	14	36	17	23	40
	Mean (range)	149 (120, 178)	170 (125, 239)	157 (125, 239)	147 (111, 182)	152 (125, 214)	149 (111, 214)
	Mean Change	11	27	17	5.8	9.6	8.0

QTc Findings in Treated Patients

Capsule Patients:
One significant QTc prolongation was observed in a patient treated with ATV. The QTcB(Bazett's correction) was between 480 and 500msec (see Table 34a). This patient (Group 3 -520mg/m2) was discontinued from therapy after 31weeks. One patient receiving ATV alone had both a QTcB and a QTcF (Fridericia's correction) change from baseline greater than 60msec. One additional patient receiving ATV alone only had a QTcF change from baseline greater than 60msec.

Powder Patients:
No significant reports of QTc prolongation (>480msec) were noted for any of the ATV powder-RTV patients (see Table 34b). Four ATV powder-RTV patients had a QTcB change from baseline greater than 60msec from baseline but without a significant change of QTcF from baseline. In addition, one patient only had a QTcF change greater than 60msec from baseline but without a significant change in QTcF from baseline.

Table 34a: QTc Findings in Capsule Treated Patients

	ATV (N=63)	**ATV-RTV (N=41)**	**TOTAL (N=104)**
QTcB Interval N (%)[+]			
<= 450msec	54 (89)	38 (932)	92 (90)
>450 – 480 msec	6 (10)	3 (7)	9 (9)
>480 – 500 msec	1 (2)	0	1 (<1)
> 500msec	0	0	0
MISSING	2	0	2
QTcB change from baseline N (%)[+]			
<30 msec	21 (54)	29 (71)	50 (63)
30 – 60 msec	17 (44)	12 (29)	29 (36)
>60 msec	1 (3) [#]	0	1 (<1)
MISSING	24	0	0
QTcF Interval N (%)[+]			
<= 450msec	61(100)	41 (100)	102 (100)
>450 – 480 msec	0	0	0
>480 – 500 msec	0	0	0
> 500msec	0	0	0
MISSING	2	0	2

QTcF change from baseline N (%)[+]			
<30 msec	28 (72)*	36 (88)	64 (80)*
30 – 60 msec	9 (23)*	5 (12)	14 (18)*
>60 msec	2 (5)[#*]	0	2 (2)*
MISSING	24	0	24

[+] Percentage (%) is fraction of patients with a measured value for a given parameter
[#] Patient 800301 has a >60msec increase from baseline for both QTcB and QTcF
* Two patient discrepancy from Applicant's data display

Table 34b: QTc Findings in Powder Treated Patients

	Group 5 (N=21)	**Group 6 (N=26)**	**TOTAL (N=47)**
QTcB Interval N (%)[+]			
<= 450msec	21 (100)	24 (92)	45 (96)
>450 – 480 msec	0	2 (8)	2 (4)
>480 – 500 msec	0	0	0
> 500msec	0	0	0
MISSING	0	0	0
QTcB change from baseline N (%)[+]			
<30 msec	16 (76)	17 (65)	33 (70)
30 – 60 msec	4 (19)	6 (23)	10 (21)
>60 msec	1 (5)	3 (12)	4 (9)
MISSING	0	0	0
QTcF Interval N (%)[+]			
<= 450msec	21 (100)	26 (100)	47 (100)
>450 – 480 msec	0	0	0
>480 – 500 msec	0	0	0
> 500msec	0	0	0
QTcF change from baseline N (%)[+]			
<30 msec	13 (62)	18 (69)	31 (66)
30 – 60 msec	7 (33)	8 (31)	15 (32)
>60 msec	1 (5)	0	1 (2)
MISSING	0	0	0

[+] Percentage (%) is fraction of patients with a measured value for a given parameter

Other Cardiac AEs (Table 35)

Capsule Patients:

The frequency of treatment emergent Grade 2-4 and ungraded cardiac AEs was low in capsule treated patients. Five percent of ATV alone treated patients had reports of Grade 2-3 AV block and compared to zero reports for the ATV-RTV patients. The remaining cardiac AEs were at a frequency of 3% or less. One patient with cardiomegaly / cardiomyopathy died of heart failure and this case is discussed in Section 7.4.1.

Powder Patients:

No patients treated with ATV powder-RTV experienced a treatment emergent Grade 2-4 or any cardiac-related AE .

Table 35: Grade 2-4 and Ungraded Treatment Emergent Cardiac Diagnoses and Symptoms in Capsule Treated Patients

Cardiac AE Preferred Term N (%)	ATV (n=63)	ATV-RTV (n=41)	TOTAL (n=104)
Atrioventricular Block (Grades 2-3)	3 (5)	0	3 (3)
Bradycardia	1 (2)	1 (2) [sinus bradycardia]	2 (2)
Congestive Heart Failure	1 (2)	0	1 (1)
Cardiomegaly / Cardiomyopathy#	1 (2)	0	1 (1)
Cor Pulmonale	2 (3)	0	2 (2)

Patient with cardiac SAEs who subsequently died of heart failure

Rash and Hypersensitivity

In adult clinical trials, rash (all grades, regardless of causality) occurred in 21% of patients treated with ATV. The median time to onset of rash was 8 weeks after initiation of REYATAZ and the median duration of rash was 1.3 weeks. Rashes were generally mild-to-moderate maculopapular skin eruptions. For the majority of patients with rash, ATV was continued without interruption. The discontinuation rate for rash in adult clinical trials was 0.4%. The label has specific warnings to discontinue ATV if a severe rash develops or a rash develops with one or more of the following: fever, general malaise, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, granulocytopenia, lymphadenopathy, and renal dysfunction. Hypersensitivity reactions such as Stevens-Johnson syndrome and erythema multiforme have been reported in patients receiving ATV. As part of this review, 3 adult cases of toxic skin eruptions were identified in post-marketing reports and the Applicant has agreed to include this finding in labeling.

Capsule Patients (see Table 36a):

Overall 44% of all patients receiving the capsule formulation had a Grade 1-4 rash which is twice the frequency in adults. Grade 2-4 rash occurred in 14% of capsule treated patients which is also about twice the frequency observed in adults. One patient each treated with ATV-RTV developed a treatment emergent hypersensitivity reaction of erythema multiforme and Grade 2 urticaria.

Powder Formulation (see Table 36b):
Overall 57% of the ATV powder-RTV patients had a Grade 1-4 rash as compared to the capsule formulation in which 44% had a Grade 1-4 rash. The frequency of a mild Grade 1 rash was more common in the ATV powder-RTV patients as compared to the ATV capsule patients, 57% versus 37%, respectively. However the frequency of Grade 2-4 or Ungraded rash was quite low at 2% (N=1) in ATV powder-RTV patients as compared to the 14% frequency in ATV capsule patients. No patients in the ATV powder-RTV group experienced a severe cutaneous skin reaction such as erythema multiforme or Grade 2 urticaria.

Reviewer Comments: 1) The overall frequency of Grade 1-4 rash is similar in both ATV capsule and ATV powder treated patients Age related differences are possible in the two treatment cohorts and may explain why Grade 1 rash is more common in ATV powder patients while Grade 2-4 rash is almost exclusively seen in ATV capsule patients. The review team has recommended the Grade 2-4 rash frequency in capsule treated patients of 14% in pediatric patients and the possibility of a severe rash associated with hypersensitivity is included in labeling.

Table 36a: Grade 1-4 and Ungraded Treatment-Emergent Rash AEs in ATV Capsule Treated Patients

Rash AE Preferred Term N (%)	ATV (n=63)	ATV-RTV (n=41)	TOTAL (n=104)
Grade 1-4 Rash	30 (48)	16 (39)	46 (44)
Grade 1 Rash (rash, generalized rash, rash papular)	26 (41)	12 (29)	38 (37)
Grade 2-4 or Ungraded Rash (rash, generalized rash, rash papular, urticaria, erythema multiforme, drug eruption)	9 (14)	5 (12)	14 (14)
(Erythema multiforme)	0	1 (2)	1 (1)
(Urticaria)	0	1 (2)	1 (1)

Table 36b: Grade 2-4 and Ungraded Treatment-Emergent Rash AEs in ATV Powder-RTV Treated Patients

Rash AE Preferred Term N (%)	Group 5 (n=21)	Group 6 (n=26)	TOTAL (n=47)
Grade 1-4 Rash	11 (52)	16 (62)	27 (57)
Grade 1 Rash (rash, generalized rash, rash papular, Grade 1 urticaria)	11 (52)	16 (62)	27 (57)
Grade 2-4 or Ungraded Rash (rash, generalized rash, rash papular, urticaria, erythema multiforme, drug eruption)	0	1(4)	1(2)

Hyperglycemia, Nephrolithiasis, and Fat Redistribution
In the capsule cohort, one patient each developed hyperglycemia and nephrolithiasis and fat redistribution. These types of adverse events, especially fat redistribution, are typically seen with prolonged ATV treatment. Given the relatively short duration of treatment and follow-up in the submitted pediatric trials, the isolated occurrences of these AEs were not unexpected. Higher rates of hyperglycemia and nephrolithiasis and fat redistribution are possible with longer durations of therapy.

7.5 Supportive Safety Results

Capsule Patients (see Table 37a):

In identifying common moderate, severe, and life-threatening treatment-emergent symptoms and diagnoses, the adverse event dataset was analyzed with supporting information from the Applicant see Appendix Tables A1, A2 & A3). Given almost all treatment-emergent diagnoses were not graded, they were assumed to be at least Grade-2 for the analysis. Grade 2-4 Investigation abnormalities were the most common but are discussed in the laboratory section. The next most common abnormality was the infection related diagnoses which was reported in 73% of the patients in the capsule treatment cohort under review. Of the three most common infections observed in at least 15% of patients: pharyngitis / tonsillitis (21%), Tinea infections (20%), and otitis media (16%), there appeared to be a higher frequency in patients treated with ATV alone as compared to ATV-RTV. Of the non-infectious, non-laboratory abnormality Grade 2-4 diagnoses or symptoms, the following were the most common (>5%): cough (22%), fever (18%), asthma-related [diagnoses and symptoms as a group] (14%), rash (14%), jaundice / ocular icterus (14%), conjunctivitis-related [diagnoses and symptoms as a group] (12%), diarrhea (10%), vomiting (9%), musculoskeletal related pain [diagnoses and symptoms as a group] 9%, headache (6%), rhinorrhea (6%), and stomatitis related [diagnoses and symptoms as a group] 6%. A comparison of the frequency of common adult Grade 2-4 AEs listed in the current label was made to the frequency of pediatric AEs (see Table 38a). The AE frequency of the common AEs was similar except that rash and vomiting occurred at twice the frequency in pediatric patients as compared to adults, 14% versus 5-7% and 8% versus 3-4%, respectively.

Reviewer Comment: The Applicants common pediatric Grade 2-4 AEs frequencies were within 1-2% of the review team's number (difference of 1-2 patients) so the Applicant's number will be used in the updated product label

Powder Patients (see Table 37b):
The analysis and identification of treatment-emergent adverse events for the ATV powder-RTV treated patients were done by the same methods described for the ATV capsule and ATV capsule-RTV treated patients. Laboratory abnormality AEs were the most common but are discussed in the laboratory section. The next most common abnormality was the infection related diagnoses which reported in 79% of the patients which was similar to the frequency of capsule treated patients (73%). The four most common infections observed in at least 15% of patients were: otitis media (36%), pharyngitis / tonsillitis (30%), impetigo/furuncle (15%) and

acarodermatitis (15%). The higher frequency of these four infections in ATV-powder-RTV patients is clearly reflective of age related differences in the incidence of these infections in pediatric patients. Of the non-infectious, non-laboratory abnormality Grade 2-4 diagnoses or symptoms, the following were the most common (>5%): asthma-related [diagnoses and symptoms as a group] (21%), cough (17%), eczema (17%), pulmonary symptoms [rhonchi & dyspnea] (13%), fever (11%), conjunctivitis-related [diagnoses and symptoms as a group] (11%), vomiting (9%), rhinorrhea /nasal congestion (9%), iron deficiency anemia (9%), ear infection related [ear pain & otorrhea] (9%), diarrhea (6%), rash (6%), and pharyngolaryngeal pain (6%). This adverse event profile for ATV powder-RTV was similar to the ATV capsule patients but with differing frequencies that are also reflective of age related differences between the powder and capsule patients. For example, otitis media, pneumonia, pharyngitis, eczema, and iron deficiency anemia are more common in patients six years and younger (primarily powder patients) as compared to those patients older than six years of age (primarily capsule patients).

TABLE 37A: SUMMARY OF GRADE 2-4 AND UNGRADED TREATMENT EMERGENT AEs (DIAGNOSES AND SYMPTOMS) OF PEDIATRIC PATIENTS SIX TO LESS THAN 18 YEARS TREATED WITH CAPSULES

NOTE –Preferred Terms are listed for those with a frequency of ≥ 5%

	NUMBER OF SUBJECTS (%)		
SYSTEM ORGAN CLASS Preferred Term	ATV (N=63)	ATV/RTV (N=41)	Total (N=104)
ANY ADVERSE EXPERIENCE (Diagnosis or Symptom)	63(100)	41 (100)	104(100)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2(3)	1 (2)	3(3)
EAR AND LABYRINTH DISORDERS	4 (6)	2(5)	6 (6)
CARDIAC DISORDER	5 (8)	1 (2)	6 (6)
EYE DISORDERS (w/o icterus)	9 (14)	4 (10)	13 (12)
Conjunctivitis-related (conjunctivitis, eye discharge, eye swelling, ocular hyperemia)	8 (13)	4 (10)	12 (12)
GASTROINTESTINAL DISORDERS	17 (27)	11 (27)	28 (27)
Abdominal Pain	1 (2)	2 (5)	3 (3)
Apthous stomatitis / Mouth ulceration / stomatitis	3 (5)	3 (7)	6 (6)
Diarrhea	7 (11)	3 (7)	10 (10)
Nausea / Vomiting (combined)	5 (8)	6 (15)	11 (11)
Nausea	0	2 (5)	2 (2)
Vomiting	5 (8)	4 (10)	9 (9)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	16 (25)	9 (22)	25 (24)
Pyrexia	14 (22)	5 (12)	19 (18)
HEPATOBILIARY DISORDERS	10 (16)	5 (12)	15 (14)
Jaundice and ocular icterus	10 (16)	5 (12)	15 (14)

IMMUNE SYSTEM (serum sickness related to trimethopim sulfa)	0	1 (2)	1 (1)
INFECTIONS AND INFESTATIONS (note: bilateral parotitis, viral rash, pneumonia AEs received intensity grading)	49 (78)	27 (66)	76 (73)
Acarodermatitis	5 (8)	3 (7)	8 (8)
Sinusitis (including PT acute sinusitis)	13 (19)	1	14 (13)
Cellulitis	3 (5)	1 (2)	4 (4)
Gastroenteritis (including viral)	3 (5)	3 (7)	6 (6)
Herpes Simplex (including herpetic stomatitis)	2 (3)	2 (5)	4 (4)
Herpes Zoster	3 (5)	2 (5)	5 (5)
Impetigo	3 (5)	2 (5)	5 (5)
Oral candidiasis	8 (13)	0	8 (8)
Otitis Externa (including bacterial)	4 (6)	2 (5)	6 (6)
Otitis media (including acute and bacterial)	12 (19)	5 (12)	17 (16)
Parotitis	4 (6)	0	4 (4)
Pharyngitis / Tonsillitis	16 (25)	6 (15)	22 (21)
Pneumonia (including bacterial and viral)	8 (13)	1 (2)	9 (9)
Tinea Infections (including T. pedis, T. capitis, T. versicolor)	15 (24)	6 (15)	21 (20)
Upper Respiratory Infection	5 (8)	0	5 (5)
Urinary Tract Infections (including E. coli)	6 (10)	0	6 (6)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	6 (10)	1 (2)	7 (7)
Musculoskeletal Injuries (1 patient on ATV alone had grade 2 AE)	6 (10)	0	6 (6)
INVESTIGATIONS	53 (84)	38 (93)	91 (88)
METABOLISM AND NUTRITION DISORDERS	5 (8)	1 (2)	6 (6)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	4 (6)	6 (15)	10 (10)
Arthralgia, joint swelling, myalgia, extremity pain, neck pain, costochondritis	3 (5)	6 (15)	9 (9)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	3 (5)	1 (2)	4 (4)*
NERVOUS SYSTEM DISORDERS (excluding pre-existing case (e.g. neuropathy case below))	5 (8)	3 (7)	8 (8)
Headache (grade 2)	4 (6)	2 (5)	6 (6)
PREGNANCY	1 (2)	0	1 (1)
PSYCHIATRIC DISORDERS	9 (14)	3 (7)	12 (12)
Depression (including Major)	3 (5)	1 (2)	4 (4)
Suicidal Ideation^	1 (2)	0	1 (1)
Learning Disorder	4 (6)	0	4 (4)
RENAL AND URINARY DISORDERS	2 (3)	0	2 (2)

REPRODUCTIVE SYSTEM AND BREAST DISORDERS	2 (3)	2 (5)	4 (4)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	23 (36)	11 (27)	34 (33)
Cough	15 (22)	7 (17)	22 (21)
Asthma Related (Asthma (including exercise induced), bronchial hyperreactivity, brochospasm, wheezing)	9 (14)	6 (15)	15 (14)
[Asthma specific (including exercise induced)]	6 (10)	4 (10)	10 (10)
Rhinorrhea	5 (8)	1 (2)	6 (6)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	15 (24)	9 (27)	24 (23)
Acne	3 (5)	0	3 (3)
Eczema	3 (5)	3 (7)	6 (6)
Rash (rash, generalized rash, rash papular, urticaria, erythema multiforme, drug eruption)	9 (14)	5 (12)	14 (14)
VASCULAR DISORDER (venous thrombosis)	1 (2)	0	1 (1)

^ Suicidal Ideation frequently associated with depression but this subject was not coded as being depressed

TABLE 37B: SUMMARY OF GRADE 2-4 AND UNGRADED TREATMENT EMERGENT AEs OF PEDIATRIC PATIENTS ATV POWDER-RTV

NOTE –Preferred Terms are listed for those with a frequency of ≥ 5%

	NUMBER OF SUBJECTS (%)		
SYSTEM ORGAN CLASS Preferred Term	Grp 5 (N=21)	Grp 6 (N=26)	Total (N=47)
ANY ADVERSE EXPERIENCE (Diagnosis or Symptom)	21 (100)	25 (96)	46(98)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2 (10)	2 (8)	4 (9)
Iron Deficiency Anemia	2 (10)	2 (8)	4 (9)
CARDIAC DISORDER	0	0	0
EAR AND LABYRINTH DISORDERS	2 (10)	3 (12)	5 (11)
Ear infection related (otorrhea & ear pain)	1 (5)	3 (12)	4 (9)
EYE DISORDERS (w/o icterus)	2 (10)	3 (12)	5 (11)
Conjunctivitis-related (conjunctivitis, eye discharge, eye swelling, ocular hyperemia)	2 (10)	3 (12)	5 (11)
GASTROINTESTINAL DISORDERS	3 (14)	5 (19)	8 (17)
Abdominal Pain	1 (5)	0	1 (2)
Apthous stomatitis / Mouth ulceration / stomatitis	1 (5)	1 (4)	2 (4)
Gingivitis	1 (5)	1 (4)	2 (4)

Diarrhea	1 (5)	2 (8)	3 (6)
Nausea / Vomiting (combined)	1 (5)	3 (12)	4 (9)
Nausea	0	1 (4)	1 (2)
Vomiting	1 (5)	3 (12)	4 (9)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	3 (14)	4 (15)	7 (15)
Developmental Delay	2 (10)	0	2 (4)
Pyrexia	1 (5)	4 (15)	5 (11)
HEPATOBILIARY DISORDERS	0	0	0
Jaundice and ocular icterus	0	0	0
IMMUNE SYSTEM	0	0	0
INFECTIONS AND INFESTATIONS (note: bilateral parotitis, viral rash, pneumonia AEs received intensity grading)	15 (71)	22 (85)	37 (79)
Abscess (Staphylococcus and subcutaneous)	2 (10)	1 (4)	3 (6)
Acarodermatitis	4 (19)	3 (12)	7 (15)
AIDS encephalopathy	1 (5)	0	1 (2)
Bronchiolitis	2 (10)	1 (4)	3 (6)
Bronchitis	1 (5)	2 (8)	3 (6)
Sinusitis (including PT acute sinusitis)	0	2 (8)	2 (4)
Cellulitis	0	2 (8)	2 (4)
Gastroenteritis (including viral)	3 (14)	3 (12)	6 (13)
Herpes Simplex (including herpetic stomatitis)	1 (5)	1 (4)	2 (4)
Herpes Zoster	0	2 (8)	2 (4)
Impetigo / Furuncle	3 (14)	4 (15)	7 (15)
Oral candidiasis	2 (10)	1 (4)	3 (6)
Otitis Externa (including bacterial)	0	0	0
Otitis media (including acute and bacterial)	8 (38)	9 (35)	17 (36)
Otitis media chronic	1 (5)	2 (8)	3 (6)
Parotitis	0	0	0
Pharyngitis / Tonsillitis	5 (24)	9 (35)	14 (30)
Pneumonia (including bacterial and viral)	5 (24)	4 (15)	9 (19)
Tinea Infections (including T. pedis, T. capitis, T. versicolor)	3 (14)	3 (12)	6 (13)
Other topical fungal infection (onchyomycosis, candida nappy rash)	1 (5)	1 (4)	2 (4)
Upper Respiratory Infection	0	0	0
Urinary Tract Infections (including E. coli)	0	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0	0
Musculoskeletal Injuries (1 patient on ATV alone had grade 2 AE)	0	0	0
INVESTIGATIONS	18 (86)	23 (88)	41 (87)
METABOLISM AND NUTRITION	2 (10)	0	2 (4)

DISORDERS			
Failure to thrive	2 (10)	0	2 (4)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	0	0
Arthralgia, joint swelling, myalgia, extremity pain, neck pain, costochondritis	0	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	2 (8)	2 (4)
Skin papilloma	0	2 (8)	2 (4)
NERVOUS SYSTEM DISORDERS (excluding pre-existing case (e.g. neuropathy case below))	0	0	0
Headache (grade 2)	0	0	0
PREGNANCY	0	0	0
PSYCHIATRIC DISORDERS	0	1 (4)	1 (2)
Depression (including Major)	0	1 (4)	1 (2)
Suicidal Ideation^	0	0	0
Learning Disorder	0	0	0
RENAL AND URINARY DISORDERS	1 (5)	1 (4)	2 (4)
Renal failure	1 (5)	0	1 (2)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	1 (4)	1 (2)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	6 (29)	10 (38)	16 (34)
Cough	1 (5)	7 (27)	8 (17)
Asthma Related (Asthma (including exercise induced), bronchial hyperreactivity, brochospasm, wheezing)	5 (24)	5 (19)	10 (21)
[Asthma specific (including exercise induced)]	3 (14)	2 (8)	5 (11)
Rhinorrhea / Nasal Congestion	0	4 (15)	4 (9)
Pulmonary findings (rhonchi, dyspnea)	2 (10)	4 (15)	6 (13)
Pharyngolaryngeal pain	0	3 (12)	3 (6)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	5 (24)	11 (42)	16 (34)
Eczema (including PT atopic dermatitis)	4 (19)	4 (15)	8 (17)
Rash (rash, generalized rash, rash papular, urticaria, erythema multiforme, drug eruption)	0	3 (12)	3 (6)

Table 38: Comparison of Adult and Pediatric Capsule Grade 2-4 AE Frequencies

Common Adverse Event (adults ≥2%)	Adult Frequency	Pediatric Frequency	Pediatric AE Comments
nausea	3-14%	2%	
jaundice/scleral icterus	7-9%	13%	
rash	5-7% (<2% ATV/RTV)	14%	
headache	1-6% (<2% ATV/RTV)	7%	
abdominal pain	4% (<2% ATV/RTV)	3%	
vomiting	3-4% (<2% ATV/RTV)	8%	
insomnia	<1% to 3% (<2% ATV/RTV)	0%	
peripheral neurologic symptoms	<1% to 3% (<2% ATV/RTV)	<1%	
dizziness	<1% to 3% (<2% ATV/RTV)	(8%)**	** all pediatric AEs Grade-1
myalgia	4% (all ATV/RTV)	9%	musculoskeletal AEs included: arthralgia, myalgia, other musculoskeletal pain
diarrhea	1-3%	8%	
depression	2% (all ATV/RTV)	4%	2 AEs ungraded, 2 Aes Grade-2, 2 AEs-Grade 1
fever	2% (all ATV/RTV)	19%	

NOTE: All Adult AEs are ≥ Grade 2 and Pediatric AEs are ≥ Grade 2 unless otherwise specified

AIDS-Related Diagnoses (only capsule patients analyzed))

For this safety analysis, the determination of treatment-emergent AIDS related diagnoses will be primarily focused on the capsule treated patients since their immune status (via CD4 count) was also reviewed. Twenty three percent of the capsule treated patients had severe immune suppression with a baseline CD4 count less than 200. Approximately one-third of these severely immune suppressed patients (7% of all capsule patients) had a CD4 count less than 50. Therefore, it is not unexpected that five percent of the patients six years to less than 18 years of age treated with the capsule formulation developed AIDS-related diagnoses such as AIDS encephalopathy, HIV wasting syndrome and esophageal candidiasis (see Table 39:). Overall similar rate of AIDS-related diagnoses were observed in the ATV and ATV-RTV treatment groups.

Table 39: AIDS-Related Diagnoses - Treated Subjects – Capsule Formulation
Age >=6 yrs - <18 yrs Occurring Up To 56 Days After Last Dose of Drug

SYSTEM ORGAN CLASS PREFERRED TERM	NUMBER OF SUBJECTS (%) ATV (N= 63)	 ATV/RTV (N= 41)	 TOTAL (N= 104)
ANY ADVERSE EXPERIENCE	3(5)	2(5)	5(5)
INFECTIONS AND INFESTATIONS	3(5)	2(5)	5(5)
AIDS ENCEPHALOPATHY	1(2)	1(2)	2(2)
HIV WASTING SYNDROME	0	1(2)	1(< 1)
OESOPHAGEAL CANDIDIASIS	2(3)	0	2(2)

Multiple MedDRA Versions

7.5.1 Laboratory Findings

Liver Related Enzyme Abnormalities

Capsule Patients
The overall incidence of either Grade 3-4 AST , ALT, or GGT abnormalities in the ATV capsule patients was 2-3% (Table 40a). No Grade 3-4 alkaline phosphatase abnormalities were observed. The number of patients with Grade 2-4 abnormalities was too small to make any conclusions about the influence of RTV on these abnormalities. In adult studies with ATV, Grade 3-4 AST or ALT abnormalities were observed at frequencies of 3-9%.

Powder Patients:
The overall incidence of either Grade 3-4 AST , ALT, or GGT abnormalities in the ATV powder-RTV patients was 4-6% (Table 40b) which was higher than the ATV capsule patients but the numbers of patients with abnormalities were small for both treatment groups so no definitive conclusion can be made. Grade 3-4 alkaline phosphatase abnormalities were seen in 11% of patients. In comparison, no patients in the ATV capsule cohort developed Grade 3-4 alkaline phosphatase abnormalities. Serum alkaline phosphatase is derived from multiple sources in the body including liver, bone, intestinal mucosa, and kidney and in the absence of other liver test abnormalities the cause of the Grade 3-4 laboratory abnormalities in the ATV powder-RTV patients is likely non-hepatic.

Reviewer Comment: The alkaline phosphatase abnormality should be followed up

Table 40a: Grade 3-4 Liver Related Enzyme Abnormalities in Capsule Treated Patients

		ATV	ATV-RTV	TOTAL
Lab Test	**BASELINE**	**Grade 3-4**	**Grade 3-4**	**Grade 3-4**
ALT	ALL	2/63 (3)	1/41 (2)	3/104 (3)
	NORMAL	2/52 (4)	0/36	2/88 (2)
	ABNORMAL	0/10	1/5 (20)	1/15 (7)
	MISSING	0/1	0/0	0/1
AST	ALL	2/63 (3)	0/41	2/104 (2)
	NORMAL	0/53	0/37	0/90
	ABNORMAL	2/9 (22)	0/4	2/13 (15)
	MISSING	0/1	0/0	0/1

Alkaline Phosphatase	ALL	0/36	0/26	0/62
	NORMAL	0/27	0/25	0/52
	ABNORMAL	0/1	0/0	0/1
	MISSING	0/8	0/1	0/9
GGT	ALL	2/63 (3)	1/41 (2)	3/104 (3)
	NORMAL	1/51 (2)	0/38	1/89 (1)
	ABNORMAL	0/8	1/3 (33)	1/11 (9)
	MISSING	1/4 (25)	0/0	1/4 (25)

NOTE: Normal laboratory values obtained from Robertson; "J. Blood Chemistries and Body Fluids" Chapter 25 in the 17th edition of The Harriet Lane Handbook; 2005 (Applicant also provides a copy of this chapter in their submission.

Table 40b: Grade 3-4 Liver Related Enzyme Abnormalities in ATV Powder-RTV Treated Patients

		Group 5	**Group 6**	**TOTAL**
Lab Test	**BASELINE**	**Grade 3-4**	**Grade 3-4**	**Grade 3-4**
ALT	ALL	2/21 (10)	0/26	2/47 (4)
	NORMAL	2/15 (13)	0/23	2/38 (5)
	ABNORMAL	0/6	0/3	0/9
	MISSING	0	0	0
AST	ALL	2/21 (10)	0/26	2/47 (4)
	NORMAL	2/17 (12)	0/21	2/38 (5)
	ABNORMAL	0/4	0/5	0/9
	MISSING	0	0	0
Alkaline Phosphatase	ALL	1/5 (20)	1/14 (7)	2/19 (11)
	NORMAL	1/5 (20)	1/12 (8)	2/17 (12)
	ABNORMAL	0	0	0
	MISSING	0	0/2	0/2
GGT	ALL	3/21 (14)	0/26	3/47 (6)
	NORMAL	3/19 (16)	0/22	3/41 (7)
	ABNORMAL	0/2	0/4	0/6

NOTE: Normal laboratory values obtained from Robertson; "J. Blood Chemistries and Body Fluids" Chapter 25 in the 17th edition of The Harriet Lane Handbook; 2005 (Applicant also provides a copy of this chapter in their submission.

Potential Drug Induced Liver Injury (Hy's Law)

Capsule Patients
One adolescent (13 to less than 18 years of age) patient treated with ATV alone (Group 4) had total bilirubin values greater than two times the upper limit of normal also had concomitant elevations in AST and/or ALT three to eight times the upper limit of normal. This case was evaluated based on Hy's Law [see Table 40a]. Despite the concomitant total bilirubin and AST/ALT increases, this patient had a normal direct (conjugated) bilirubin (liver specific) which makes a drug induced liver abnormality for this patient less likely.

Powder Patients:
One patient treated with ATV powder-RTV developed elevations in total bilirubin values greater than two times the upper limit of normal with concomitant elevations in AST four times the upper limit of normal. This case was evaluated based on Hy's Law [see Table 40b]. The repeat total bilirubin and conjugated bilirubin were normal on the following day; therefore, the possibility of a drug induced liver injury was excluded.

Table 40a Adolescent Patient (13 to < 18 years of Age) Treated with ATV Capsules Alone meeting Hy's Law Laboratory Criteria

PID Dates	Total Bilirubin values (ULN =1.2mg/dL)	ALT (x ULN) U/L	AST (x ULN) U/L	D-Bili mg/dL
710217)	4.0, 3.1	166 (4.2 x), 298 (7.5x)	139 (3.1 x), 360 (8x)	0.3 (0.75x)#

direct bilirubin less than 2X ULN

Table 40b Infant to Pre-School Patient (3months to ≤ 2 years) Treated with ATV powder-RTV Meeting Hy's Law Laboratory Criteria

PID Date	Total Bilirubin (ULN =1.2mg/dL)	ALT U/L	AST (x ULN) U/L	D-Bili (x ULN) mg/dL
509943	5.1 repeated next day to 0.5	20* , 42*	249 (4.2X)	4.7 (15.7X) repeated next day to 0

rmal value

Pancreas Related Enzyme Abnormalities (Table 41)

Amylase is a non-specific marker for pancreatic injury since the enzyme can be elevated for other reasons such as parotitis (increased salivary amylase) which is relatively common in HIV patients. Lipase is also a non-specific marker for pancreatic injury. Elevated lipase may also be a sign of intestinal, gastric, or hepatic disease. In the April 1994 Division of AIDS (DAIDS)

Toxicity Table for Pediatric Adverse Experiences used by the PACTG in the submitted study, grading of amylase and lipase were done together and the assignment of the grade would be the lower of the two values (e.g. Grade 3 lipase and Grade 2 amylase would result in an assigned toxicity Grade of 2). In the December 2004 DAIDS table, amylase, and lipase are graded separately.

Capsule Patients (see Table 41a):
In the ATV capsule alone group, 9% of patients developed Grade 3-4 amylase. Approximately half of the patients with a Grade 3-4 amylase had an abnormal amylase at baseline possibly due to other reasons such as parotitis. In two adult trials (AI424-007, -008), the overall frequency of Grade 3-4 amylase abnormalities was 14%. Depending on the criteria for the ULN for lipase, the frequency of Grade 3-4 lipase varied from 1% (ULN 150-220 U/L based on age)to 9%(ULN 60U/L). Using the more conservative ULN of 60, approximately half of the patients with Grade 3-4 lipase elevation had an abnormal baseline. In adult trials, the frequency of Grade 3-4 lipase abnormalities was <1% to 5% but direct comparisons between pediatric and adult abnormalities can not be made without correcting for differences in grading lipase abnormalities. The 2004 DAIDS table defines a Grade3-4 lipase abnormality as ≥ 3.1 X ULN while the adult trials used the definition of ≥ 2.1 X ULN.

Using the 1994 DAIDS table criteria for grading amylase and lipase together, one patient had a combined lipase-amylase Grade 3-4 abnormality. This patient was discontinued from the trial for the SAE of pancreatitis (see Clinical Summary in Appendix). This 15 year old male patient had been initially treated with 600 mg daily with stavudine and didanosine for 25 days then was increased to 800 mg daily due to a PK adjustment. On Days 77-78, the patient developed nausea and vomiting after taking his study medications on an empty stomach. On Day 78, he developed severe abdominal pain and vomiting and had a lipase of 235 U/L with normal amylase, AST and ALT. Patient was clinically diagnosed with pancreatitis and study medications were discontinued on Day 79. By Day 134 the pancreatitis had resolved but had a second episode on Days 153 to 158 along with a seizure on Day 161. The patient was reported to have taken alternate antiretroviral therapy with ritonavir, lopinavir, efavirenz, and tenofovir from an unknown date until Day 177. He was discontinued from the study on Day 274 due to completion of the protocol-defined period of study evaluation.

Powder Patients (see Table 41b):
In ATV powder-RTV patients, 19% of patients developed Grade 3-4 amylase which was approximately twice the frequency observed in ATV capsule patients. Approximately two-thirds of the patients with a Grade 3-4 amylase had an abnormal amylase at baseline possibly due to other reasons such as parotitis. Depending on the criteria for the ULN for lipase, the frequency of Grade 3-4 lipase varied from zero (ULN 128-220 U/L based on age)to 4%(ULN 60U/L). Using the more conservative ULN of 60, approximately half of the patients with Grade 3-4 lipase elevation (N=2) had an abnormal baseline. Using the 1994 DAIDS table criteria for grading amylase and lipase together, no patients treated with ATV powder-RTV had a combined lipase-amylase Grade3-4 abnormality.

Table 41a: Grade 3-4 Treatment Emergent Lipase and Amylase Results in Capsule Treated Patients

		ATV	ATV-RTV	TOTAL
Lab Test	**BASELINE**	**Grade 3-4**	**Grade 3-4**	**Grade 3-4**
Amylase * (ULN 131 U/L)	ALL	9/63 (14)	0/41	9/104 (9)
	NORMAL	4/43 (9)	0/37	4/80 (5)
	ABNORMAL	5/20 (25)	0/4	5/24 (21)
Lipase ** (ULN 60 U/L)	ALL	4/63 (6)	5/41 (12)	9/104 (9)
	NORMAL	3/57 (5)	1/27 (4)	4/84 (5)
	ABNORMAL	1/6 (17)	4/14 (29)	5/20 (25)
Lipase (U/L)*** (ULN 150 < 12 yrs) (ULN 220 >12 yrs.)	ALL	1/63[#] (2)	0/41	1/104 [#] (1)
	NORMAL	1/62 [#] (2)	0/40	1/102 [#] (1)
	ABNORMAL	0/1	0/1	0/2
Both Lipase and Amylase Grade3,4 [#]	ALL	1/63 [#](2)	0/41	1/104 [#] (1)

*Total amylase measured. Grading was done based on 2004 DAID's table for range of pancreatic amylase. Other causes of increased amylase such as parotitis are possible.

** Lipase upper limit of normal (ULN) of 60 U/L is used as sensitive cut-off by many gastroenterologist. Grading was done based on 2004 DAID's table for range of lipase.

*** The less conservative ULN for lipase was obtained from Robertson; "J. Blood Chemistries and Body Fluids" Chapter 25 in the 17th edition of The Harriet Lane Handbook; 2005. Grading was done based on 2004 DAID's table for range of lipase

Patient 400031 was discontinued from the study due to pancreatitis. after 11 weeks on therapy.

[#] One patient from Group 4 (ATV ->13 years of age) was discontinued from the trial due to pancreatitis

Table 41b: Grade 3-4 Treatment Emergent Lipase and Amylase Results in ATV Powder- RTV Treated Patients

		Group 5 (N=21)	Group 6 (N=26)	TOTAL (N=47)
Lab Test	BASELINE	Grade 3-4	Grade 3-4	Grade 3-4
Amylase * (ULN 131 U/L)	ALL	6/21 (29)	3/26 (12)	9/47 (19)
	NORMAL	3/14 (21)	0/15	3/29 (10)
	ABNORMAL	3/7 (43)	3/11 (27)	6/18 (33)
Lipase ** (ULN 60 U/L)	ALL	1/21 (5)	1/26 (4)	2/47 (4)
	NORMAL	1/19 (5)	0/25	1/44 (2)
	ABNORMAL	0/2	1/1 (100)	1/3 (33)
Lipase (U/L) *** (ULN 128: 3 to <12 months) (ULN 150: 1 to < 12 yrs.) (ULN 220 >12 yrs.)	ALL	0/21	0/26	0/47
	NORMAL	0/20	0/25	0/45
	ABNORMAL	0/1	0/1	0/2
Both Lipase and Amylase Grade3,4 concurrently	ALL	0/21	0/26	0/47

*Total amylase measured. Grading was done based on DAID's table for ranges of pancreatic amylase. Other causes of increased amylase such as parotitis are possible.
** Lipase upper limit of normal (ULN) of 60 U/L is used as sensitive cut-off by many gastroenterologist
*** The less conservative ULN for lipase was obtained from Robertson; "J. Blood Chemistries and Body Fluids" Chapter 25 in the 17th edition of The Harriet Lane Handbook; 2005

Hematological Abnormalities

Capsule Patients (Table 42a):
No Grade 3-4 thrombocytopenia was observed during the trial. The frequency of Grade 3-4 anemia was 2% overall. The frequency of Grade 3-4 neutropenia was 7%. Patients receiving ATV-RTV were more likely to develop Grade 3-4 neutropenia than patients receiving ATV alone, 12% versus 3%, respectively. About half the patients with Grade 3-4 neutropenia had an abnormal neutrophil count at baseline.

Powder Patients (Table 42b):
No Grade 3-4 thrombocytopenia or anemia was observed during the trial. The frequency of Grade 3-4 neutropenia was 26%. Younger ATV powder-RTV patients three months to two years of age had a higher frequency of Grade 3-4 neutropenia than older patient two years to less than 13 years of age [mostly patient two to 6 years of age], 33% versus 19%, respectively. Analyzing the results for both powder and capsule ATV-RTV treated patients, the frequency of Grade 3-4 neutropenia for these patients may be age related because the frequency declines with age: 33% (less than two years of age), 19% (two to six years of age) and 12% (six to less than 18 years of age). Whether the different formulations play a role in the incidence of Grade 3-4 neutropenia is unclear. About one-third of the ATV powder-RTV patients with Grade 3-4 neutropenia had an abnormal neutrophil count at baseline.

Table 42a: GRADE 3-4 TREATMENT EMERGENT HEMATOLOGICAL ABNORMALITIES IN ATV CAPSULE PATIENTS

		ATV	ATV-RTV	TOTAL
Lab Test	BASELINE	Grade 3-4	Grade 3-4	Grade 3-4
Hemoglobin (decreased)	ALL	1/63 (2)	1/41 (2)	2/104 (2)
	NORMAL	1/61 (2)	1/39 (3)	2/100 (2)
	ABNORMAL	0/2	0/2	0/4
Neutrophils (decreased)	ALL	2/63 (3)	5/41 (12)	7/104 (7)
	NORMAL	1/52 (2)	3/30 (10)	4/82 (5)
	ABNORMAL	1/11 (9)	2/11 (18)	3/22 (14)
Platelets (decreased)	ALL	0/63	0/41	0/104
	NORMAL	0/60	0/40	0/100
	ABNORMAL	0/3	0/1	0/4

NOTE: The December 2004 version of the Division of AIDS Table For Grading the Severity of Adult and Pediatric AE was used to grade laboratory values.

Reviewer Comment: The Applicant used the April 1999 version of the DAIDS chart and this explains the difference from the Applicant's laboratory summary.

Table 42b: GRADE 3-4 TREATMENT EMERGENT HEMATOLOGICAL ABNORMALITIES IN ATV POWDER-RTV PATIENTS

		Group 5	Group 6	TOTAL
Lab Test	BASELINE	Grade 3-4	Grade 3-4	Grade 3-4
Hemoglobin (decreased)	ALL	0/21	0/26	0/47
	NORMAL	0/13	0/22	0/35
	ABNORMAL	0/8	0/4	0/12
Neutrophils (decreased)	ALL	7/21 (33)	5/26 (19)	12/47 (26)
	NORMAL	6/16 (38)	2/21 (10)	8/37 (22)
	ABNORMAL	1/5 (20)	3/5 (60)	4/10 (40)
Platelets (decreased)	ALL	0/21	0/26	0/47
	NORMAL	0/19	0/26	0/45
	ABNORMAL	0/2	0	0/2

NOTE: The December 2004 version of the Division of AIDS Table For Grading the Severity of Adult and Pediatric AE was used to grade laboratory values.

Serum Chemistry Abnormalities

Capsule Patients (Table 43a):
Additional Grade 3-4 laboratory abnormalities included creatinine (2%), BUN (2%), and CK (2%) elevations. In comparison, 6 -11% of adults developed Grade 3-4 abnormalities in CK; however, the cut-off for Grade 3-4 in adults was 5.1 X ULN as compared to 10 X ULN in the December 2004 DAIDS Toxicity Tables used for the pediatric patients in this trial. When using the adult cut-off of 5.1 X ULN, the frequency of CK abnormalities in the pediatric trial increases to 6% which is similar to the adults. Grade 3-4 uric acid abnormalities were not seen.

Powder Patients (Table 43b):
Grade 3-4 BUN, creatinine, CK, or uric acid abnormalities were not seen in the ATV powder-RTV patients.

Table 43a: **Grade 3-4 Chemistry Abnormalities in Capsule Treated Patients**

		ATV	ATV-RTV	TOTAL
Lab Test	BASELINE	Grade 3-4	Grade 3-4	Grade 3-4
CK	ALL	1/27 (4)	0/20	1/47 (2)
	NORMAL	0/16	0/11	0/27
	ABNORMAL	1/3 (33)	0/1	1/4 (25)
	MISSING	0/8	0/8	0/16

BUN	ALL	1/63 (2)	1/41 (2)	2/104 (2)
	NORMAL	1/61 (2)	1/40 (2)	2/101 (2)
	ABNORMAL	0/2	0/1	0/3
Creatinine	ALL	0/63	2/41 (5)	2/104 (2)
	NORMAL	0/60	2/40 (5)	2/100 (2)
	ABNORMAL	0/3	0/1	0/4
Serum Uric Acid	ALL	0/18	0/10	0/28
	NORMAL	0/15	0/9	0/24
	ABNORMAL	0/1	0/0	0/1
	MISSING	0/2	0/1	0/3

[&]Fraction of patients with Grade 3-4 abnormalities that have a NORMAL or ABNORMAL baseline value (Grade 1 or above)
NOTE: The December 2004 version of the Division of AIDS Table For Grading the Severity of Adult and Pediatric AE was used to grade laboratory values.

Table 43a: **Grade 3-4 Chemistry Abnormalities in ATV Powder- RTV Treated Patients**

		Group 5	Group 6	TOTAL
Lab Test	BASELINE[&]	Grade 3-4	Grade 3-4	Grade 3-4
CK	ALL	0/5	0/9	0/14
	NORMAL	0/2	0/3	0/5
	ABNORMAL	0	0/1	0/1
	MISSING	0/3	0/5	0/8
BUN	ALL	0/21	0/26	0/47
	NORMAL	0/19	0/26	0/45
	ABNORMAL	0/1	0	0/1
	MISSING	0/1	0	0/1
Creatinine	ALL	0/21	0/26	0/47
	NORMAL	0/20	0/26	0/46
	ABNORMAL	0	0	0
	MISSING	0/1	0	0/1
Serum Uric Acid	ALL	0/3	0/5	0/8
	NORMAL	0/3	0/5	0/8
	ABNORMAL	0	0	0
	MISSING	0	0	0

NOTE: The December 2004 version of the Division of AIDS Table For Grading the Severity of Adult and Pediatric AE was used to grade laboratory values.

Reviewer Comment: The Applicant used the April 1999 version of the DAIDS chart and this explains the difference from the Applicant's laboratory summary.

Total Cholesterol and Triglycerides (Tables 44a and b)

Capsule and Powder Patients:
Some clinicians consider ATV less likely to cause lipid changes than other protease inhibitors. However in adult clinical trials, the addition of RTV as a pharmacological enhancer for ATV does increase the frequency of lipid abnormalities to being comparable to other protease inhibitors such as lopinavir/RTV. Two patients (2%) in the capsule cohort had Grade 3-4 cholesterol abnormalities and one patient (<1%) had a Grade 3-4 triglyceride. In ATV powder-RTV patients, only one patient had a Grade 3-4 total cholesterol abnormality and no Grade 3-4 triglyceride abnormality was observed.

Glucose Abnormalities (Tables 44a and b)
Capsule and Powder Patients:
New onset diabetes mellitus, exacerbation of preexisting diabetes mellitus and hyperglycemia have been reported in adults during postmarketing surveillance in HIV infected patients receiving protease inhibitor therapy. One patient receiving ATV capsule-RTV developed treatment-emergent hyperglycemia. Hypoglycemia developed in three ATV capsule patients. No ATV powder-RTV treated patients developed either hypoglycemia or hyperglycemia.

Table 44a: Total Cholesterol, Triglyceride, and Glucose Abnormalities in Capsule Treated Patients

	NUMBER OF SUBJECTS (%)		
	TREATMENT REGIMEN		
TEST	ATV N = 63	ATV/RTV N = 41	TOTAL N = 104
TOTAL CHOLESTEROL			
ALL SUBJECTS	1/ 63 (2)	1/ 41 (2)	2/ 104 (2)
NORMAL BASELINE	1/ 61 (2)	0/ 39	1/ 100 (1)
ABNORMAL BASELINE	0/ 1	1/ 2 (50)	1/ 3 (33)
MISSING BASELINE	0/ 1	0/ 0	0/ 1
TRIGLYCERIDES			
ALL SUBJECTS	1/ 63 (2)	0/ 41	1/ 104 (<1)
NORMAL BASELINE	1/ 60 (2)	0/ 38	1/ 98 (1)
ABNORMAL BASELINE	0/ 3	0/ 3	0/ 6
HYPOGLYCEMIA			
ALL SUBJECTS	2/ 63 (3)	1/ 41 (2)	3/ 104 (3)
BASELINE: > 64 mg/dL	2/ 59 (3)	1/ 41 (2)	3/ 100 (3)
HYPERGLYCEMIA			
ALL SUBJECTS	0/ 63	1/ 41 (2)	1/ 104 (<1)
BASELINE: < 116 mg/dL	0/ 59	1/ 40 (3)	1/ 99 (1)

Total cholesterol Grade 3 - 4 abnormalities are >= 300 mg/dL and normal baseline is < 200 mg/dL.
Triglyceride Grade 3 - 4 abnormalities are >= 751 mg/dL and normal baseline is < 250 mg/dL.
Hypoglycemia Grade 3 - 4 abnormalities are < 40 mg/dL.
Hyperglycemia Grade 3 - 4 abnormalities are >= 251 mg/dL.
Includes fasting and non-fasting measurements.

Table 44b: Total Cholesterol, Triglyceride and Glucose Abnormalities in ATV Powder-RTV Treated Patients

		Group 5	Group 6	TOTAL
Lab Test	BASELINE	Grade 3-4	Grade 3-4	Grade 3-4
TOTAL CHOLESTEROL	ALL	1/21 (5)	0/26	1/47 (2)
	NORMAL	1/21 (5)	0/25	1/46 (2)
	ABNORMAL	0	0/1	0/1
	MISSING	0	0	0
TRIGLYCERIDES	ALL	0/21	0/26	0/47
	NORMAL	0/18	0/24	0/42
	ABNORMAL	0/3	0/2	0/5
	MISSING	0	0	0
HYPOGLYCEMIA				
All Subjects		0/21	0/26	0/47
Baseline > 64mg/dL		0/15	0/24	0/39
Missing from Baseline		0/1	0	0/1
HYPERGLYCEMIA				
All Subjects		0/21	0/26	0/47
Baseline <116mg/dL		0/20	0/26	0/46
Missing from Baseline		0/1	0	0/1

[&]Fraction of patients with Grade 3-4 abnormalities that have a NORMAL or ABNORMAL baseline value (Grade 1 or above)
Total cholesterol Grade 3 - 4 abnormalities are >= 300 mg/dL and
normal baseline is < 200 mg/dL.
Triglyceride Grade 3 - 4 abnormalities are >= 751 mg/dL and normal baseline is < 250 mg/dL.
Hypoglycemia Grade 3 - 4 abnormalities are < 40 mg/dL.
Hyperglycemia Grade 3 - 4 abnormalities are >= 251 mg/dL.
Includes fasting and non-fasting measurements.

7.5.2 Vital Signs

Vital sign changes submitted in the Applicant interim study report were reviewed and no significant changes of concern were noted.

7.5.3 Electrocardiograms (ECGs)

See subsection PR Interval Prolongation and Other Cardiac AEs in Section 7.45 Submission-Specific Primary Safety Concerns for an analysis of significant ECG findings.

7.5.4

7.6 Other Safety Explorations

7.6.1 Dose Dependency for Adverse Events

The evaluation of dose-response relationship was not possible because too few patient data were available in each dosing cohort. However the increased incidence of type I AV block in the ATV dosing groups does suggest higher ATV Cmax achieved in patients with ATV doses greater than 400mg may explain this increase.

8 Postmarketing Experience

Three reported cases of toxic drug eruptions in adult patients possibly related to ATV therapy from France were identified in the AERS database. This information was added to the hypersensitivity warning in the revised label's CONTRAINDICATIONS section, severe rash description in 5.3 Rash in the WARNING AND PRECAUTIONS section, and another severe rash description in 17.4 Rash in the PATIENT COUNSELING section.

9 Appendices

9.1 Labeling Recommendations (pediatric and safety related changes excerpted from proposed labeling)

2.2 Recommended Pediatric Dosage

The recommended dosage of REYATAZ for pediatric patients (6 to less than 18 years of age) is based on body weight and should not exceed the recommended adult dosage. REYATAZ Capsules must be taken with food. The data are insufficient to recommend dosing of REYATAZ for any of the following: (1) patients less than 6 years of age, (2) without ritonavir in patients less than 13 years of age, and (3) treatment-experienced pediatric patients with body weight less than 25 kg.

Therapy-Naive Pediatric Patients

The recommended dosage of REYATAZ with ritonavir in treatment-naive patients at least 6 years of age is shown in Table 1.

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

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

Body Weight (kg)	Body Weight (lbs)	REYATAZ dose[a,b] (mg)	ritonavir dose[b] (mg)
1 15 to less than 25	2 33 to less than 55	3 150	4 80[c]
5 25 to less than 32	6 55 to less than 70	7 200	8 100[d]
9 32 to less than 39	10 70 to less than 86	11 250	12 100[d]
13 at least 39	14 at least 86	15 300	16 100[d]

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

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

- 15 kg to less than 20 kg: REYATAZ 8.5 mg/kg with ritonavir 4 mg/kg once daily with food.
- at least 20 kg: REYATAZ 7 mg/kg with ritonavir 4 mg/kg once daily with food not to exceed REYATAZ 300 mg and ritonavir 100 mg.

19 [c] Ritonavir liquid.

20 [d] Ritonavir capsule or liquid.

Therapy-Experienced Pediatric Patients

The recommended dosage of REYATAZ with ritonavir in treatment-experienced patients at least 6 years of age is shown in Table 2.

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

Body Weight (kg)	Body Weight (lbs)	REYATAZ dose[a,b] (mg)	ritonavir dose[b] (mg)
21 25 to less than 32	22 55 to less than 70	23 200	24 100[c]
25 32 to less than 39	26 70 to less than 86	27 250	28 100[c]
29 at least 39	30 at least 86	31 300	32 100[c]

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

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

35 [c] Ritonavir capsule or liquid.

4 CONTRAINDICATIONS

REYATAZ (atazanavir sulfate) is contraindicated:

- in patients with previously demonstrated clinically significant hypersensitivity (e.g., Stevens-Johnson syndrome or erythema multiforme, or **toxic skin eruptions)** to any of the components of this product or to atazanavir.

5.3 Rash

In controlled clinical trials (n=1597), rash (all grades, regardless of causality) occurred in 21% of patients treated with REYATAZ. The median time to onset of rash was 8 weeks after initiation of REYATAZ and the median duration of rash was 1.3 weeks. Rashes were generally mild-to-moderate maculopapular skin eruptions. Dosing with REYATAZ was often continued without interruption in patients who developed rash. The discontinuation rate for rash in clinical trials was 0.4%. REYATAZ should be discontinued if severe rash develops. Cases of Stevens-Johnson syndrome, erythema multiforme, and **toxic skin eruptions** have been reported in patients receiving REYATAZ. [See *Contraindications (4).*]

6.2 Clinical Trial Experience in Pediatric Patients

The safety and tolerability of REYATAZ Capsules with and without ritonavir have been established in pediatric patients at least 6 years of age from the open-label, multicenter clinical trial PACTG 1020A. Use of REYATAZ in pediatric patients less than 6 years of age is under investigation.

The safety profile of REYATAZ in pediatric patients (6 to less than 18 years of age) was comparable to that observed in clinical studies of REYATAZ in adults. The most common Grade 2–4 adverse events (≥5%, regardless of causality) reported in pediatric patients were cough (21%), fever (19%), rash (14%), jaundice/scleral icterus (13%), diarrhea (8%), vomiting (8%), headache (7%), and rhinorrhea (6%). Asymptomatic second-degree atrioventricular block was reported in 2% of patients. The most common Grade 3–4 laboratory abnormality was elevation of total bilirubin (≥3.2 mg/dL) which occurred in 49% of pediatric patients. All other Grade 3–4 laboratory abnormalities occurred with a frequency of less than 3%.

8.4 Pediatric Use

REYATAZ should not be administered to pediatric patients below the age of 3 months due to the risk of kernicterus.

The safety, activity, and pharmacokinetic profiles of REYATAZ in pediatric patients ages 3 months to less than 6 years have not been established.

The safety, pharmacokinetic profile, and virologic response of REYATAZ were evaluated in pediatric patients in an open-label, multicenter clinical trial PACTG 1020A [see *Clinical Pharmacology (12.3)* and *Clinical Studies (14.3)*]. The safety profile in pediatric patients was comparable to that observed in adults [see *Adverse Reactions (6.2)*]. Please see *Dosage and Administration (2.2)* for dosing recommendations for pediatric patients 6 years of age and older.

12.3 Pharmacokinetics

Special Populations

Pediatrics

The pharmacokinetic data from pediatric patients receiving REYATAZ Capsules with ritonavir based on body surface area are presented in Table 12.

Table 12: Steady-State Pharmacokinetics of Atazanavir with ritonavir in HIV-Infected Pediatric Patients (6 to less than 18 years of age) in the Fed State

		205 mg/m^2 atazanavir with 100 mg/m^2 ritonavir once daily Age Range (years)	
		at least 6 to 13 (n=17)	**at least 13 to 18 (n=10)**
5	Dose *mg*	7	9
6	Median [min-max]	8 200 [150–400]	10 400 [250–500]
11	C_{max} ng/mL Geometric Mean (CV%)	12 4451 (33)	13 3711 (46)
14	AUC ng•h/mL Geometric Mean (CV%)	15 42503 (36)	16 44970 (34)
17	C_{min} ng/mL	18	19

Table 12: Steady-State Pharmacokinetics of Atazanavir with ritonavir in HIV-Infected Pediatric Patients (6 to less than 18 years of age) in the Fed State

	205 mg/m^2 atazanavir with 100 mg/m^2 ritonavir once daily	
	Age Range (years)	
	at least 6 to 13 (n=17)	at least 13 to 18 (n=10)
Geometric Mean (CV%)	535 (62)	1090 (60)

14.3 Pediatric Patients

Assessment of the pharmacokinetics, safety, tolerability, and efficacy of REYATAZ is based on data from the open-label, multicenter clinical trial PACTG 1020A conducted in patients from 3 months to 21 years of age. In this study, 182 patients (83 antiretroviral-naive and 99 antiretroviral-experienced) received once daily REYATAZ, with or without ritonavir, in combination with two NRTIs.

Ninety-nine patients (6 to less than 18 years of age) treated with the REYATAZ capsule formulation, with or without ritonavir, were evaluated. In this cohort, the overall proportions of antiretroviral-naive and -experienced patients with HIV RNA <400 copies/mL at week 24 were 68% (28/41) and 33% (19/58), respectively. The overall proportions of antiretroviral-naive and -experienced patients with HIV RNA <50 copies/mL at week 24 were 59% (24/41) and 24% (14/58), respectively. The median increase from baseline in absolute CD4 count at 20 weeks of therapy was 171 cells/mm^3 in antiretroviral-naive patients and 116 cells/mm^3 in antiretroviral-experienced patients.

17 PATIENT COUNSELING INFORMATION

17.4 Rash

Patients should be informed that mild rashes without other symptoms have been reported with REYATAZ use. These rashes go away within two weeks with no change in treatment. However, there have been a few reports of severe skin reactions (e.g., Stevens-Johnson syndrome and erythema multiforme, and **toxic skin eruptions**) with REYATAZ use. Patients developing signs or symptoms of severe skin reactions or hypersensitivity reactions (including, but not

limited to, severe rash or rash accompanied by one or more of the following: fever, general malaise, [redacted] muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, and/or hepatitis, eosinophilia, granulocytopenia, lymphadenopathy, and renal dysfunction) must discontinue REYATAZ and seek medical evaluation immediately.

17.1 FDA-Approved Patient Labeling

Patient Information

The following side effects have been reported with REYATAZ:

- **mild rash** (redness and itching) without other symptoms sometimes occurs in patients taking REYATAZ, most often in the first few weeks after the medicine is started. Rashes usually go away within 2 weeks with no change in treatment. Tell your healthcare provider if rash occurs.
- **severe rash:** In a small number of patients, a rash can develop that is associated with other symptoms which could be serious and potentially cause death.

  If you develop a rash with any of the following symptoms stop using REYATAZ and call your healthcare provider right away:

  - shortness of breath
  - general ill feeling or "flu-like" symptoms
  - fever
  - muscle or joint aches
  - conjunctivitis (red or inflamed eyes, like "pink eye")
  - blisters
  - mouth sores
  - swelling of your face

9.2 Supporting Tables Provided By Applicant and Clinical Summaries for Patients that Died and other Significant Clinical Events [e.g. Pancreatitis] (below)

Table A1: Pre-Existing Diagnoses - Treated Subjects - Capsule Formulation
Age >=6 yrs - <18 yrs Occurring Up To 56 Days After Last Dose of Drug

Table A2 SAE and Signs and Symptoms (Grade 2 - 4) with at Least 5% Frequency - Treated Subjects - Capsule Formulation Age >=6 yrs - <18 yrs Occurring Up To 56 Days After Last Dose of Drug

Table A3: Treatment-Emergent Diagnoses - Treated Subjects - Capsule Formulation Age >=6 yrs - <18 yrs Occurring Up To 56 Days After Last Dose of Drug

Table A1:

Pre-Existing Diagnoses - Treated Subjects - Capsule Formulation Age >=6 yrs - <18 yrs
Occurring Up To 56 Days After Last Dose of Drug

SYSTEM ORGAN CLASS PREFERRED TERM	NUMBER OF SUBJECTS (%) ATV (N= 63)	 ATV/RTV (N= 41)	 TOTAL (N= 104)
ANY ADVERSE EXPERIENCE	51(81)	30(73)	81(78)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	11(17)	5)	13(13)
ANAEMIA	1(2)	2(	1(< 1)
AUTOIMMUNE THROMBOCYTOPENIA	3(5)	0	3(3)
IDIOPATHIC THROMBOCYTOPENIC PURPURA	1(2)	0 5)	3(3)
IRON DEFICIENCY ANAEMIA	2(3)	2(	2(2)
LEUKOPENIA	1(2)	0	1(< 1)
LYMPHADENOPATHY	1(2)	0	1(< 1)
NEUTROPENIA	2(3)	0	2(2)
THROMBOCYTOPENIA	2(3)	0	2(2)
CARDIAC DISORDERS	6(10)	0 2)	7(7)
CARDIOMEGALY	1(2)	1(	1(< 1)
CARDIOMYOPATHY	2(3)	0 2)	3(3)
COR PULMONALE	2(3)	1(	2(2)
DILATATION VENTRICULAR	1(2)	0	1(< 1)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	3(5)	0 4(10)	7(7)
CATARACT CONGENITAL	1(2)		1(< 1)
CEREBRAL PALSY	0	0 2)	1(< 1)
CONGENITAL CENTRAL NERVOUS SYSTEM ANOMALY	0	1(2)	1(< 1)
CONGENITAL HEART VALVE DISORDER	0	1(2)	1(< 1)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS		1(	
CONGENITAL SYPHILIS	1(2)		1(< 1)
MICROCEPHALY	1(2)	0	1(< 1)
THALASSAEMIA BETA	0	0 2)	1(< 1)
EAR AND LABYRINTH DISORDERS	1(2)	1(2)	2(2)
DEAFNESS	0	1(2)	1(< 1)
DEAFNESS BILATERAL	1(2)	1(	1(< 1)
EYE DISORDERS	1(2)	0 2)	2(2)
CONJUNCTIVITIS ALLERGIC	0	1(2)	1(< 1)
STRABISMUS	1(2)	1(	1(< 1)
GASTROINTESTINAL DISORDERS	3(5)	0 2)	4(4)
APHTHOUS STOMATITIS	1(2)	1(	1(< 1)
DIARRHOEA	0	0 2)	1(< 1)
		1(	

DIARRHOEA HAEMORRHAGIC	1(2)				1(< 1)
MOUTH CYST	1(2)	0			1(< 1)
RECTAL HAEMORRHAGE	0	0	2)		1(< 1)
		1(			
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	4(6)				4(
DEVELOPMENTAL DELAY	4(6)	0			4(4)
		0			4)
INFECTIONS AND INFESTATIONS	43(68)		25(61)		68(65)
ACARODERMATITIS	1(2)		5)		3(
ACUTE SINUSITIS	5(8)	2(			5(3)
AIDS ENCEPHALOPATHY	2(3)	0	4(10)		6(5)
ANOGENITAL WARTS	1(2)		2)		2(6)
ATYPICAL MYCOBACTERIAL LYMPHADENITIS	0	1(	2)		1(< 1)
BACTERIAL DIARRHOEA	1(2)	1(			1(< 1)
BRONCHIECTASIS	2(3)	0			2(
CELLULITIS	2(3)	0	2)		3(2)
CHRONIC SINUSITIS	2(3)	1(	5)		4(3)
DENGUE FEVER	1(2)	2(			1(< 1)
DISSEMINATED TUBERCULOSIS	1(2)	0	2)		2(
ERYTHEMA INFECTIOSUM	1(2)	1(			1(< 1)
GASTROENTERITIS CRYPTOSPORIDIAL	1(2)	0			1(< 1)
GENITAL CANDIDIASIS	1(2)	0			1(< 1)
HEPATITIS A	0	0	2)		1(< 1)
HERPES SIMPLEX	1(2)	1(	2)		2(
HERPES ZOSTER	6(10)	1(	7)		9(2)
HERPES ZOSTER OPHTHALMIC	0	3(	2)		1(< 1)
HERPETIC GINGIVOSTOMATITIS	1(2)	1(			1(< 1)
HIV WASTING SYNDROME	0	0	2)		1(< 1)
MASTOIDITIS	1(2)	1(			1(< 1)
MENINGITIS ASEPTIC	1(2)	0			1(< 1)
MENINGITIS MENINGOCOCCAL	1(2)	0			1(< 1)
MOLLUSCUM CONTAGIOSUM	3(5)	0			3(
MYCOBACTERIUM AVIUM COMPLEX INFECTION	1(2)	0			1(< 1)
ORAL CANDIDIASIS	5(8)	0	5(12)		10(10)
OTITIS MEDIA	1(2)		5)		3(
OTITIS MEDIA ACUTE	5(8)	2(	5(12)		10(10)
OTITIS MEDIA CHRONIC	3(5)		2)		4(4)
PAROTITIS	12(19)	1(	5)		14(13)
PHARYNGEAL CANDIDIASIS	1(2)	2(			1(< 1)
PNEUMOCOCCAL BACTERAEMIA	0	0	2)		1(< 1)
PNEUMOCOCCAL SEPSIS	1(2)	1(			1(< 1)
PNEUMOCYSTIS JIROVECI PNEUMONIA	0	0	5)		2(
PNEUMONIA	11(17)	2(	12(29)		23(22)
PNEUMONIA PNEUMOCOCCAL	2(3)				2(
PULMONARY TUBERCULOSIS	5(8)	0	2)		6(2)
SALMONELLA SEPSIS	0	1(	2)		1(< 1)
SINUSITIS	2(3)	1(			2(
STAPHYLOCOCCAL ABSCESS	0	0	2)		1(< 1)
TINEA INFECTION	3(5)	1(	5)		5(
TOOTH ABSCESS	0	2(	2)		1(< 1)
		1(			

TUBERCULOSIS	1(2)	5)	3(3)
URINARY TRACT INFECTION BACTERIAL	0	2(2)	1(< 1)
VAGINAL CANDIDIASIS	0	1(2)	1(< 1)
VAGINAL INFECTION	1(2)	1(	1(< 1)
VARICELLA	4(6)	0	4(4)
		0	
METABOLISM AND NUTRITION DISORDERS	6(10)	2)	7(7)
FAILURE TO THRIVE	4(6)	1(2)	5(5)
MALNUTRITION	1(2)	1(	1(< 1)
WEIGHT GAIN POOR	1(2)	0	1(< 1)
		0	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1(2)		1(< 1)
ARTHRITIS	1(2)	0	1(< 1)
		0	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1(2)		1(< 1)
SKIN PAPILLOMA	1(2)	0	1(< 1)
		0	
NERVOUS SYSTEM DISORDERS	2(3)	5(12)	7(7)
CEREBRAL INFARCTION	0	2)	1(< 1)
EPILEPSY	1(2)	1(2)	2(2)
FEBRILE CONVULSION	0	1(2)	1(< 1)
MENTAL RETARDATION SEVERITY UNSPECIFIED	0	1(2)	1(< 1)
MILD MENTAL RETARDATION	0	1(2)	1(< 1)
NEUROPATHY	0	1(2)	1(< 1)
SPEECH DISORDER DEVELOPMENTAL	1(2)	1(	1(< 1)
		0	
PSYCHIATRIC DISORDERS	6(10)	5)	8(8)
ADJUSTMENT DISORDER	1(2)	2(	1(< 1)
AFFECTIVE DISORDER	1(2)	0	1(< 1)
ANXIETY DISORDER	1(2)	0	1(< 1)
ATTENTION DEFICIT/HYPERACTIVITY DISORDER	5(8)	0 5)	7(7)
		2(	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	2(3)	2)	3(3)
AMENORRHOEA	0	1(2)	1(< 1)
EPIDIDYMITIS	1(2)	1(	1(< 1)
GENITAL ULCERATION	1(2)	0	1(< 1)
		0	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	19(30)	9(22)	28(27)
ASTHMA	6(10)	4(10)	10(10)
BRONCHIAL HYPERREACTIVITY	4(6)	5)	6(6)
INTERSTITIAL LUNG DISEASE	12(19)	2(7)	15(14)
		3(	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	8(13)	4(10)	12(12)
DERMATITIS	2(3)		2(2)
DERMATITIS ALLERGIC	1(2)	0	1(< 1)
DERMATITIS ATOPIC	2(3)	0	2(2)
ECZEMA	2(3)	0 5)	4(4)
EOSINOPHILIC PUSTULAR FOLLICULITIS	1(2)	2(	1(< 1)
LIPOATROPHY	0	0 2)	1(< 1)
LIPODYSTROPHY ACQUIRED	0	1(2)	1(< 1)
		1(	

NEURODERMATITIS	0	2)	1(< 1)
		1(	
SOCIAL CIRCUMSTANCES	0	2)	1(< 1)
LEARNING DISABILITY	0	1(2)	1(< 1)
		1(	

Table A2

SAE and Signs and Symptoms (Grade 2 - 4) with at Least 5% Frequency - Treated Subjects - Capsule Formulation Age >=6 yrs - <18 yrs Occurring Up To 56 Days After Last Dose of Drug

	NUMBER OF SUBJECTS (%)		
SYSTEM ORGAN CLASS PREFERRED TERM	ATV (N= 63)	ATV/RTV (N= 41)	TOTAL (N= 104)
ANY ADVERSE EXPERIENCE	46(73)	28(68)	74(71)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1(2)		1(< 1)
		0	
CARDIAC DISORDERS	5(8)		5(5)
		0	
EAR AND LABYRINTH DISORDERS	3(5)	5)	5(5)
		2(	
EYE DISORDERS	8(13)	6(15)	14(13)
OCULAR ICTERUS	6(10)	5(12)	11(11)
GASTROINTESTINAL DISORDERS	11(17)	7(17)	18(17)
DIARRHOEA	6(10)	5)	8(8)
VOMITING	5(8)	2(7)	8(8)
		3(	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	16(25)	10(24)	26(25)
PYREXIA	14(22)	5(12)	19(18)
HEPATOBILIARY DISORDERS	3(5)		3(3)
		0	
INFECTIONS AND INFESTATIONS	2(3)		2(2)
		0	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1(2)	2)	2(2)
		1(	
INVESTIGATIONS	28(44)	21(51)	49(47)
BLOOD BILIRUBIN INCREASED	25(40)	20(49)	45(43)
METABOLISM AND NUTRITION DISORDERS	2(3)		2(2)
		0	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2(3)	6(15)	8(8)

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1(2)		1(< 1)
NERVOUS SYSTEM DISORDERS	5(8)	0	7(
HEADACHE	5(8)	5) 2(5)	7(7)
PSYCHIATRIC DISORDERS	3(5)	2) 2(	4(7)
RENAL AND URINARY DISORDERS	1(2)	1(	4) 1(< 1)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	0 2)	1(< 1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	20(32)	1(10(24)	30(29)
RHINORRHOEA	13(21)	8(20)	21(20)
COUGH	5(8)	2) 1(	6(6)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
WHEEZING	2(3)	4(10)	6(6)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	11(17)	7(17)	18(17)
RASH	7(11)	2) 1(	8(8)

NOTE: PREFERRED TERMS ARE DISPLAYED ONLY IF THE TOTAL INCIDENCE IN COLUMN 3 IS AT LEAST 5%
Multiple MedDRA Versions

Table A3:

Treatment-Emergent Diagnoses - Treated Subjects - Capsule Formulation Age >=6 yrs - <18 yrs
Occurring Up To 56 Days After Last Dose of Drug

	NUMBER OF SUBJECTS (%)		
SYSTEM ORGAN CLASS PREFERRED TERM	ATV (N= 63)	ATV/RTV (N= 41)	TOTAL (N= 104)
ANY ADVERSE EXPERIENCE	53(84)	30(73)	83(80)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1(2)	2)	2(2)
IRON DEFICIENCY ANAEMIA	0	1(2)	1(< 1)
NEUTROPENIA	1(2)	1(	1(< 1)
CARDIAC DISORDERS	5(8)	0 2)	6(6)
ATRIOVENTRICULAR BLOCK	1(2)	1(	1(< 1)
ATRIOVENTRICULAR BLOCK FIRST DEGREE	3(5)	0	3(3)
CARDIOMYOPATHY	1(2)	0	1(< 1)
SINUS BRADYCARDIA	0	0 2) 1(	1(< 1)

CONGENITAL, FAMILIAL AND GENETIC DISORDERS	0		2)	1(< 1)
THALASSAEMIA BETA	0	1(	2)	1(< 1)
		1(		
EAR AND LABYRINTH DISORDERS	1(2)			1(< 1)
DEAFNESS	1(2)	0		1(< 1)
		0		
EYE DISORDERS	7(11)		5)	9(9)
CONJUNCTIVITIS	7(11)	2(	5)	9(9)
RETINAL DETACHMENT	1(2)	2(		1(< 1)
GASTROINTESTINAL DISORDERS	8(13)	0	4(10)	12(12)
APHTHOUS STOMATITIS	1(2)		5)	3(3)
DIARRHOEA	1(2)	2(	2)	2(2)
GASTRITIS	1(2)	1(	2)	2(2)
GASTROOESOPHAGEAL REFLUX DISEASE	1(2)	1(		1(< 1)
GINGIVITIS	2(3)	0		2(2)
MOUTH ULCERATION	1(2)	0		1(< 1)
PANCREATITIS	1(2)	0		1(< 1)
RECTAL FISSURE	0	0	2)	1(< 1)
		1(		
HEPATOBILIARY DISORDERS	1(2)			1(< 1)
JAUNDICE	1(2)	0		1(< 1)
		0		
IMMUNE SYSTEM DISORDERS	0		2)	1(< 1)
SERUM SICKNESS	0	1(	2)	1(< 1)
		1(		
INFECTIONS AND INFESTATIONS	49(78)	27(66)		76(73)
ACARODERMATITIS	5(8)		7)	8(8)
ACUTE SINUSITIS	12(19)	3(		12(12)
ACUTE TONSILLITIS	1(2)	0		1(< 1)
BODY TINEA	1(2)	0	2)	2(2)
BRONCHIECTASIS	1(2)	1(		1(< 1)
BRONCHITIS	1(2)	0		1(< 1)
BRONCHOPNEUMONIA	1(2)	0		1(< 1)
CELLULITIS	3(5)	0	2)	4(4)
CELLULITIS ORBITAL	1(2)	1(		1(< 1)
CHRONIC SINUSITIS	1(2)	0		1(< 1)
COXSACKIE VIRAL INFECTION	1(2)	0		1(< 1)
DERMATOPHYTOSIS	1(2)	0		1(< 1)
EPIDEMIC NEPHROPATHY	1(2)	0		1(< 1)
ESCHERICHIA URINARY TRACT INFECTION	1(2)	0		1(< 1)
GASTROENTERITIS	2(3)	0	7)	5(5)
GASTROENTERITIS VIRAL	1(2)	3(		1(< 1)
HERPES SIMPLEX	3(5)	0	2)	4(4)
HERPES ZOSTER	3(5)	1(	5)	5(5)
HERPETIC STOMATITIS	0	2(	2)	1(< 1)
IMPETIGO	3(5)	1(	5)	5(5)
INFECTION PARASITIC	1(2)	2(		1(< 1)
LICE INFESTATION	1(2)	0		1(< 1)
LYMPHADENITIS BACTERIAL	0	0	2)	1(< 1)
		1(		

MOLLUSCUM CONTAGIOSUM	2 (3)			2 (2)			
NAIL TINEA	0			1 (< 1)			
OESOPHAGEAL CANDIDIASIS	2 (3)			2 (2)			
ORAL CANDIDIASIS	8 (13)			8 (8)			
OTITIS EXTERNA	3 (5)			5 (5)			
OTITIS EXTERNA BACTERIAL	1 (2)			1 (< 1)			
OTITIS MEDIA	1 (2)			3 (3)			
OTITIS MEDIA ACUTE	11 (17)			14 (13)			
PAROTITIS	4 (6)			4 (4)			
PELVIC INFLAMMATORY DISEASE	1 (2)			1 (< 1)			
PERTUSSIS	0			1 (< 1)			
PHARYNGITIS	7 (11)			10 (10)			
PHARYNGITIS STREPTOCOCCAL	5 (8)			6 (6)			
PNEUMONIA	8 (13)			8 (8)			
PNEUMONIA ADENOVIRAL	0			1 (< 1)			
PNEUMONIA BACTERIAL	1 (2)			1 (< 1)			
PNEUMONIA STREPTOCOCCAL	1 (2)			1 (< 1)			
PSEUDOMONAS INFECTION	1 (2)			1 (< 1)			
PULMONARY TUBERCULOSIS	1 (2)			1 (< 1)			
RESPIRATORY TRACT INFECTION	1 (2)			1 (< 1)			
SINUSITIS	3 (5)			4 (4)			
STAPHYLOCOCCAL ABSCESS	0			1 (< 1)			
STAPHYLOCOCCAL SEPSIS	1 (2)			1 (< 1)			
SUBCUTANEOUS ABSCESS	1 (2)			1 (< 1)			
TINEA CAPITIS	3 (5)			3 (3)			
TINEA INFECTION	11 (17)			16 (15)			
TINEA PEDIS	0			1 (< 1)			
TINEA VERSICOLOUR	3 (5)			3 (3)			
TONSILLITIS	5 (8)			7 (7)			
TONSILLITIS STREPTOCOCCAL	0			1 (< 1)			
UPPER RESPIRATORY TRACT INFECTION	5 (8)			5 (5)			
URINARY TRACT INFECTION	5 (8)			5 (5)			
VAGINAL CANDIDIASIS	1 (2)			2 (2)			
VAGINAL INFECTION	1 (2)			1 (< 1)			
VARICELLA	2 (3)			2 (2)			
VIRAL INFECTION	1 (2)			1 (< 1)			
VIRAL RASH	1 (2)			1 (< 1)			
VIRAL UPPER RESPIRATORY TRACT INFECTION	1 (2)			1 (< 1)			
VULVOVAGINITIS	0			1 (< 1)			
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	5 (8)			5 (5)			
ANKLE FRACTURE	1 (2)			1 (< 1)			
JOINT DISLOCATION	1 (2)			1 (< 1)			
JOINT INJURY	1 (2)			1 (< 1)			
MOUTH INJURY	1 (2)			1 (< 1)			
THERMAL BURN	1 (2)			1 (< 1)			
UPPER LIMB FRACTURE	1 (2)			1 (< 1)			
WRIST FRACTURE	2 (3)			2 (2)			
INVESTIGATIONS	0			1 (< 1)			

CARDIAC MURMUR	0	2)	1(< 1)
METABOLISM AND NUTRITION DISORDERS	2(3)	1(	2(
DEHYDRATION	1(2)	0	1(< 1)
FAILURE TO THRIVE	1(2)	0	1(< 1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2(3)	0	2(
COSTOCHONDRITIS	1(2)	0	1(< 1)
SCOLIOSIS	1(2)	0	1(< 1)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1(2)	2)	2(
SKIN PAPILLOMA	1(2)	1(2)	2(2)
NERVOUS SYSTEM DISORDERS	2(3)	1(	2(
EPILEPSY	1(2)	0	1(< 1)
NEUROPATHY PERIPHERAL	1(2)	0	1(< 1)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	1(2)	0	1(< 1)
PREGNANCY	1(2)	0	1(< 1)
PSYCHIATRIC DISORDERS	6(10)	0	5) 8(
ATTENTION DEFICIT/HYPERACTIVITY DISORDER	2(3)	2(2)	3(8)
DEPRESSION	1(2)	1(	1(3)
GENERALISED ANXIETY DISORDER	0	0 2)	1(< 1)
LEARNING DISORDER	3(5)	1(	3(
MAJOR DEPRESSION	1(2)	0	1(3)
RENAL AND URINARY DISORDERS	1(2)	0	1(< 1)
NEPHROLITHIASIS	1(2)	0	1(< 1)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1(2)	0	2) 2(
AMENORRHOEA	1(2)	1(2)	2(2)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	9(14)	1(4(10)	2) 13(13)
ASTHMA	6(10)	2)	7(
ASTHMA EXERCISE INDUCED	0	1(2)	1(7)
BRONCHIAL HYPERREACTIVITY	2(3)	1(5)	4(
INTERSTITIAL LUNG DISEASE	2(3)	2(	2(4)
PNEUMONITIS	0	0 2)	1(2)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	12(19)	1(7(17)	19(18)
ALOPECIA	3(5)		3(
ACNE DERMATITIS ALLERGIC	0	0 2)	1(3)
DERMATITIS ATOPIC	0	1(2)	1(< 1)
DERMATITIS PAPILLARIS CAPILLITII	1(2)	1(	1(< 1)
DRUG ERUPTION	1(2)	0	1(< 1)
ECZEMA	0	0 2)	1(< 1)
EOSINOPHILIC PUSTULAR FOLLICULITIS	4(6)	1(7)	7(
ERYTHEMA MULTIFORME	2(3)	3(	2(7)
	0	0 2)	1(2)
		1(	1(< 1)

KERATOSIS PILARIS	1(2)		1(< 1)
NEURODERMATITIS	0	0 2)	1(< 1)
PITYRIASIS ROSEA	1(2)	1(	1(< 1)
URTICARIA CHRONIC	0	0 2)	1(< 1)
		1(	
VASCULAR DISORDERS	1(2)		1(< 1)
VENOUS THROMBOSIS LIMB	1(2)	0	1(< 1)

========== Multiple MedDRA Versions

CLINICAL DEATH SUMMARIES

1) AI424020-450087

Clinical Summary: The subject initiated therapy with atazanavir 700 mg daily on [redacted] (Day 1). This dose was corrected to 600 mg daily on [redacted] (Day 19). On [redacted] (Day 112), a predose electrocardiogram (EKG) revealed sinus rhythm with an SAE of first degree atrioventricular block (PR interval 0.212 seconds, upper limit of normal range 0.20 seconds). This was judged by the investigator to be mild and related to the study medication. The subject was asymptomatic and had no history of cardiac conduction abnormalities. Study medication was discontinued on [redacted] (Day 112) due to the event. On [redacted] (Day 119), a repeat EKG revealed normal sinus rhythm with a PR interval of 0.172 seconds without any abnormalities. The subject was noted to have been non-compliant with treatment, with a CD4 cell count < 50 cells/mL for 2.5 years. He was discontinued from the study on [redacted] (Day 292). He died at an outlying hospital on [redacted] (Day 351), approximately 239 days after the last dose of study therapy due to acute respiratory distress syndrome and sepsis. The family refused post mortem examination.

2) AI424020-500311

Clinical Summary: The subject initiated therapy with atazanavir 800 mg daily on [redacted] (Day 1). She had a prior history of HIV cardiomyopathy. On [redacted] (Day 74), she experienced worsening cardiomyopathy. An echocardiogram on that date revealed dilated cardiomyopathy with increased left atrial and left ventricular enlargement and decreased left ventricular function. Mild tricuspid and trivial mitral regurgitation were observed with otherwise normal flows. Study medication was discontinued on that date due to cardiac abnormalities. On [redacted] (Day 76), she was evaluated by a cardiologist who diagnosed worsening HIV cardiomyopathy. No symptoms were reported. She was treated with digoxin, enalapril, and furosemide. On [redacted] (Day 85), 12 days after discontinuation of study medication, an SAE of cardiomyopathy was reported. This was judged by the investigator to be severe and related to the study medication. Study medication had already been discontinued. On [redacted] (Day 91), the patient began alternate antiretroviral therapy with lopinavir, ritonavir, stavudine, and lamivudine. She was hospitalized from [redacted] (Days 188 to 195) for esophageal candidiasis. On [redacted] (Day 196), she saw her primary care physician, and was referred to the emergency room due to decompensated congestive heart failure and mitral valve insufficiency with respiratory distress, ischemic distal extremities, and hypoxia. She was admitted to the pediatric intensive care unit. A chest x-ray indicated pericardial effusion, pulmonary edema and right middle lobe consolidation. She was also found to have thrombocytopenia and elevated liver enzymes (results not reported). She was treated with dobutamine, dopamine, digoxin, enalapril, furosemide, trimethoprim/sulfamethoxazole, ranitidine, magnesium carbonate, midazolam, and total parenteral nutrition. On [redacted] (Day 198), blood cultures were positive for Streptococcus pneumoniae, and amoxicillin and meropenem were added. Antiretroviral therapy was held on [redacted] (Day 198) due to elevated hepatic enzymes (results not reported). She experienced anemia and received packed red blood cell transfusions. Her clinical condition improved, and thrombocytopenia resolved on [redacted] (Day 204). On [redacted] (Day 205), lopinavir, ritonavir, stavudine, and lamivudine were restarted. On [redacted] (Day 206) she experienced fever and severe

respiratory distress with hypoxia. Pentamidine was administered for possible *Pneumocystis jiroveci* pneumonia (PCP). Her condition continued to deteriorate with worsening cardiac failure and pulmonary edema. She required ventilatory assistance, experienced bradycardia that did not respond to medication, and expired in cardiorespiratory arrest on [redacted] (Day 207). On that day, 134 days after discontinuation of study medication, an SAE of cardiomyopathy was reported again, judged by the investigator to be fatal and not related to the study medication. On [redacted] (Day 209), 136 days after discontinuation of study medication, an SAE of congestive heart failure was reported, judged by the investigator to be fatal and not related to the study medication. Death was attributed to congestive heart failure secondary to HIV cardiomyopathy. No autopsy was reported.

3)AI424020-800288 (<u>Not Part of Capsule Treatment Cohort</u>)
Clinical Summary
A 23 month old male with a complicated prior medical history of being a floppy infant, hypotonia, cerebral palsy and encephalitis, epilepsy with convulsion, pulmonary tuberculosis, lymphadenopathy, porphyria, hepatomegaly and splenomegaly, acrodermatitis and rash, cough, nasal congestion initiated therapy with atazanavir 150 mg daily on [redacted] (Day 1). On [redacted] (Day 98), the subject experienced SAE's of hemorrhagic pneumonia and acute renal failure. These were judged by the investigator to be fatal. The pneumonia was judged by the investigator to be unrelated to the study medication. The investigator was unable to judge the relationship of the renal failure to the study medication.

The subject presented to the hospital on [redacted] (Day 98) with a one-day history of fever, cough, and vomiting, and a one-hour history of persistent seizure. At admission, he was post-ictal, afebrile, tachycardic, and tachypneic with harsh breath sounds. Laboratory evaluation revealed decreased carbon dioxide (unspecified) and increased urea (6.2 mmol/l, normal range 1.1-4.3 mmol/l), creatinine (72 µmol/L, normal range 35-62 µmol/L), and valproic acid (773 µmol/l, normal range 350-700 µmol/L) levels. Therapy with sodium valproate was held and cefotaxime was initiated. Study medication was discontinued on [redacted] (Day 99) due to the events. On [redacted] (Day 99), he was clinically stable. Urea level was 11.0 mmol/L (normal range 1.1-4.3 mmol/L), creatinine was 50 µmol/L (normal range 35-62 µmol/L), and anion gap was 22 mmol/L (normal range 7-17 mmol/L). A cerebral spinal fluid sample from [redacted] (Day 98) revealed a very high neutrophil count of 51.8% (normal range 2-5.5%), without bacterial growth present. On [redacted] (Day 100), the patient's temperature spiked up to 39°C, urea was 17.1 mmol/l (normal range 1.1- 4.3 mmol/L), and creatinine was 85 µmol/L (normal range 35-62 µmol/L). Sodium valproate level had decreased to 231 µmol/l (normal range 350-700 µmol/L). From [redacted] (Day 99 to 100), the subject experienced medication error, as his mother accidentally administered stavudine, lamivudine and ritonavir twice daily instead of once daily. On [redacted] (Day 101), increased respiratory distress was noted, with bronchospasm and an oxygen saturation of 74% during administration on oxygen by nasal cannula. The patient was put in an "oxygen box," suctioned, and given

nebulizer treatment. One hour later, he was noted to be apneic and certified dead (2 days after discontinuation of study drug).

Post-mortem examination revealed diffuse, bilateral consolidation of both lungs with macroscopic features of hemorrhagic bronchopneumonia; microscopic examination revealed intra-alveolar hemorrhage, edema, and acute inflammation, with acute suppurative inflammation involving the bronchi and extensive lymphocytic infiltrate widening the septae. The findings were consistent with bronchopneumonia and superimposed lymphocytic interstitial pneumonia. A Ziehl-Neelsen stain was negative. The right kidney showed minimal dystrophic calcification and the left kidney showed no significant pathological changes. The skull and dura showed no significant pathological changes. There was frothy exudate involving the basal meninges and a ruptured porencephalic cyst. The cause of death was considered to be pneumonia and renal failure.

PANCREATITIS IN ATV ALONE PATIENT

Patient Identifier: AI424020-400-031

Event (MedDRA term): Pancreatitis **Study Day:** 78

Intensity: Very severe **Relationship:** Possible **Action Taken:** Drug was discontinued

Investigator Term (if different): **CARES ID #:** 10920098

Reason(s) for Narrative: *(check all that apply)* ☐ Death ☒ SAE ☒ AE leading to discontinuation ☐ Other event of clinical interest

Study Medication: Atazanavir capsule 520 mg/m^2 (Grp 4) & Stavudine capsule 80 mg & Didanosine tablet 400 mg

Medication Start Date:

Age: 15 **Gender:** Male **Race:** NA **Ethnicity:** Hispanic/Latino

General Medical History:

Sinusitis (30-Jan-1991), molluscum (21-Jan-2000), seizure (01-Apr-2001)

Test:	Baseline			At time of event		
	Study Day	Value (Absolute)	Value (%)	Study Day	Value (Absolute)	Value (%)
CD4 count:	1	173 cells/mL	4	78	342 cells/mL	11
HIV Viral load:	1	1,099144 copies/mL	--	78	459	--

Concomitant Medication(s):

Pentamidine (26-Jan-2001-C)	Gabapentin (02-Apr-2001-C)	Azithromycin (Day 4-8, 13-18)
Multivitamin w/minerals (Day 22-47)	Beclomethasone (Day 24-Day 176)	Cetirizine (Day 63-C)
Benzoyl peroxide (UNK-C)	Ranitidine (UNK-Day 104)	Cimetidine (UNK-Day 176)
Levetiracetam (UNK-C)	Triamcinolone topical (UNK-C)	Tenofovir ((UNK- Day 177)
Efavirenz (UNK- Day 177)	Lopinavir/ritonavir (UNK- Day 177)	

Prior Antiretroviral Therapy:

Zidovudine (01-Dec-1989 - 10-Nov-1994)	Zalcitabine (10-May-1993 - 02-Nov-1994)
Didanosine/nevirapine (11-Nov-1994-07 - Aug-1996)	Lamivudine/stavudine (07-Aug-1996 - 24-Apr-1997)
Lamivudine/zidovudine (24-Apr-1997 - 16-Jul-1999)	Ritonavir (24-Apr-1997 - 25-Jul-1997)
Nelfinavir (25-Jul-1997 - 16-Jul-1999)	Ritonavir/saquinavir/stavudine (16-Jul-1999 - 22-Sep-2000)

Other Post Randomization Adverse Events (day of onset): Eye twitching (Day 47), abdominal pain (Day 79, 102, 177), fatigue (Day 147), seizure (Day 161), headache (Day 166, 177), diarrhea and nausea (Day 177)

Clinical Summary: The subject initiated therapy with atazanavir 600 mg daily on (Day 1). On (Day 25), the dose of atazanavir was increased 800 mg daily due to a PK adjustment. On (Day 77), the subject developed nausea and vomiting after taking his study medications on an empty stomach. On (Day 78), he was seen for a routine study visit. That morning he had vomited again after taking his study medications on an empty stomach, and also complained of mild right-sided abdominal pain, which was attributed to a muscle strain from vomiting. That same day, lipase was found to be elevated at 235 U/L (normal range 0-60 U/L, prior value 48 U/L on 22-Sep-2000), consistent with an SAE of pancreatitis. Amylase, SGOT and SGPT were normal. This was judged by the investigator to be very severe and possibly related to the study medication. On (Day 79), the subject presented to the Emergency Room complaining of severe abd and vomiting, and was

admitted to the hospital for pain control for presumed clinical pancreatitis. Laboratory tests obtained on admission showed an elevated lipase of 1393 U/L (normal range 0-60 U/L), and an elevated amylase of393 U/L (normal range 19-176 IU/L, prior value 106 on 16-Jul-2001). Subject was hospitalized with a diagnosis of clinical pancreatitis. Study medications were discontinued on [redacted] (Day 79) due to the event. Concomitant medications included cetirizine and gabapentin. The subject received unspecified treatment and his condition improved. Date of hospital discharge is unknown. The event was reported resolved on [redacted] (Day 134), 55 days after onset. The subject again experienced abdominal pain on [redacted] (Day 102) which was resolved on [redacted] (Day 134). He experienced fatigu [redacted] (Day 147 to 149), pancreatitis from [redacted] (Day 153 to 158), seizure on [redacted] (Day 161), and headache from [redacted] (Day 166 to 172). The ported to have taken alternate an ritonavir, lopinavir, efavirenz, and tenofovir from an unknown date until [redacted] (Day 177). From [redacted] (Day 177 to 178), he experienced ab , nausea, diarrhea. He also experienced headache from [redacted] (Day 177 to 194). He was discontinued from the study on [redacted] (Day 274) due to completion of the protocol-defined period of study evaluation.
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/s/

Alan Shapiro
4/28/2008 06:58:10 PM
MEDICAL OFFICER

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