CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 021567/S-019

Trade Name: **REYATAZ**

Generic Name: **Atazanavir Sulfate**

Sponsor: **Bristol-Myers Squibb Company**

Approval Date: 11/05/2009

Indications: REYATAZ is a protease inhibitor indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection.

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021567/S-019 **SUPPLEMENT APPROVAL**

Bristol-Myers Squibb Company
Attention: Lisa Percival, Associate Director
5 Research Parkway
Signature 91 Bldg.-3SIG-515
Wallingford, CT 06492

Dear Ms. Percival:

Please refer to your supplemental new drug application dated January 5, 2009, received January 5, 2009, submitted under section 505(b) of the Federal, Food, Drug, and Cosmetic Act (FDCA) for REYATAZ® (atazanavir sulfate) 100mg, 150 mg, 200 mg, and 300 mg capsules.

We acknowledge receipt of your submissions dated September 9, 2009, September 28, 2009, November 2, 2009, and November 4, 2009.

This supplemental new drug application updates the package insert with the 96 week results from the antiretroviral treatment-naive adult Study AI424-138.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. that is identical to enclosed labeling (text for the package insert, text for the patient package insert). For administrative purposes, please designate this submission, "SPL for approved NDA 021567/S-019".

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
5600 Fishers Lane, Room 12B05
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Sherly Abraham, R.Ph., Regulatory Project Manager, at (301)796-3198 or 301-796-1500.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosures

Package Insert
Patient Package Insert

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21567	SUPPL-19	BRISTOL MYERS SQUIBB CO	REYATAZ (ATAZANAVIR SULFATE)

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

/s/

SHERLY ABRAHAM
11/05/2009

JEFFREY S MURRAY
11/05/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021567/S-019

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use REYATAZ safely and effectively. See full prescribing information for REYATAZ.

REYATAZ® (atazanavir sulfate) Capsules
Initial U.S. Approval: 2003

----------RECENT MAJOR CHANGES----------
Indications and Usage (1) 11/2009

----------INDICATIONS AND USAGE----------
REYATAZ is a protease inhibitor indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection. (1)

----------DOSAGE AND ADMINISTRATION----------
- *Treatment-naive patients* REYATAZ 300 mg with ritonavir 100 mg once daily with food or REYATAZ 400 mg once daily with food. When coadministered with tenofovir, the recommended dose is REYATAZ 300 mg with ritonavir 100 mg. (2.1)
- *Treatment-experienced patients* REYATAZ 300 mg with ritonavir 100 mg once daily with food. (2.1)
- *Pediatric patients (6 to less than 18 years of age)* Dosage is based on body weight not to exceed the adult dose. (2.2)
- *Concomitant therapy* Dosing modifications may be required. (2.1, 7)
- *Renal impairment* Dosing modifications may be required. (2.3)
- *Hepatic impairment* Dosing modifications may be required. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------
- Capsules: 100 mg, 150 mg, 200 mg, 300 mg. (3, 16)

----------CONTRAINDICATIONS----------
- REYATAZ is contraindicated in patients with previously demonstrated hypersensitivity (eg, Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components of this product. (4)
- Coadministration with triazolam, orally administered midazolam, ergot derivatives, rifampin, irinotecan, lovastatin, simvastatin, indinavir, cisapride, pimozide, and St. John's wort. (4)

----------WARNINGS AND PRECAUTIONS----------
- *Cardiac conduction abnormalities* PR interval prolongation may occur in some patients. Use with caution in patients with preexisting conduction system disease or when administered with other drugs that may prolong the PR interval. (5.2, 6.4, 7.3, 12.2, 17.3)
- *Rash* Discontinue if severe rash develops. (5.3, 6.4, 17.4)
- *Hyperbilirubinemia* Most patients experience asymptomatic increases in indirect bilirubin, which is reversible upon discontinuation. Do not dose reduce. If a concomitant transaminase increase occurs, evaluate for alternative etiologies. (5.4, 6.2)
- *Hepatotoxicity* Patients with hepatitis B or C are at risk of increased transaminases or hepatic decompensation. Monitor liver function tests prior to therapy and during treatment. (2.4, 5.5, 6.3, 6.4, 8.8)
- *Nephrolithiasis* has been reported. Consider temporary interruption or discontinuation. (5.6, 6.4)
- Patients receiving REYATAZ may develop new onset or exacerbations of diabetes mellitus/hyperglycemia (5.7, 6.4), immune reconstitution syndrome (5.8), and redistribution/accumulation of body fat. (5.9)
- *Hemophilia* Spontaneous bleeding may occur and additional factor VIII may be required. (5.10)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥2%) are nausea, jaundice/scleral icterus, rash, headache, abdominal pain, vomiting, insomnia, peripheral neurologic symptoms, dizziness, myalgia, diarrhea, depression, and fever. (6.1, 6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------
Coadministration of REYATAZ can alter the concentration of other drugs and other drugs may alter the concentration of atazanavir. The potential drug-drug interactions must be considered prior to and during therapy. (4, 5.1, 7, 12.3)

----------USE IN SPECIFIC POPULATIONS----------
- *Pregnancy* Use only if the potential benefit justifies the potential risk to the fetus. Physicians are encouraged to register patients in the Antiretroviral Pregnancy Registry by calling 1-800-258-4263. (8.1)
- *Nursing mothers* should be instructed not to breast-feed due to the potential for postnatal HIV transmission. (8.3)
- *Hepatitis B or C co-infection* Monitor liver enzymes. (5.5, 6.3)
- *Renal impairment* Do not use in treatment-experienced patients with end stage renal disease managed with hemodialysis. (2.3, 8.7)
- *Hepatic impairment* Do not use REYATAZ in patients with severe hepatic impairment. REYATAZ/ritonavir is not recommended. (2.4, 8.8)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 11/2009

FULL PRESCRIBING INFORMATION: CONTENTS*

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

REYATAZ® (atazanavir sulfate) is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. This indication is based on analyses of plasma HIV-1 RNA levels and CD4+ cell counts from controlled studies of 96 weeks duration in antiretroviral-naive and 48 weeks duration in antiretroviral-treatment-experienced adult and pediatric patients at least 6 years of age.

The following points should be considered when initiating therapy with REYATAZ:

- In Study AI424-045 REYATAZ/ritonavir and lopinavir/ritonavir were similar for the primary efficacy outcome measure of time-averaged difference in change from baseline in HIV RNA level. This study was not large enough to reach a definitive conclusion that REYATAZ/ritonavir and lopinavir/ritonavir are equivalent on the secondary efficacy outcome measure of proportions below the HIV RNA lower limit of detection [see *Clinical Studies (14.2)*].

- The number of baseline primary protease inhibitor mutations affects the virologic response to REYATAZ/ritonavir [see *Clinical Pharmacology (12.4)*].

2 DOSAGE AND ADMINISTRATION

General Dosing Recommendations:

- REYATAZ Capsules must be taken with food.
- The recommended oral dosage of REYATAZ depends on the treatment history of the patient and the use of other coadministered drugs. When coadministered with H_2-receptor antagonists or proton-pump inhibitors, dose separation may be required [see *Dosage and Administration (2.1)*].
- When coadministered with didanosine buffered or enteric-coated formulations, REYATAZ should be given (with food) 2 hours before or 1 hour after didanosine.
- REYATAZ without ritonavir is not recommended for treatment-experienced patients with prior virologic failure [see *Clinical Studies (14)*].

- Efficacy and safety of REYATAZ with ritonavir in doses greater than 100 mg once daily have not been established. The use of higher ritonavir doses might alter the safety profile of atazanavir (cardiac effects, hyperbilirubinemia) and, therefore, is not recommended. Prescribers should consult the complete prescribing information for NORVIR® (ritonavir) when using this agent.

2.1 Recommended Adult Dosage

Dose Recommendations for Therapy-Naive Patients

- For treatment-naive patients, the recommended dosage is REYATAZ 300 mg with ritonavir 100 mg once daily (all as a single dose with food).

OR

- For treatment-naive patients who are unable to tolerate ritonavir, the recommended dosage is REYATAZ 400 mg (without ritonavir) once daily taken with food.

Concomitant Therapy:

- REYATAZ 300 mg with ritonavir 100 mg once daily (all as a single dose with food) if combined with any of the following:
  - tenofovir
  - H_2-receptor antagonist: The H_2-receptor antagonist dose should not exceed a dose comparable to famotidine 40 mg twice daily. REYATAZ 300 mg and ritonavir 100 mg should be administered simultaneously with, and/or at least 10 hours after, the dose of the H_2-receptor antagonist. For patients unable to tolerate ritonavir, REYATAZ 400 mg once daily with food should be administered at least 2 hours before and at least 10 hours after the H_2-receptor antagonist. For these patients, no single dose of the H_2-receptor antagonist should exceed a dose comparable to famotidine 20 mg, and the total daily dose should not exceed a dose comparable to famotidine 40 mg.
  - proton-pump inhibitors: The proton-pump inhibitor dose should not exceed a dose comparable to omeprazole 20 mg and must be taken approximately 12 hours prior to the REYATAZ 300 mg and ritonavir 100 mg dose.
  - If REYATAZ is combined with efavirenz, REYATAZ 400 mg (two 200-mg capsules) with ritonavir 100 mg should be administered once daily all as a single dose

with food, and efavirenz should be administered on an empty stomach, preferably at bedtime.

Dose Recommendations for Therapy-Experienced Patients

REYATAZ 300 mg with ritonavir 100 mg once daily (all as a single dose with food).

Concomitant Therapy:

- Whenever an H_2-receptor antagonist is given to a patient receiving REYATAZ with ritonavir, the H_2-receptor antagonist dose should not exceed a dose comparable to famotidine 20 mg twice daily, and the REYATAZ and ritonavir doses should be administered simultaneously with, and/or at least 10 hours after, the dose of the H_2-receptor antagonist.
    - REYATAZ 300 mg with ritonavir 100 mg once daily (all as a single dose with food) if taken with an H_2-receptor antagonist.
    - REYATAZ 400 mg (two 200-mg capsules) with ritonavir 100 mg once daily (all as a single dose with food) if taken with both tenofovir and an H_2-receptor antagonist.
- Proton-pump inhibitors should not be used in treatment-experienced patients receiving REYATAZ.
- Efavirenz: Do not coadminister REYATAZ with efavirenz in treatment-experienced patients due to decreased atazanavir exposure.

[For these drugs and other antiretroviral agents for which dosing modification may be appropriate, see *Drug Interactions (7)*.]

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)
15 to less than 25	33 to less than 55	150	80[c]
25 to less than 32	55 to less than 70	200	100[d]
32 to less than 39	70 to less than 86	250	100[d]
at least 39	at least 86	300	100[d]

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

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

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

[c] Ritonavir liquid.

[d] Ritonavir capsule or liquid.

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)
25 to less than 32	55 to less than 70	200	100[c]
32 to less than 39	70 to less than 86	250	100[c]
at least 39	at least 86	300	100[c]

[a] The recommended dosage of REYATAZ can be achieved using a combination of commercially

available capsule strengths.

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

[c] Ritonavir capsule or liquid.

2.3 Renal Impairment

For patients with renal impairment, including those with severe renal impairment who are not managed with hemodialysis, no dose adjustment is required for REYATAZ. Treatment-naive patients with end stage renal disease managed with hemodialysis should receive REYATAZ 300 mg with ritonavir 100 mg. REYATAZ should not be administered to HIV-treatment-experienced patients with end stage renal disease managed with hemodialysis. [See *Use in Specific Populations (8.7)*.]

2.4 Hepatic Impairment

REYATAZ should be used with caution in patients with mild-to-moderate hepatic impairment. For patients with moderate hepatic impairment (Child-Pugh Class B) who have not experienced prior virologic failure, a dose reduction to 300 mg once daily should be considered. REYATAZ should not be used in patients with severe hepatic impairment (Child-Pugh Class C). REYATAZ/ritonavir has not been studied in subjects with hepatic impairment and is not recommended. [See *Warnings and Precautions (5.5)* and *Use in Specific Populations (8.8)*.]

3 DOSAGE FORMS AND STRENGTHS

- 100 mg capsule with blue cap and white body, printed with white ink “BMS 100 mg” on the cap and with blue ink “3623” on the body.
- 150 mg capsule with blue cap and powder blue body, printed with white ink “BMS 150 mg” on the cap and with blue ink “3624” on the body.
- 200 mg capsule with blue cap and blue body, printed with white ink “BMS 200 mg” on the cap and with white ink “3631” on the body.
- 300 mg capsule with red cap and blue body, printed with white ink “BMS 300 mg” on the cap and with white ink “3622” on the body.

4 CONTRAINDICATIONS

REYATAZ (atazanavir sulfate) is contraindicated:

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

- when coadministered with drugs that are highly dependent on CYP3A or UGT1A1 for clearance, and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These and other contraindicated drugs are listed in Table 3.

Table 3: Drugs That Are Contraindicated with REYATAZ

Drug class	Drugs within class that are contraindicated with REYATAZ	Clinical Comment
Antimycobacterials	Rifampin	Rifampin substantially decreases plasma concentrations of atazanavir, which may result in loss of therapeutic effect and development of resistance.
Antineoplastics	Irinotecan	Atazanavir inhibits UGT1A1 and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities.
Benzodiazepines	Triazolam, orally administered midazolam[a]	Triazolam and orally administered midazolam are extensively metabolized by CYP3A4. Coadministration of triazolam or orally administered midazolam with REYATAZ may cause large increases in the concentration of these benzodiazepines. Potential for serious and/or life-threatening events such as prolonged or increased sedation or respiratory depression.
Ergot Derivatives	Dihydroergotamine, ergotamine, ergonovine, methylergonovine	Potential for serious and/or life-threatening events such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI Motility Agent	Cisapride	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products	St. John's wort (*Hypericum perforatum*)	Patients taking REYATAZ should not use products containing St. John's wort because coadministration may be expected to reduce plasma concentrations of atazanavir. This may result in loss of therapeutic effect and development of resistance.
HMG-CoA Reductase Inhibitors	Lovastatin, simvastatin	Potential for serious reactions such as myopathy including rhabdomyolysis.
Neuroleptic	Pimozide	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Protease Inhibitors	Indinavir	Both REYATAZ and indinavir are associated with indirect (unconjugated) hyperbilirubinemia.

[a] See *Drug Interactions, Table 13 (7)* for parenterally administered midazolam.

5 WARNINGS AND PRECAUTIONS

5.1 Drug Interactions

See Table 3 for a listing of drugs that are contraindicated for use with REYATAZ due to potentially life-threatening adverse events, significant drug interactions, or loss of virologic activity. [See *Contraindications (4).*] Please refer to Table 13 for established and other potentially significant drug interactions [see *Drug Interactions (7.3)*].

5.2 Cardiac Conduction Abnormalities

Atazanavir has been shown to prolong the PR interval of the electrocardiogram in some 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 [see *Adverse Reactions (6.4)* and *Overdosage (10)*]. In clinical trials that included electrocardiograms, 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 patients and 5% (6/116) of lopinavir/ritonavir-treated patients who had on-study electrocardiogram measurements. Because of limited clinical experience in patients with preexisting conduction system disease (eg, marked first-degree AV block or second- or third-degree AV block), atazanavir should be used with caution in these patients. [See *Clinical Pharmacology (12.2)*.]

Atazanavir in combination with diltiazem increased diltiazem plasma concentration by 2-fold with an additive effect on the PR interval. When used in combination with atazanavir, a dose reduction of diltiazem by one half should be considered and ECG monitoring is recommended. 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. [See *Drug Interactions (7)* and *Clinical Pharmacology (12.2)*.] Pharmacokinetic studies between atazanavir and other drugs that prolong the PR interval including beta blockers [other than atenolol, see *Drug Interactions (7)*], 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 (eg, verapamil).

5.3 Rash

In controlled clinical trials, rash (all grades, regardless of causality) occurred in approximately 20% of patients treated with REYATAZ. The median time to onset of rash in clinical studies was 7.3 weeks and the median duration of rash was 1.4 weeks. Rashes were generally mild-to-moderate maculopapular skin eruptions. Treatment-emergent adverse reactions of moderate or severe rash (occurring at a rate of ≥2%) are presented for the individual clinical studies [see *Adverse Reactions (6.1)*]. Dosing with REYATAZ was often continued without interruption in patients who developed rash. The discontinuation rate for rash in clinical trials was <1%. 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).*]

5.4 Hyperbilirubinemia

Most patients taking REYATAZ experience asymptomatic elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl transferase (UGT). This hyperbilirubinemia is reversible upon discontinuation of REYATAZ. Hepatic transaminase elevations that occur with hyperbilirubinemia should be evaluated for alternative etiologies. No long-term safety data are available for patients experiencing persistent elevations in total bilirubin >5 times ULN. Alternative antiretroviral therapy to REYATAZ may be considered if jaundice or scleral icterus associated with bilirubin elevations presents cosmetic concerns for patients. Dose reduction of atazanavir is not recommended since long-term efficacy of reduced doses has not been established. [See *Adverse Reactions (6.1, 6.2).*]

5.5 Hepatotoxicity

Caution should be exercised when administering REYATAZ to patients with hepatic impairment because atazanavir concentrations may be increased. [See *Dosage and Administration (2.4).*] Patients with underlying hepatitis B or C viral infections or marked elevations in transaminases before treatment may be at increased risk for developing further transaminase elevations or hepatic decompensation. In these patients, appropriate laboratory testing should be conducted prior to initiating therapy with REYATAZ and these patients should be monitored during treatment. [See *Adverse Reactions (6.3)* and *Use in Specific Populations (8.8).*]

5.6 Nephrolithiasis

Cases of nephrolithiasis were reported during postmarketing surveillance in HIV-infected patients receiving REYATAZ therapy. Because these events were reported voluntarily during clinical practice, estimates of frequency cannot be made. If signs or symptoms of nephrolithiasis occur, temporary interruption or discontinuation of therapy may be considered. [See *Adverse Reactions (6.4).*]

5.7 Diabetes Mellitus/Hyperglycemia

New-onset diabetes mellitus, exacerbation of preexisting diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established. [See *Adverse Reactions (6.4).*]

5.8 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including REYATAZ. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jiroveci* pneumonia, or tuberculosis), which may necessitate further evaluation and treatment.

5.9 Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and “cushingoid appearance” have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

5.10 Hemophilia

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia type A and B treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship between protease inhibitor therapy and these events has not been established.

5.11 Resistance/Cross-Resistance

Various degrees of cross-resistance among protease inhibitors have been observed. Resistance to atazanavir may not preclude the subsequent use of other protease inhibitors. [See *Clinical Pharmacology (12.4)*.]

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- cardiac conduction abnormalities [see *Warnings and Precautions (5.2)*]
- rash [see *Warnings and Precautions (5.3)*]
- hyperbilirubinemia [see *Warnings and Precautions (5.4)*]
- nephrolithiasis [see *Warnings and Precautions (5.6)*]

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trial Experience in Adults

Treatment-Emergent Adverse Reactions in Treatment-Naive Patients

The safety profile of REYATAZ in treatment-naive adults is based on 1625 HIV-1 infected patients in clinical trials. 536 patients received REYATAZ 300 mg with ritonavir 100 mg and 1089 patients received REYATAZ 400 mg or higher (without ritonavir).

The most common adverse reactions are nausea, jaundice/scleral icterus, and rash.

Selected clinical adverse reactions of moderate or severe intensity reported in ≥2% of treatment-naive patients receiving combination therapy including REYATAZ 300 mg with ritonavir 100 mg and REYATAZ 400 mg (without ritonavir) are presented in Tables 4 and 5, respectively.

Table 4: Selected Treatment-Emergent Adverse Reactions[a] of Moderate or Severe Intensity Reported in ≥2% of Adult Treatment-Naive Patients,[b] Study AI424-138

	96 weeks[c] REYATAZ 300 mg with ritonavir 100 mg (once daily) and tenofovir with emtricitabine[d] (n=441)	96 weeks[c] lopinavir 400 mg with ritonavir 100 mg (twice daily) and tenofovir with emtricitabine[d] (n=437)
Digestive System		
Nausea	4%	8%
Jaundice/scleral icterus	5%	*
Diarrhea	2%	12%
Skin and Appendages		
Rash	3%	2%

* None reported in this treatment arm.

[a] Includes events of possible, probable, certain, or unknown relationship to treatment regimen.

[b] Based on the regimen containing REYATAZ.

[c] Median time on therapy.

[d] As a fixed-dose combination: 300 mg tenofovir, 200 mg emtricitabine once daily.

Table 5: Selected Treatment-Emergent Adverse Reactions[a] of Moderate or Severe Intensity Reported in ≥2% of Adult Treatment-Naive Patients,[b] Studies AI424-034, AI424-007, and AI424-008

	Study AI424-034		Studies AI424-007, -008	
	64 weeks[c] REYATAZ 400 mg once daily + lamivudine + zidovudine[e] (n=404)	64 weeks[c] efavirenz 600 mg once daily + lamivudine + zidovudine[e] (n=401)	120 weeks[c,d] REYATAZ 400 mg once daily + stavudine + lamivudine or didanosine (n=279)	73 weeks[c,d] nelfinavir 750 mg TID or 1250 mg BID + stavudine + lamivudine or didanosine (n=191)
Body as a Whole				
Headache	6%	6%	1%	2%
Digestive System				
Nausea	14%	12%	6%	4%
Jaundice/scleral icterus	7%	*	7%	*
Vomiting	4%	7%	3%	3%
Abdominal pain	4%	4%	4%	2%
Diarrhea	1%	2%	3%	16%
Nervous System				
Insomnia	3%	3%	<1%	*
Dizziness	2%	7%	<1%	*
Peripheral neurologic symptoms	<1%	1%	4%	3%
Skin and Appendages				
Rash	7%	10%	5%	1%

* None reported in this treatment arm.

[a] Includes events of possible, probable, certain, or unknown relationship to treatment regimen.

[b] Based on regimens containing REYATAZ.

[c] Median time on therapy.

[d] Includes long-term follow-up.

[e] As a fixed-dose combination: 150 mg lamivudine, 300 mg zidovudine twice daily.

Treatment-Emergent Adverse Reactions in Treatment-Experienced Patients

The safety profile of REYATAZ in treatment-experienced adults is based on 119 HIV-1 infected patients in clinical trials.

The most common adverse reactions are jaundice/scleral icterus and myalgia.

Selected clinical adverse reactions of moderate or severe intensity reported in ≥2% of treatment-experienced patients receiving REYATAZ/ritonavir are presented in Table 6.

Table 6: Selected Treatment-Emergent Adverse Reactions[a] of Moderate or Severe Intensity Reported in ≥2% of Adult Treatment-Experienced Patients,[b] Study AI424-045

	48 weeks[c] REYATAZ/ritonavir 300/100 mg once daily + tenofovir + NRTI (n=119)	48 weeks[c] lopinavir/ritonavir 400/100 mg twice daily[d] + tenofovir + NRTI (n=118)
Body as a Whole		
Fever	2%	*
Digestive System		
Jaundice/scleral icterus	9%	*
Diarrhea	3%	11%
Nausea	3%	2%
Nervous System		
Depression	2%	<1%
Musculoskeletal System		
Myalgia	4%	*

* None reported in this treatment arm.

a Includes events of possible, probable, certain, or unknown relationship to treatment regimen.

b Based on the regimen containing REYATAZ.

c Median time on therapy.

d As a fixed-dose combination.

Laboratory Abnormalities in Treatment-Naive Patients

The percentages of adult treatment-naive patients treated with combination therapy including REYATAZ (atazanavir sulfate) 300 mg with ritonavir 100 mg and REYATAZ 400 mg (without ritonavir) with Grade 3–4 laboratory abnormalities are presented in Tables 7 and 8, respectively.

Table 7: Grade 3–4 Laboratory Abnormalities Reported in ≥2% of Adult Treatment-Naive Patients,[a] Study AI424-138

Variable	Limit[c]	96 weeks[b] REYATAZ 300 mg with ritonavir 100 mg (once daily) and tenofovir with emtricitabine[d] (n=441)	96 weeks[b] lopinavir 400 mg with ritonavir 100 mg (twice daily) and tenofovir with emtricitabine[d] (n=437)
Chemistry	High		
SGOT/AST	≥5.1 x ULN	3%	1%
SGPT/ALT	≥5.1 x ULN	3%	2%
Total Bilirubin	≥2.6 x ULN	44%	<1%
Lipase	≥2.1 x ULN	2%	2%
Creatine Kinase	≥5.1 x ULN	8%	7%
Total Cholesterol	≥240 mg/dL	11%	25%
Hematology	Low		
Neutrophils	<750 cells/mm^3	5%	2%

[a] Based on the regimen containing REYATAZ.

[b] Median time on therapy.

[c] ULN = upper limit of normal.

[d] As a fixed-dose combination: 300 mg tenofovir, 200 mg emtricitabine once daily.

Table 8: Grade 3–4 Laboratory Abnormalities Reported in ≥2% of Adult Treatment-Naive Patients,[a] Studies AI424-034, AI424-007, and AI424-008

		Study AI424-034		Studies AI424-007, -008	
		64 weeks[b] REYATAZ 400 mg once daily + lamivudine + zidovudine[e]	64 weeks[b] efavirenz 600 mg once daily + lamivudine + zidovudine[e]	120 weeks[b,c] REYATAZ 400 mg once daily + stavudine + lamivudine or + stavudine + didanosine	73 weeks[b,c] nelfinavir 750 mg TID or 1250 mg BID + stavudine + lamivudine or + stavudine + didanosine
Variable	**Limit[d]**	**(n=404)**	**(n=401)**	**(n=279)**	**(n=191)**
Chemistry	High				
SGOT/AST	≥5.1 x ULN	2%	2%	7%	5%
SGPT/ALT	≥5.1 x ULN	4%	3%	9%	7%
Total Bilirubin	≥2.6 x ULN	35%	<1%	47%	3%
Amylase	≥2.1 x ULN	*	*	14%	10%
Lipase	≥2.1 x ULN	<1%	1%	4%	5%
Creatine Kinase	≥5.1 x ULN	6%	6%	11%	9%
Total Cholesterol	≥240 mg/dL	6%	24%	19%	48%
Triglycerides	≥751 mg/dL	<1%	3%	4%	2%
Hematology	Low				
Hemoglobin	<8.0 g/dL	5%	3%	<1%	4%
Neutrophils	<750 cells/mm^3	7%	9%	3%	7%

* None reported in this treatment arm.

[a] Based on regimen(s) containing REYATAZ.

[b] Median time on therapy.

[c] Includes long-term follow-up.

[d] ULN = upper limit of normal.

[e] As a fixed-dose combination: 150 mg lamivudine, 300 mg zidovudine twice daily.

Laboratory Abnormalities in Treatment-Experienced Patients

The percentages of adult treatment-experienced patients treated with combination therapy including REYATAZ/ritonavir with Grade 3–4 laboratory abnormalities are presented in Table 9.

Table 9: Grade 3–4 Laboratory Abnormalities Reported in ≥2% of Adult Treatment-Experienced Patients, Study AI424-045[a]

Variable	Limit[c]	48 weeks[b] REYATAZ/ritonavir 300/100 mg once daily + tenofovir + NRTI (n=119)	48 weeks[b] lopinavir/ritonavir 400/100 mg twice daily[d] + tenofovir + NRTI (n=118)
Chemistry	High		
SGOT/AST	≥5.1 x ULN	3%	3%
SGPT/ALT	≥5.1 x ULN	4%	3%
Total Bilirubin	≥2.6 x ULN	49%	<1%
Lipase	≥2.1 x ULN	5%	6%
Creatine Kinase	≥5.1 x ULN	8%	8%
Total Cholesterol	≥240 mg/dL	25%	26%
Triglycerides	≥751 mg/dL	8%	12%
Glucose	≥251 mg/dL	5%	<1%
Hematology	Low		
Platelets	<50,000 cells/mm^3	2%	3%
Neutrophils	<750 cells/mm^3	7%	8%

[a] Based on regimen(s) containing REYATAZ.
[b] Median time on therapy.
[c] ULN = upper limit of normal.
[d] As a fixed-dose combination.

Lipids, Change from Baseline in Treatment-Naive Patients

For Study AI424-138 and Study AI424-034, changes from baseline in LDL-cholesterol, HDL-cholesterol, total cholesterol, and triglycerides are shown in Tables 10 and 11, respectively.

Table 10: Lipid Values, Mean Change from Baseline, Study AI424-138

	REYATAZ/ritonavir[a,b]					lopinavir/ritonavir[b,c]				
	Baseline	Week 48		Week 96		Baseline	Week 48		Week 96	
	mg/dL (n=428[e])	mg/dL (n=372[e])	Change[d] (n=372[e])	mg/dL (n=342[e])	Change[d] (n=342[e])	mg/dL (n=424[e])	mg/dL (n=335[e])	Change[d] (n=335[e])	mg/dL (n=291[e])	Change[d] (n=291[e])
LDL-Cholesterol[f]	92	105	+14%	105	+14%	93	111	+19%	110	+17%
HDL-Cholesterol[f]	37	46	+29%	44	+21%	36	48	+37%	46	+29%
Total Cholesterol[f]	149	169	+13%	169	+13%	150	187	+25%	186	+25%
Triglycerides[f]	126	145	+15%	140	+13%	129	194	+52%	184	+50%

a REYATAZ 300 mg with ritonavir 100 mg once daily with the fixed-dose combination: 300 mg tenofovir, 200 mg emtricitabine once daily.

b Values obtained after initiation of serum lipid-reducing agents were not included in these analyses. At baseline, serum lipid-reducing agents were used in 1% in the lopinavir/ritonavir treatment arm and 1% in the REYATAZ/ritonavir arm. Through Week 48, serum lipid-reducing agents were used in 8% in the lopinavir/ritonavir treatment arm and 2% in the REYATAZ/ritonavir arm. Through Week 96, serum lipid-reducing agents were used in 10% in the lopinavir/ritonavir treatment arm and 3% in the REYATAZ/ritonavir arm.

c Lopinavir 400 mg with ritonavir 100 mg twice daily with the fixed-dose combination 300 mg tenofovir, 200 mg emtricitabine once daily.

d The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 48 or Week 96 values and is not a simple difference of the baseline and Week 48 or Week 96 mean values, respectively.

e Number of patients with LDL-cholesterol measured.

f Fasting.

Table 11: Lipid Values, Mean Change from Baseline, Study AI424-034

	REYATAZ[a,b]			efavirenz[b,c]		
	Baseline mg/dL (n=383[e])	Week 48 mg/dL (n=283[e])	Week 48 Change[d] (n=272[e])	Baseline mg/dL (n=378[e])	Week 48 mg/dL (n=264[e])	Week 48 Change[d] (n=253[e])
LDL-Cholesterol[f]	98	98	+1%	98	114	+18%
HDL-Cholesterol	39	43	+13%	38	46	+24%
Total Cholesterol	164	168	+2%	162	195	+21%
Triglycerides[f]	138	124	-9%	129	168	+23%

[a] REYATAZ 400 mg once daily with the fixed-dose combination: 150 mg lamivudine, 300 mg zidovudine twice daily.

[b] Values obtained after initiation of serum lipid-reducing agents were not included in these analyses. At baseline, serum lipid-reducing agents were used in 0% in the efavirenz treatment arm and <1% in the REYATAZ arm. Through Week 48 serum lipid-reducing agents were used in 3% in the efavirenz treatment arm and 1% in the REYATAZ arm.

[c] Efavirenz 600 mg once daily with the fixed-dose combination: 150 mg lamivudine, 300 mg zidovudine twice daily.

[d] The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 48 values and is not a simple difference of the baseline and Week 48 mean values.

[e] Number of patients with LDL-cholesterol measured.

[f] Fasting.

Lipids, Change from Baseline in Treatment-Experienced Patients

For Study AI424-045, changes from baseline in LDL-cholesterol, HDL-cholesterol, total cholesterol, and triglycerides are shown in Table 12. The observed magnitude of dyslipidemia was less with REYATAZ/ritonavir than with lopinavir/ritonavir. However, the clinical impact of such findings has not been demonstrated.

Table 12: Lipid Values, Mean Change from Baseline, Study AI424-045

	REYATAZ/ritonavir[a,b]			lopinavir/ritonavir[b,c]		
	Baseline mg/dL (n=111[e])	Week 48 mg/dL (n=75[e])	Week 48 Change[d] (n=74[e])	Baseline mg/dL (n=108[e])	Week 48 mg/dL (n=76[e])	Week 48 Change[d] (n=73[e])
LDL-Cholesterol[f]	108	98	−10%	104	103	+1%
HDL-Cholesterol	40	39	−7%	39	41	+2%
Total Cholesterol	188	170	−8%	181	187	+6%
Triglycerides[f]	215	161	−4%	196	224	+30%

[a] REYATAZ 300 mg once daily + ritonavir + tenofovir + 1 NRTI.

[b] Values obtained after initiation of serum lipid-reducing agents were not included in these analyses. At baseline, serum lipid-reducing agents were used in 4% in the lopinavir/ritonavir treatment arm and 4% in the REYATAZ/ritonavir arm. Through Week 48, serum lipid-reducing agents were used in 19% in the lopinavir/ritonavir treatment arm and 8% in the REYATAZ/ritonavir arm.

[c] Lopinavir/ritonavir (400/100 mg) BID + tenofovir + 1 NRTI.

[d] The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 48 values and is not a simple difference of the baseline and Week 48 mean values.

[e] Number of patients with LDL-cholesterol measured.

[f] Fasting.

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%.

6.3 Patients Co-infected With Hepatitis B and/or Hepatitis C Virus

Liver function tests should be monitored in patients with a history of hepatitis B or C.

In study AI424-138, 60 patients treated with REYATAZ/ritonavir 300 mg/100 mg once daily, and 51 patients treated with lopinavir/ritonavir 400 mg/100 mg twice daily, each with fixed dose tenofovir-emtricitabine, were seropositive for hepatitis B and/or C at study entry. ALT levels >5 times ULN developed in 10% (6/60) of the REYATAZ/ritonavir-treated patients and 8% (4/50) of the lopinavir/ritonavir-treated patients. AST levels >5 times ULN developed in 10% (6/60) of the REYATAZ/ritonavir-treated patients and none (0/50) of the lopinavir/ritonavir-treated patients.

In study AI424-045, 20 patients treated with REYATAZ/ritonavir 300 mg/100 mg once daily, and 18 patients treated with lopinavir/ritonavir 400 mg/100 mg twice daily, were seropositive for hepatitis B and/or C at study entry. ALT levels >5 times ULN developed in 25% (5/20) of the REYATAZ/ritonavir-treated patients and 6% (1/18) of the lopinavir/ritonavir-treated patients. AST levels >5 times ULN developed in 10% (2/20) of the REYATAZ/ritonavir-treated patients and 6% (1/18) of the lopinavir/ritonavir-treated patients.

In studies AI424-008 and AI424-034, 74 patients treated with 400 mg of REYATAZ (atazanavir sulfate) once daily, 58 who received efavirenz, and 12 who received nelfinavir were seropositive for hepatitis B and/or C at study entry. ALT levels >5 times the upper limit of normal (ULN) developed in 15% of the REYATAZ-treated patients, 14% of the efavirenz-treated patients, and 17% of the nelfinavir-treated patients. AST levels >5 times ULN developed in 9% of the REYATAZ-treated patients, 5% of the efavirenz-treated patients, and 17% of the nelfinavir-treated patients. Within atazanavir and control regimens, no difference in frequency of bilirubin elevations was noted between seropositive and seronegative patients. [See *Warnings and Precautions (5.5)*.]

6.4 Postmarketing Experience

The following events have been identified during postmarketing use of REYATAZ. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: edema

Cardiovascular System: second-degree AV block, third-degree AV block, left bundle branch block, QTc prolongation [see *Warnings and Precautions (5.2)*]

Gastrointestinal System: pancreatitis

Hepatic System: hepatic function abnormalities

Hepatobiliary Disorders: cholelithiasis, cholecystitis, cholestasis

Metabolic System and Nutrition Disorders: diabetes mellitus, hyperglycemia [see *Warnings and Precautions (5.7)*]

Musculoskeletal System: arthralgia

Renal System: nephrolithiasis [see *Warnings and Precautions (5.6)*]

Skin and Appendages: alopecia, maculopapular rash [see *Contraindications (4)* and *Warnings and Precautions (5.3)*], pruritus

7 DRUG INTERACTIONS

See also *Contraindications (4)* and *Clinical Pharmacology (12.3)*.

7.1 Potential for REYATAZ to Affect Other Drugs

Atazanavir is an inhibitor of CYP3A and UGT1A1. Coadministration of REYATAZ and drugs primarily metabolized by CYP3A or UGT1A1 may result in increased plasma concentrations of the other drug that could increase or prolong its therapeutic and adverse effects.

Atazanavir is a weak inhibitor of CYP2C8. Caution should be used when REYATAZ without ritonavir is coadministered with drugs highly dependent on CYP2C8 with narrow therapeutic indices (eg, paclitaxel, repaglinide). When REYATAZ with ritonavir is coadministered with substrates of CYP2C8, clinically significant interactions are not expected. [See *Clinical Pharmacology, Table 14 (12.3).*]

The magnitude of CYP3A-mediated drug interactions on coadministered drug may change when REYATAZ is coadministered with ritonavir. See the complete prescribing information for NORVIR® (ritonavir) for information on drug interactions with ritonavir.

7.2 Potential for Other Drugs to Affect Atazanavir

Atazanavir is a CYP3A4 substrate; therefore, drugs that induce CYP3A4 may decrease atazanavir plasma concentrations and reduce REYATAZ's therapeutic effect.

Atazanavir solubility decreases as pH increases. Reduced plasma concentrations of atazanavir are expected if proton-pump inhibitors, antacids, buffered medications, or H_2-receptor antagonists are administered with atazanavir.

7.3 Established and Other Potentially Significant Drug Interactions

Table 13 provides dosing recommendations as a result of drug interactions with REYATAZ. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

Table 13: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies[a] or Predicted Interactions (Information in the table applies to REYATAZ with or without ritonavir, unless otherwise indicated)

Concomitant Drug Class: **Specific Drugs**	**Effect on Concentration of Atazanavir or Concomitant Drug**	**Clinical Comment**
HIV Antiviral Agents		
Nucleoside Reverse Transcriptase Inhibitors (NRTIs) didanosine buffered formulations enteric-coated (EC) capsules	↓ atazanavir ↓ didanosine	Coadministration of REYATAZ with didanosine buffered tablets resulted in a marked decrease in atazanavir exposure. It is recommended that REYATAZ be given (with food) 2 h before or 1 h after didanosine buffered formulations. Simultaneous administration of didanosine EC and REYATAZ with food results in a decrease in didanosine exposure. Thus, REYATAZ and didanosine EC should be administered at different times.
Nucleotide Reverse Transcriptase Inhibitors tenofovir disoproxil fumarate	↓ atazanavir ↑ tenofovir	Tenofovir may decrease the AUC and C_{min} of atazanavir. When coadministered with tenofovir, it is recommended that REYATAZ 300 mg be given with ritonavir 100 mg and tenofovir 300 mg (all as a single daily dose with food). **REYATAZ without ritonavir should not be coadministered with tenofovir.** REYATAZ increases tenofovir concentrations. The mechanism of this interaction is unknown. Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders. Patients receiving REYATAZ and tenofovir should be monitored for tenofovir-associated adverse events.

Table 13: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies[a] or Predicted Interactions (Information in the table applies to REYATAZ with or without ritonavir, unless otherwise indicated)

Concomitant Drug Class: **Specific Drugs**	**Effect on Concentration of Atazanavir or Concomitant Drug**	**Clinical Comment**
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs) efavirenz	↓ atazanavir	Efavirenz decreases atazanavir exposure. ***In treatment-naive patients:*** If REYATAZ is combined with efavirenz, REYATAZ 400 mg (two 200-mg capsules) with ritonavir 100 mg should be administered once daily all as a single dose with food, and efavirenz 600 mg should be administered once daily on an empty stomach, preferably at bedtime. ***In treatment-experienced patients:*** Do not coadminister REYATAZ with efavirenz in treatment-experienced patients due to decreased atazanavir exposure.
Non-nucleoside Reverse Transcriptase Inhibitors nevirapine	↓ atazanavir ↑ nevirapine	Do not coadminister REYATAZ with nevirapine because: • Nevirapine substantially decreases atazanavir exposure. • Potential risk for nevirapine associated toxicity due to increased nevirapine exposures.
Protease Inhibitors saquinavir (soft gelatin capsules)	↑ saquinavir	Appropriate dosing recommendations for this combination, with or without ritonavir, with respect to efficacy and safety have not been established. In a clinical study, saquinavir 1200 mg coadministered with REYATAZ 400 mg and tenofovir 300 mg (all given once daily) plus nucleoside analogue reverse transcriptase inhibitors did not provide adequate efficacy [see *Clinical Studies (14.2)*].
Protease Inhibitors ritonavir	↑ atazanavir	If REYATAZ is coadministered with ritonavir, it is recommended that REYATAZ 300 mg once daily be given with ritonavir 100 mg once daily with food. See the complete prescribing information for NORVIR® (ritonavir) for information on drug interactions with ritonavir.
Protease Inhibitors others	↑ other protease inhibitor	***REYATAZ/ritonavir:*** Although not studied, the coadministration of REYATAZ/ritonavir and other protease inhibitors would be expected to increase exposure to the other protease inhibitor. Such coadministration is not recommended.
Other Agents		
Antacids and buffered medications	↓ atazanavir	Reduced plasma concentrations of atazanavir are expected if antacids, including buffered medications, are administered with REYATAZ. REYATAZ should be administered 2 hours before or 1 hour after these medications.
Antiarrhythmics amiodarone, bepridil, lidocaine (systemic), quinidine	↑ amiodarone, bepridil, lidocaine (systemic), quinidine	Coadministration with REYATAZ has the potential to produce serious and/or life-threatening adverse events and has not been studied. Caution is warranted and therapeutic concentration monitoring of these drugs is recommended if they are used concomitantly with REYATAZ (atazanavir sulfate).
Anticoagulants warfarin	↑ warfarin	Coadministration with REYATAZ has the potential to produce serious and/or life-threatening bleeding and has not been studied. It is recommended that INR (International Normalized Ratio) be monitored.
Antidepressants tricyclic antidepressants	↑ tricyclic antidepressants	Coadministration with REYATAZ has the potential to produce serious and/or life-threatening adverse events and has not been studied. Concentration monitoring of these drugs is recommended if they are used concomitantly with REYATAZ.

Table 13: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies[a] or Predicted Interactions (Information in the table applies to REYATAZ with or without ritonavir, unless otherwise indicated)

Concomitant Drug Class: **Specific Drugs**	**Effect on Concentration of Atazanavir or Concomitant Drug**	**Clinical Comment**
trazodone	↑ trazodone	Concomitant use of trazodone and REYATAZ with or without ritonavir may increase plasma concentrations of trazodone. Adverse events of nausea, dizziness, hypotension, and syncope have been observed following coadministration of trazodone and ritonavir. If trazodone is used with a CYP3A4 inhibitor such as REYATAZ, the combination should be used with caution and a lower dose of trazodone should be considered.
Antifungals ketoconazole, itraconazole	***REYATAZ/ ritonavir:*** ↑ ketoconazole ↑ itraconazole	Coadministration of ketoconazole has only been studied with REYATAZ without ritonavir (negligible increase in atazanavir AUC and C_{max}). Due to the effect of ritonavir on ketoconazole, high doses of ketoconazole and itraconazole (>200 mg/day) should be used cautiously with REYATAZ/ritonavir.
Antifungals voriconazole	Effect is unknown	Coadministration of voriconazole with REYATAZ, with or without ritonavir, has not been studied. Administration of voriconazole with ritonavir 100 mg every 12 hours decreased voriconazole steady-state AUC by an average of 39%. Voriconazole should not be administered to patients receiving REYATAZ/ritonavir, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole. Coadministration of voriconazole with REYATAZ (without ritonavir) may increase atazanavir concentrations; however, no data are available.
Antimycobacterials rifabutin	↑ rifabutin	A rifabutin dose reduction of up to 75% (eg, 150 mg every other day or 3 times per week) is recommended.
Benzodiazepines parenterally administered midazolam[b]	↑ midazolam	Concomitant use of parenteral midazolam with REYATAZ may increase plasma concentrations of midazolam. Coadministration should be done in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered. Coadministration of oral midazolam with REYATAZ is CONTRAINDICATED.
Calcium channel blockers diltiazem	↑ diltiazem and desacetyl-diltiazem	Caution is warranted. A dose reduction of diltiazem by 50% should be considered. ECG monitoring is recommended. Coadministration of REYATAZ/ritonavir with diltiazem has not been studied.
eg, felodipine, nifedipine, nicardipine, and verapamil	↑ calcium channel blocker	Caution is warranted. Dose titration of the calcium channel blocker should be considered. ECG monitoring is recommended.
HMG-CoA reductase inhibitors atorvastatin, rosuvastatin	↑ atorvastatin ↑ rosuvastatin	Use the lowest possible dose of atorvastatin or rosuvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with REYATAZ (with or without ritonavir). The risk of myopathy, including rhabdomyolysis, may be increased when HIV protease inhibitors, including REYATAZ, are used in combination with these drugs.

Table 13: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies[a] or Predicted Interactions (Information in the table applies to REYATAZ with or without ritonavir, unless otherwise indicated)

Concomitant Drug Class: **Specific Drugs**	**Effect on Concentration of Atazanavir or Concomitant Drug**	**Clinical Comment**
H_2-Receptor antagonists	↓ atazanavir	Plasma concentrations of atazanavir were substantially decreased when REYATAZ 400 mg once daily was administered simultaneously with famotidine 40 mg twice daily, which may result in loss of therapeutic effect and development of resistance. ***In treatment-naive patients:*** REYATAZ 300 mg with ritonavir 100 mg once daily with food should be administered simultaneously with, and or at least 10 hours after, a dose of the H_2-receptor antagonist. An H_2-receptor antagonist dose comparable to famotidine 20 mg once daily up to a dose comparable to famotidine 40 mg twice daily can be used with REYATAZ 300 mg with ritonavir 100 mg in treatment-naive patients. OR For patients unable to tolerate ritonavir, REYATAZ 400 mg once daily with food should be administered at least 2 hours before and at least 10 hours after a dose of the H_2-receptor antagonist. No single dose of the H_2-receptor antagonist should exceed a dose comparable to famotidine 20 mg, and the total daily dose should not exceed a dose comparable to famotidine 40 mg. ***In treatment-experienced patients:*** Whenever an H_2-receptor antagonist is given to a patient receiving REYATAZ with ritonavir, the H_2-receptor antagonist dose should not exceed a dose comparable to famotidine 20 mg twice daily, and the REYATAZ and ritonavir doses should be administered simultaneously with, and/or at least 10 hours after, the dose of the H_2-receptor antagonist. • REYATAZ 300 mg with ritonavir 100 mg once daily (all as a single dose with food) if taken with an H_2-receptor antagonist. • REYATAZ 400 mg with ritonavir 100 mg once daily (all as a single dose with food) if taken with both tenofovir and an H_2-receptor antagonist.
Immunosuppressants cyclosporin, sirolimus, tacrolimus	↑ immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with REYATAZ (atazanavir sulfate).
Inhaled/nasal steroid fluticasone	***REYATAZ*** ↑ fluticasone	Concomitant use of fluticasone propionate and REYATAZ (without ritonavir) may increase plasma concentrations of fluticasone propionate. Use with caution. Consider alternatives to fluticasone propionate, particularly for long-term use.
	REYATAZ/ritonavir ↑ fluticasone	Concomitant use of fluticasone propionate and REYATAZ/ritonavir may increase plasma concentrations of fluticasone propionate, resulting in significantly reduced serum cortisol concentrations. Systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression, have been reported during postmarketing use in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate. Coadministration of fluticasone propionate and REYATAZ/ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects [see *Warnings and Precautions (5.1)*].

Table 13: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies[a] or Predicted Interactions (Information in the table applies to REYATAZ with or without ritonavir, unless otherwise indicated)

Concomitant Drug Class: **Specific Drugs**	**Effect on Concentration of Atazanavir or Concomitant Drug**	**Clinical Comment**
Macrolide antibiotics clarithromycin	↑ clarithromycin ↓ 14-OH clarithromycin ↑ atazanavir	Increased concentrations of clarithromycin may cause QTc prolongations; therefore, a dose reduction of clarithromycin by 50% should be considered when it is coadministered with REYATAZ. In addition, concentrations of the active metabolite 14-OH clarithromycin are significantly reduced; consider alternative therapy for indications other than infections due to *Mycobacterium avium* complex. Coadministration of REYATAZ/ritonavir with clarithromycin has not been studied.
Hormonal contraceptives ethinyl estradiol and norgestimate or norethindrone	↓ ethinyl estradiol ↑ norgestimate[c]	Use with caution if coadministration of REYATAZ or REYATAZ/ritonavir with oral contraceptives is considered. If an oral contraceptive is administered with REYATAZ plus ritonavir, it is recommended that the oral contraceptive contain at least 35 mcg of ethinyl estradiol. If REYATAZ is administered without ritonavir, the oral contraceptive should contain no more than 30 mcg of ethinyl estradiol.
	↑ ethinyl estradiol ↑ norethindrone[d]	Potential safety risks include substantial increases in progesterone exposure. The long-term effects of increases in concentration of the progestational agent are unknown and could increase the risk of insulin resistance, dyslipidemia, and acne. Coadministration of REYATAZ or REYATAZ/ritonavir with other hormonal contraceptives (eg, contraceptive patch, contraceptive vaginal ring, or injectable contraceptives) or oral contraceptives containing progestagens other than norethindrone or norgestimate, or less than 25 mcg of ethinyl estradiol, has not been studied; therefore, alternative methods of contraception are recommended.
PDE5 inhibitors sildenafil, tadalafil, vardenafil	↑ sildenafil ↑ tadalafil ↑ vardenafil	Coadministration with REYATAZ has not been studied but may result in an increase in PDE5 inhibitor-associated adverse events, including hypotension, visual changes, and priapism. Use sildenafil with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events. Use tadalafil with caution at reduced doses of 10 mg every 72 hours with increased monitoring for adverse events. Use vardenafil with caution at reduced doses of no more than 2.5 mg every 72 hours with increased monitoring for adverse events.
Proton-pump inhibitors omeprazole	↓ atazanavir	Plasma concentrations of atazanavir were substantially decreased when REYATAZ 400 mg or REYATAZ 300 mg/ritonavir 100 mg once daily was administered with omeprazole 40 mg once daily, which may result in loss of therapeutic effect and development of resistance. ***In treatment-naive patients:*** The proton-pump inhibitor dose should not exceed a dose comparable to omeprazole 20 mg and must be taken approximately 12 hours prior to the REYATAZ 300 mg with ritonavir 100 mg dose. ***In treatment-experienced patients:*** Proton-pump inhibitors should not be used in treatment-experienced patients receiving REYATAZ.

[a] For magnitude of interactions see *Clinical Pharmacology, Tables 16* and *17 (12.3)*.

[b] See *Contraindications (4), Table 3* for orally administered midazolam.

[c] In combination with atazanavir 300 mg and ritonavir 100 mg once daily.

[d] In combination with atazanavir 400 mg once daily.

7.4 Drugs with No Observed or Predicted Interactions with REYATAZ

Clinically significant interactions are not expected between atazanavir and substrates of CYP2C19, CYP2C9, CYP2D6, CYP2B6, CYP2A6, CYP1A2, or CYP2E1. Clinically significant interactions are not expected between atazanavir when administered with ritonavir and substrates of CYP2C8. See the complete prescribing information for NORVIR® for information on other potential drug interactions with ritonavir.

Based on known metabolic profiles, clinically significant drug interactions are not expected between REYATAZ (atazanavir sulfate) and fluvastatin, pravastatin, dapsone, trimethoprim/sulfamethoxazole, azithromycin, or erythromycin. REYATAZ does not interact with substrates of CYP2D6 (eg, nortriptyline, desipramine, metoprolol). Additionally, no clinically significant drug interactions were observed when REYATAZ was coadministered with methadone, fluconazole, acetaminophen, or atenolol. [See *Clinical Pharmacology, Tables 16* and *17 (12.3).*]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well controlled studies of atazanavir use during pregnancy. Cases of lactic acidosis syndrome and symptomatic hyperlactatemia have occurred in pregnant women using REYATAZ in combination with nucleoside analogues. In animal reproduction and pre- and post-natal development studies, there was no evidence of adverse fetal effects or teratogenicity. Because animal reproduction studies are not always predictive of human response, REYATAZ should be used during pregnancy only if clearly needed.

Cases of lactic acidosis syndrome, sometimes fatal, and symptomatic hyperlactatemia have been reported in patients (including pregnant women) receiving REYATAZ in combination with nucleoside analogues. Nucleoside analogues are associated with an increased risk of lactic acidosis syndrome. In addition, hyperbilirubinemia occurred frequently during treatment with REYATAZ. It is not known whether REYATAZ administered during pregnancy will exacerbate physiological hyperbilirubinemia or increase the risk of kernicterus in neonates and young

infants. In the prepartum period, additional monitoring and alternative therapy should be considered.

In animal reproduction studies, there was no evidence of teratogenicity in offspring born to animals exposed to atazanavir levels one (in rabbits) to two times (in rats) those observed at the human clinical dose (400 mg once daily). In pre- and post-natal development studies in rats, there were no adverse effects on offspring following maternal exposure to atazanavir levels equivalent to those in humans taking 400 mg once daily. Weight loss and weight gain suppression occurred in pups with maternal atazanavir exposures two times the human exposure at 400 mg once daily; however, maternal toxicity also occurred at this exposure level.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to REYATAZ, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

8.3 Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. It is not known whether atazanavir is present in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are taking REYATAZ**.

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.

8.5 Geriatric Use

Clinical studies of REYATAZ did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Based on a comparison of mean single-dose pharmacokinetic values for C_{max} and AUC, a dose adjustment based upon age is not recommended. In general, appropriate caution should be exercised in the administration and monitoring of REYATAZ in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Age/Gender

A study of the pharmacokinetics of atazanavir was performed in young (n=29; 18–40 years) and elderly (n=30; ≥65 years) healthy subjects. There were no clinically important pharmacokinetic differences observed due to age or gender.

8.7 Impaired Renal Function

In healthy subjects, the renal elimination of unchanged atazanavir was approximately 7% of the administered dose. REYATAZ has been studied in adult subjects with severe renal impairment (n=20), including those on hemodialysis, at multiple doses of 400 mg once daily. The mean atazanavir C_{max} was 9% lower, AUC was 19% higher, and C_{min} was 96% higher in subjects with severe renal impairment not undergoing hemodialysis (n=10), than in age, weight, and gender matched subjects with normal renal function. Atazanavir was not appreciably cleared during hemodialysis. In a 4-hour dialysis session, 2.1% of the administered dose was removed. When atazanavir was administered either prior to, or following hemodialysis (n=10), the geometric means for C_{max}, AUC, and C_{min} were approximately 25 to 43% lower compared to subjects with normal renal function. The mechanism of this decrease is unknown. REYATAZ should not be administered to HIV-treatment experienced patients with end stage renal disease managed with hemodialysis. [See *Dosage and Administration (2.3)*.]

8.8 Impaired Hepatic Function

Atazanavir is metabolized and eliminated primarily by the liver. REYATAZ (atazanavir sulfate) has been studied in adult subjects with moderate to severe hepatic impairment (14 Child-Pugh B and 2 Child-Pugh C subjects) after a single 400-mg dose. The mean $AUC_{(0-\infty)}$ was 42% greater in subjects with impaired hepatic function than in healthy volunteers. The mean half-life of

atazanavir in hepatically impaired subjects was 12.1 hours compared to 6.4 hours in healthy volunteers. Increased concentrations of atazanavir are expected in patients with moderately or severely impaired hepatic function. The pharmacokinetics of REYATAZ in combination with ritonavir have not been studied in subjects with hepatic impairment. REYATAZ should not be administered to patients with severe hepatic impairment. REYATAZ/ritonavir is not recommended for use in patients with hepatic impairment. [See *Dosage and Administration (2.4)* and *Warnings and Precautions (5.5).*]

10 OVERDOSAGE

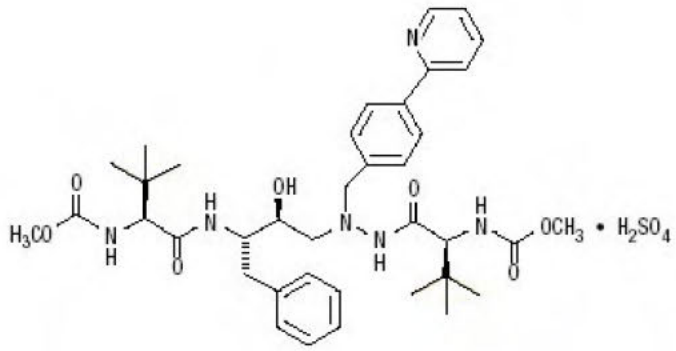
Human experience of acute overdose with REYATAZ is limited. Single doses up to 1200 mg have been taken by healthy volunteers without symptomatic untoward effects. A single self-administered overdose of 29.2 g of REYATAZ in an HIV-infected patient (73 times the 400-mg recommended dose) was associated with asymptomatic bifascicular block and PR interval prolongation. These events resolved spontaneously. At high doses that lead to high drug exposures, jaundice due to indirect (unconjugated) hyperbilirubinemia (without associated liver function test changes) or PR interval prolongation may be observed. [See *Warnings and Precautions (5.2, 5.4)* and *Clinical Pharmacology (12.2).*]

Treatment of overdosage with REYATAZ should consist of general supportive measures, including monitoring of vital signs and ECG, and observations of the patient's clinical status. If indicated, elimination of unabsorbed atazanavir should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid removal of unabsorbed drug. There is no specific antidote for overdose with REYATAZ. Since atazanavir is extensively metabolized by the liver and is highly protein bound, dialysis is unlikely to be beneficial in significant removal of this medicine.

11 DESCRIPTION

REYATAZ® (atazanavir sulfate) is an azapeptide inhibitor of HIV-1 protease.

The chemical name for atazanavir sulfate is (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). Its molecular formula is $C_{38}H_{52}N_6O_7 \bullet H_2SO_4$, which corresponds to a molecular weight of 802.9 (sulfuric acid salt). The free base molecular weight is 704.9. Atazanavir sulfate has the following structural formula:



Atazanavir sulfate is a white to pale yellow crystalline powder. It is slightly soluble in water (4–5 mg/mL, free base equivalent) with the pH of a saturated solution in water being about 1.9 at 24 ± 3° C.

REYATAZ Capsules are available for oral administration in strengths containing the equivalent of 100 mg, 150 mg, 200 mg, or 300 mg of atazanavir as atazanavir sulfate and the following inactive ingredients: crospovidone, lactose monohydrate, and magnesium stearate. The capsule shells contain the following inactive ingredients: gelatin, FD&C Blue #2, titanium dioxide, black iron oxide, red iron oxide, and yellow iron oxide. The capsules are printed with ink containing shellac, titanium dioxide, FD&C Blue #2, isopropyl alcohol, ammonium hydroxide, propylene glycol, n-butyl alcohol, simethicone, and dehydrated alcohol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Atazanavir is an antiviral drug [see *Clinical Pharmacology (12.4)*].

12.2 Pharmacodynamics

Effects on Electrocardiogram

Concentration- and dose-dependent prolongation of the PR interval in the electrocardiogram has been observed in healthy volunteers receiving atazanavir. In a placebo-controlled study (AI424-076), the mean (±SD) maximum change in PR interval from the predose value was 24 (±15) msec following oral dosing with 400 mg of atazanavir (n=65) compared to 13 (±11) msec following dosing with placebo (n=67). The PR interval prolongations in this study were asymptomatic. There is limited information on the potential for a pharmacodynamic interaction

in humans between atazanavir and other drugs that prolong the PR interval of the electrocardiogram. [See *Warnings and Precautions (5.2)*.]

Electrocardiographic effects of atazanavir were determined in a clinical pharmacology study of 72 healthy subjects. Oral doses of 400 mg and 800 mg were compared with placebo; there was no concentration-dependent effect of atazanavir on the QTc interval (using Fridericia's correction). In 1793 HIV-infected patients receiving antiretroviral regimens, QTc prolongation was comparable in the atazanavir and comparator regimens. No atazanavir-treated healthy subject or HIV-infected patient in clinical trials had a QTc interval >500 msec. [See *Warnings and Precautions (5.2)*.]

In a pharmacokinetic study between atazanavir 400 mg once daily and diltiazem 180 mg once daily, a CYP3A substrate, there was a 2-fold increase in the diltiazem plasma concentration and an additive effect on the PR interval. In a pharmacokinetic study between atazanavir 400 mg once daily and atenolol 50 mg once daily, there was no substantial additive effect of atazanavir and atenolol on the PR interval. [See *Warnings and Precautions (5.2)*.]

12.3 Pharmacokinetics

The pharmacokinetics of atazanavir were evaluated in healthy adult volunteers and in HIV-infected patients after administration of REYATAZ 400 mg once daily and after administration of REYATAZ 300 mg with ritonavir 100 mg once daily (see Table 14).

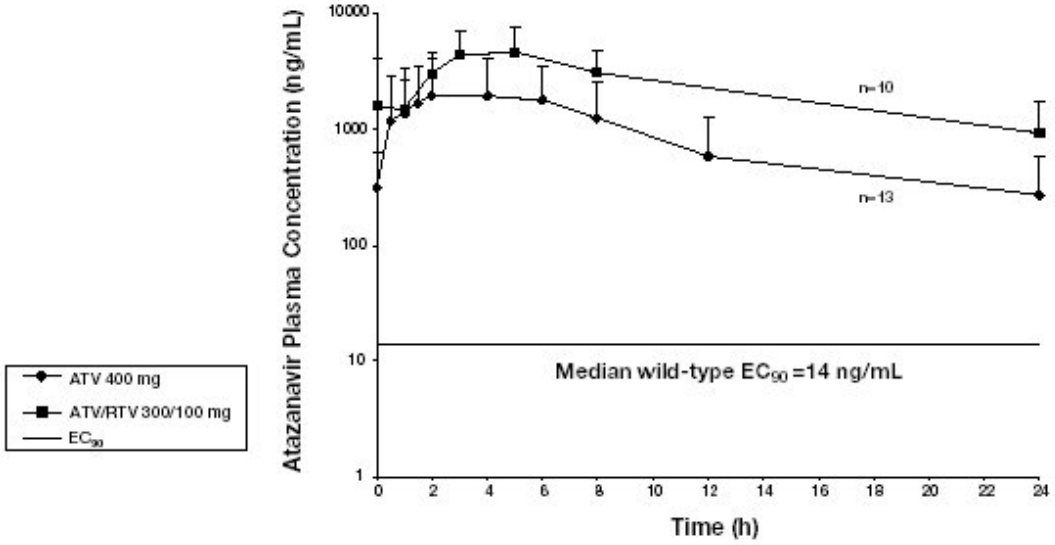
Table 14: Steady-State Pharmacokinetics of Atazanavir in Healthy Subjects or HIV-Infected Patients in the Fed State

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

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

Figure 1 displays the mean plasma concentrations of atazanavir at steady state after REYATAZ 400 mg once daily (as two 200-mg capsules) with a light meal and after REYATAZ 300 mg (as two 150-mg capsules) with ritonavir 100 mg once daily with a light meal in HIV-infected adult patients.

Figure 1: Mean (SD) Steady-State Plasma Concentrations of Atazanavir 400 mg (n=13) and 300 mg with Ritonavir (n=10) for HIV-Infected Adult Patients



Absorption

Atazanavir is rapidly absorbed with a T_{max} of approximately 2.5 hours. Atazanavir demonstrates nonlinear pharmacokinetics with greater than dose-proportional increases in AUC and C_{max} values over the dose range of 200–800 mg once daily. Steady-state is achieved between Days 4 and 8, with an accumulation of approximately 2.3-fold.

Food Effect

Administration of REYATAZ with food enhances bioavailability and reduces pharmacokinetic variability. Administration of a single 400-mg dose of REYATAZ with a light meal (357 kcal, 8.2 g fat, 10.6 g protein) resulted in a 70% increase in AUC and 57% increase in C_{max} relative to the fasting state. Administration of a single 400-mg dose of REYATAZ with a high-fat meal (721 kcal, 37.3 g fat, 29.4 g protein) resulted in a mean increase in AUC of 35% with no change in C_{max} relative to the fasting state. Administration of REYATAZ (atazanavir sulfate) with either a light meal or high-fat meal decreased the coefficient of variation of AUC and C_{max} by approximately one half compared to the fasting state.

Coadministration of a single 300-mg dose of REYATAZ and a 100-mg dose of ritonavir with a light meal (336 kcal, 5.1 g fat, 9.3 g protein) resulted in a 33% increase in the AUC and a 40% increase in both the C_{max} and the 24-hour concentration of atazanavir relative to the fasting state.

Coadministration with a high-fat meal (951 kcal, 54.7 g fat, 35.9 g protein) did not affect the AUC of atazanavir relative to fasting conditions and the C_{max} was within 11% of fasting values. The 24-hour concentration following a high-fat meal was increased by approximately 33% due to delayed absorption; the median T_{max} increased from 2.0 to 5.0 hours. Coadministration of REYATAZ with ritonavir with either a light or a high-fat meal decreased the coefficient of variation of AUC and C_{max} by approximately 25% compared to the fasting state.

Distribution

Atazanavir is 86% bound to human serum proteins and protein binding is independent of concentration. Atazanavir binds to both alpha-1-acid glycoprotein (AAG) and albumin to a similar extent (89% and 86%, respectively). In a multiple-dose study in HIV-infected patients dosed with REYATAZ 400 mg once daily with a light meal for 12 weeks, atazanavir was detected in the cerebrospinal fluid and semen. The cerebrospinal fluid/plasma ratio for atazanavir (n=4) ranged between 0.0021 and 0.0226 and seminal fluid/plasma ratio (n=5) ranged between 0.11 and 4.42.

Metabolism

Atazanavir is extensively metabolized in humans. The major biotransformation pathways of atazanavir in humans consisted of monooxygenation and dioxygenation. Other minor biotransformation pathways for atazanavir or its metabolites consisted of glucuronidation, N-dealkylation, hydrolysis, and oxygenation with dehydrogenation. Two minor metabolites of atazanavir in plasma have been characterized. Neither metabolite demonstrated *in vitro* antiviral activity. *In vitro* studies using human liver microsomes suggested that atazanavir is metabolized by CYP3A.

Elimination

Following a single 400-mg dose of ^{14}C-atazanavir, 79% and 13% of the total radioactivity was recovered in the feces and urine, respectively. Unchanged drug accounted for approximately 20% and 7% of the administered dose in the feces and urine, respectively. The mean elimination half-life of atazanavir in healthy volunteers (n=214) and HIV-infected adult patients (n=13) was approximately 7 hours at steady state following a dose of 400 mg daily with a light meal.

Special Populations

Pediatrics

The pharmacokinetic data from pediatric patients receiving REYATAZ Capsules with ritonavir based on body surface area are presented in Table 15.

Table 15: 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)**
Dose mg		
Median	200	400
[min-max]	[150–400]	[250–500]
C_{max} ng/mL		
Geometric mean (CV%)	4451 (33)	3711 (46)
AUC ng•h/mL		
Geometric mean (CV%)	42503 (36)	44970 (34)
C_{min} ng/mL		
Geometric mean (CV%)	535 (62)	1090 (60)

Drug Interaction Data

Atazanavir is a metabolism-dependent CYP3A inhibitor, with a K_{inact} value of 0.05 to 0.06 min^{-1} and K_i value of 0.84 to 1.0 µM. Atazanavir is also a direct inhibitor for UGT1A1 (K_i=1.9 µM) and CYP2C8 (K_i=2.1 µM).

Atazanavir has been shown *in vivo* not to induce its own metabolism, nor to increase the biotransformation of some drugs metabolized by CYP3A. In a multiple-dose study, REYATAZ decreased the urinary ratio of endogenous 6β-OH cortisol to cortisol versus baseline, indicating that CYP3A production was not induced.

Drug interaction studies were performed with REYATAZ and other drugs likely to be coadministered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of coadministration of REYATAZ on the AUC, C_{max}, and C_{min} are summarized in Tables 16 and 17. For information regarding clinical recommendations, see *Drug Interactions (7)*.

Table 16: Drug Interactions: Pharmacokinetic Parameters for Atazanavir in the Presence of Coadministered Drugs[a]

Coadministered Drug	Coadministered Drug Dose/Schedule	REYATAZ Dose/Schedule	Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00		
			C_{max}	AUC	C_{min}
atenolol	50 mg QD, d 7–11 (n=19) and d 19–23	400 mg QD, d 1–11 (n=19)	1.00 (0.89, 1.12)	0.93 (0.85, 1.01)	0.74 (0.65, 0.86)
clarithromycin	500 mg BID, d 7–10 (n=29) and d 18–21	400 mg QD, d 1–10 (n=29)	1.06 (0.93, 1.20)	1.28 (1.16, 1.43)	1.91 (1.66, 2.21)
didanosine (ddI) (buffered tablets) plus stavudine (d4T)[b]	ddI: 200 mg x 1 dose, d4T: 40 mg x 1 dose (n=31)	400 mg x 1 dose simultaneously with ddI and d4T (n=31)	0.11 (0.06, 0.18)	0.13 (0.08, 0.21)	0.16 (0.10, 0.27)
	ddI: 200 mg x 1 dose, d4T: 40 mg x 1 dose (n=32)	400 mg x 1 dose 1 h after ddI + d4T (n=32)	1.12 (0.67, 1.18)	1.03 (0.64, 1.67)	1.03 (0.61, 1.73)
ddI (enteric-coated [EC] capsules)[c]	400 mg d 8 (fed) (n=34) 400 mg d 19 (fed) (n=31)	400 mg QD, d 2–8 (n=34) 300 mg/ritonavir 100 mg QD, d 9–19 (n=31)	1.03 (0.93, 1.14) 1.04 (1.01, 1.07)	0.99 (0.91, 1.08) 1.00 (0.96, 1.03)	0.98 (0.89, 1.08) 0.87 (0.82, 0.92)
diltiazem	180 mg QD, d 7–11 (n=30) and d 19–23	400 mg QD, d 1–11 (n=30)	1.04 (0.96, 1.11)	1.00 (0.95, 1.05)	0.98 (0.90, 1.07)
efavirenz	600 mg QD, d 7–20 (n=27)	400 mg QD, d 1–20 (n=27)	0.41 (0.33, 0.51)	0.26 (0.22, 0.32)	0.07 (0.05, 0.10)
	600 mg QD, d 7–20 (n=13)	400 mg QD, d 1–6 (n=23) then 300 mg/ritonavir 100 mg QD, 2 h before efavirenz, d 7–20 (n=13)	1.14 (0.83, 1.58)	1.39 (1.02, 1.88)	1.48 (1.24, 1.76)
	600 mg QD, d 11–24 (pm) (n=14)	300 mg QD/ritonavir 100 mg QD, d 1–10 (pm) (n=22), then 400 mg QD/ritonavir 100 mg QD, d 11–24 (pm), (simultaneous with efavirenz) (n=14)	1.17 (1.08, 1.27)	1.00 (0.91, 1.10)	0.58 (0.49, 0.69)
famotidine	40 mg BID, d 7–12 (n=15)	400 mg QD, d 1–6 (n=45), d 7–12 (simultaneous administration) (n=15)	0.53 (0.34, 0.82)	0.59 (0.40, 0.87)	0.58 (0.37, 0.89)
	40 mg BID, d 7–12 (n=14)	400 mg QD (pm), d 1–6 (n=14), d 7–12 (10 h after, 2 h before famotidine) (n=14)	1.08 (0.82, 1.41)	0.95 (0.74, 1.21)	0.79 (0.60, 1.04)
	40 mg BID, d 11–20 (n=14)[d]	300 mg QD/ritonavir 100 mg QD, d 1–10 (n=46), d 11–20[d] (simultaneous administration) (n=14)	0.86 (0.79, 0.94)	0.82 (0.75, 0.89)	0.72 (0.64, 0.81)

Table 16: Drug Interactions: Pharmacokinetic Parameters for Atazanavir in the Presence of Coadministered Drugs[a]

Coadministered Drug	Coadministered Drug Dose/Schedule	REYATAZ Dose/Schedule	Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00		
			C_{max}	AUC	C_{min}
	20 mg BID, d 11–17 (n=18)	300 mg QD/ritonavir 100 mg QD/tenofovir 300 mg QD, d 1–10 (am) (n=39), d 11–17 (am) (simultaneous administration with am famotidine) (n=18)[e,f]	0.91 (0.84, 0.99)	0.90 (0.82, 0.98)	0.81 (0.69, 0.94)
	40 mg QD (pm), d 18–24 (n=20)	300 mg QD/ritonavir 100 mg QD/tenofovir 300 mg QD, d 1–10 (am) (n=39), d 18–24 (am) (12 h after pm famotidine) (n=20)[f]	0.89 (0.81, 0.97)	0.88 (0.80, 0.96)	0.77 (0.63, 0.93)
	40 mg BID, d 18–24 (n=18)	300 mg QD/ritonavir 100 mg QD/tenofovir 300 mg QD, d 1–10 (am) (n=39), d 18–24 (am) (10 h after pm famotidine and 2 h before am famotidine) (n=18)[f]	0.74 (0.66, 0.84)	0.79 (0.70, 0.88)	0.72 (0.63, 0.83)
	40 mg BID, d 11–20 (n=15)	300 mg QD/ritonavir 100 mg QD, d 1–10 (am) (n=46), then 400 mg QD/ritonavir 100 mg QD, d 11–20 (am) (n=15)	1.02 (0.87, 1.18)	1.03 (0.86, 1.22)	0.86 (0.68, 1.08)
fluconazole	200 mg QD, d 11–20 (n=29)	300 mg QD/ritonavir 100 mg QD, d 1–10 (n=19), d 11–20 (n=29)	1.03 (0.95, 1.11)	1.04 (0.95, 1.13)	0.98 (0.85, 1.13)
ketoconazole	200 mg QD, d 7–13 (n=14)	400 mg QD, d 1–13 (n=14)	0.99 (0.77, 1.28)	1.10 (0.89, 1.37)	1.03 (0.53, 2.01)
nevirapine[g,h]	200 mg BID, d 1–23 (n=23)	300 mg QD/ritonavir 100 mg QD, d 4–13, then 400 mg QD/ritonavir 100 mg QD, d 14–23 (n=23)[i]	0.72 (0.60, 0.86) 1.02 (0.85, 1.24)	0.58 (0.48, 0.71) 0.81 (0.65, 1.02)	0.28 (0.20, 0.40) 0.41 (0.27, 0.60)
omeprazole	40 mg QD, d 7–12 (n=16)[j]	400 mg QD, d 1–6 (n=48), d 7–12 (n=16)	0.04 (0.04, 0.05)	0.06 (0.05, 0.07)	0.05 (0.03, 0.07)
	40 mg QD, d 11–20 (n=15)[j]	300 mg QD/ritonavir 100 mg QD, d 1–20 (n=15)	0.28 (0.24, 0.32)	0.24 (0.21, 0.27)	0.22 (0.19, 0.26)
	20 mg QD, d 17–23 (am) (n=13)	300 mg QD/ritonavir 100 mg QD, d 7–16 (pm) (n=27), d 17–23 (pm) (n=13)[k,l]	0.61 (0.46, 0.81)	0.58 (0.44, 0.75)	0.54 (0.41, 0.71)

Table 16: Drug Interactions: Pharmacokinetic Parameters for Atazanavir in the Presence of Coadministered Drugs[a]

Coadministered Drug	Coadministered Drug Dose/Schedule	REYATAZ Dose/Schedule	Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00		
			C_{max}	AUC	C_{min}
	20 mg QD, d 17–23 (am) (n=14)	300 mg QD/ritonavir 100 mg QD, d 7–16 (am) (n=27), then 400 mg QD/ritonavir 100 mg QD, d 17–23 (am) (n=14)[m,n]	0.69 (0.58, 0.83)	0.70 (0.57, 0.86)	0.69 (0.54, 0.88)
rifabutin	150 mg QD, d 15–28 (n=7)	400 mg QD, d 1–28 (n=7)	1.34 (1.14, 1.59)	1.15 (0.98, 1.34)	1.13 (0.68, 1.87)
rifampin	600 mg QD, d 17–26 (n=16)	300 mg QD/ritonavir 100 mg QD, d 7–16 (n=48), d 17–26 (n=16)	0.47 (0.41, 0.53)	0.28 (0.25, 0.32)	0.02 (0.02, 0.03)
ritonavir[o]	100 mg QD, d 11–20 (n=28)	300 mg QD, d 1–20 (n=28)	1.86 (1.69, 2.05)	3.38 (3.13, 3.63)	11.89 (10.23, 13.82)
tenofovir[p]	300 mg QD, d 9–16 (n=34)	400 mg QD, d 2–16 (n=34)	0.79 (0.73, 0.86)	0.75 (0.70, 0.81)	0.60 (0.52, 0.68)
	300 mg QD, d 15–42 (n=10)	300 mg/ritonavir 100 mg QD, d 1–42 (n=10)	0.72[q] (0.50, 1.05)	0.75[q] (0.58, 0.97)	0.77[q] (0.54, 1.10)

[a] Data provided are under fed conditions unless otherwise noted.

[b] All drugs were given under fasted conditions.

[c] 400 mg ddI EC and REYATAZ were administered together with food on Days 8 and 19.

[d] REYATAZ 300 mg plus ritonavir 100 mg once daily coadministered with famotidine 40 mg twice daily resulted in atazanavir geometric mean C_{max} that was similar and AUC and C_{min} values that were 1.79- and 4.46-fold higher relative to REYATAZ 400 mg once daily alone.

[e] Similar results were noted when famotidine 20 mg BID was administered 2 hours after and 10 hours before atazanavir 300 mg and ritonavir 100 mg plus tenofovir 300 mg.

[f] Atazanavir/ritonavir/tenofovir was administered after a light meal.

[g] Study was conducted in HIV-infected individuals.

[h] Compared with atazanavir 400 mg historical data without nevirapine (n=13), the ratio of geometric means (90% confidence intervals) for $C_{max,}$ AUC, and C_{min} were 1.42 (0.98, 2.05), 1.64 (1.11, 2.42), and 1.25 (0.66, 2.36), respectively, for atazanavir/ritonavir 300/100 mg; and 2.02 (1.42, 2.87), 2.28 (1.54, 3.38), and 1.80 (0.94, 3.45), respectively, for atazanavir/ritonavir 400/100 mg.

[i] Parallel group design; n=23 for atazanavir/ritonavir plus nevirapine, n=22 for atazanavir 300 mg/ritonavir 100 mg without nevirapine. Subjects were treated with nevirapine prior to study entry.

[j] Omeprazole 40 mg was administered on an empty stomach 2 hours before REYATAZ.

[k] Omeprazole 20 mg was administered 30 minutes prior to a light meal in the morning and REYATAZ 300 mg plus ritonavir 100 mg in the evening after a light meal, separated by 12 hours from omeprazole.

[l] REYATAZ 300 mg plus ritonavir 100 mg once daily separated by 12 hours from omeprazole 20 mg daily resulted in

Table 16: Drug Interactions: Pharmacokinetic Parameters for Atazanavir in the Presence of Coadministered Drugs[a]

Coadministered Drug	Coadministered Drug Dose/Schedule	REYATAZ Dose/Schedule	Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00		
			C_{max}	AUC	C_{min}

increases in atazanavir geometric mean AUC (10%) and C_{min} (2.4-fold), with a decrease in C_{max} (29%) relative to REYATAZ 400 mg once daily in the absence of omeprazole (study days 1–6).

[m] Omeprazole 20 mg was given 30 minutes prior to a light meal in the morning and REYATAZ 400 mg plus ritonavir 100 mg once daily after a light meal, 1 hour after omeprazole. Effects on atazanavir concentrations were similar when REYATAZ 400 mg plus ritonavir 100 mg was separated from omeprazole 20 mg by 12 hours.

[n] REYATAZ 400 mg plus ritonavir 100 mg once daily administered with omeprazole 20 mg once daily resulted in increases in atazanavir geometric mean AUC (32%) and C_{min} (3.3-fold), with a decrease in C_{max} (26%) relative to REYATAZ 400 mg once daily in the absence of omeprazole (study days 1–6).

[o] Compared with atazanavir 400 mg QD historical data, administration of atazanavir/ritonavir 300/100 mg QD increased the atazanavir geometric mean values of C_{max}, AUC, and C_{min} by 18%, 103%, and 671%, respectively.

[p] Note that similar results were observed in studies where administration of tenofovir and REYATAZ was separated by 12 hours.

[q] Ratio of atazanavir plus ritonavir plus tenofovir to atazanavir plus ritonavir. Atazanavir 300 mg plus ritonavir 100 mg results in higher atazanavir exposure than atazanavir 400 mg (see footnote[o]). The geometric mean values of atazanavir pharmacokinetic parameters when coadministered with ritonavir and tenofovir were: C_{max} = 3190 ng/mL, AUC = 34459 ng•h/mL, and C_{min} = 491 ng/mL. Study was conducted in HIV-infected individuals.

Table 17: Drug Interactions: Pharmacokinetic Parameters for Coadministered Drugs in the Presence of REYATAZ[a]

Coadministered Drug	Coadministered Drug Dose/Schedule	REYATAZ Dose/Schedule	Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without REYATAZ; No Effect = 1.00		
			C_{max}	AUC	C_{min}
acetaminophen	1 gm BID, d 1–20 (n=10)	300 mg QD/ritonavir 100 mg QD, d 11–20 (n=10)	0.87 (0.77, 0 99)	0 97 (0 91, 1.03)	1 26 (1.08, 1.46)
atenolol	50 mg QD, d 7–11 (n=19) and d 19–23	400 mg QD, d 1–11 (n=19)	1.34 (1.26, 1.42)	1.25 (1.16, 1.34)	1.02 (0.88, 1.19)
clarithromycin	500 mg BID, d 7–10 (n=21) and d 18–21	400 mg QD, d 1–10 (n=21)	1.50 (1.32, 1.71) OH-clarithromycin: 0.28 (0.24, 0.33)	1.94 (1.75, 2.16) OH-clarithromycin: 0.30 (0.26, 0.34)	2.60 (2.35, 2.88) OH-clarithromycin: 0.38 (0.34, 0.42)
didanosine (ddI) (buffered tablets) plus stavudine (d4T)[b]	ddI: 200 mg x 1 dose, d4T: 40 mg x 1 dose (n=31)	400 mg x 1 dose simultaneous with ddI and d4T (n=31)	ddI: 0.92 (0.84, 1.02) d4T: 1.08 (0 96, 1 22)	ddI: 0.98 (0 92, 1.05) d4T: 1.00 (0 97, 1.03)	NA d4T: 1.04 (0.94, 1 16)
ddI (enteric-coated [EC] capsules)[c]	400 mg d 1 (fasted), d 8 (fed) (n=34)	400 mg QD, d 2–8 (n=34)	0.64 (0 55, 0.74)	0.66 (0.60, 0.74)	1 13 (0 91, 1.41)
	400 mg d 1 (fasted), d 19 (fed) (n=31)	300 mg QD/ritonavir 100 mg QD, d 9–19 (n=31)	0.62 (0 52, 0.74)	0.66 (0 59, 0.73)	1 25 (0 92, 1.69)
diltiazem	180 mg QD, d 7–11 (n=28) and d 19–23	400 mg QD, d 1–11 (n=28)	1 98 (1.78, 2 19) desacetyl-diltiazem: 2.72 (2.44, 3.03)	2 25 (2.09, 2.16) desacetyl-diltiazem: 2.65 (2.45, 2.87)	2.42 (2 14, 2.73) desacetyl-diltiazem: 2 21 (2.02, 2.42)
ethinyl estradiol & norethindrone[d]	Ortho-Novum® 7/7/7 QD, d 1–29 (n=19)	400 mg QD, d 16–29 (n=19)	ethinyl estradiol: 1.15 (0 99, 1 32) norethindrone: 1.67 (1.42, 1 96)	ethinyl estradiol: 1.48 (1 31, 1.68) norethindrone: 2.10 (1.68, 2.62)	ethinyl estradiol: 1.91 (1.57, 2.33) norethindrone: 3.62 (2 57, 5.09)
ethinyl estradiol & norgestimate[e]	Ortho Tri-Cyclen® QD, d 1–28 (n=18), then Ortho Tri-Cyclen® LO QD, d 29–42[f] (n=14)	300 mg QD/ritonavir 100 mg QD, d 29–42 (n=14)	ethinyl estradiol: 0.84 (0.74, 0 95) 17-deacetyl norgestimate:[g] 1.68 (1 51, 1.88)	ethinyl estradiol: 0.81 (0.75, 0.87) 17-deacetyl norgestimate:[g] 1.85 (1.67, 2.05)	ethinyl estradiol: 0.63 (0 55, 0.71) 17-deacetyl norgestimate:[g] 2.02 (1.77, 2.31)
fluconazole	200 mg QD, d 1–10 (n=11) and 200 mg QD, d 11–20 (n=29)	300 mg QD/ritonavir 100 mg QD, d 11–20 (n=29)	1.05 (0 99, 1 10)	1.08 (1.02, 1 15)	1.07 (1.00, 1 15)

Table 17: Drug Interactions: Pharmacokinetic Parameters for Coadministered Drugs in the Presence of REYATAZ[a]

Coadministered Drug	Coadministered Drug Dose/Schedule	REYATAZ Dose/Schedule	Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without REYATAZ; No Effect = 1.00		
			C_{max}	AUC	C_{min}
methadone	Stable maintenance dose, d 1–15 (n=16)	400 mg QD, d 2–15 (n=16)	(R)-methadone[h] 0 91 (0.84, 1.0) total: 0.85 (0.78, 0 93)	(R)-methadone[h] 1.03 (0 95, 1 10) total: 0.94 (0.87, 1.02)	(R)-methadone[h] 1 11 (1.02, 1 20) total: 1.02 (0 93, 1 12)
nevirapine[i,j]	200 mg BID, d 1–23 (n=23)	300 mg QD/ ritonavir 100 mg QD, d 4–13, then	1.17 (1.09, 1.25)	1.25 (1.17, 1.34)	1.32 (1.22, 1.43)
		400 mg QD/ ritonavir 100 mg QD, d 14–23 (n=23)	1.21 (1.11, 1.32)	1.26 (1.17, 1.36)	1.35 (1.25, 1.47)
omeprazole[k]	40 mg single dose, d 7 and d 20 (n=16)	400 mg QD, d 1–12 (n=16)	1.24 (1.04, 1.47)	1.45 (1.20, 1.76)	NA
rifabutin	300 mg QD, d 1–10 then 150 mg QD, d 11–20 (n=3)	600 mg QD,[l] d 11–20 (n=3)	1 18 (0.94, 1.48) 25-O-desacetyl-rifabutin: 8.20 (5.90, 11.40)	2.10 (1.57, 2.79) 25-O-desacetyl-rifabutin: 22.01 (15.97, 30 34)	3.43 (1.98, 5.96) 25-O-desacetyl-rifabutin: 75.6 (30.1, 190.0)
rosiglitazone[m]	4 mg single dose, d 1, 7, 17 (n=14)	400 mg QD, d 2–7, then	1.08 (1.03, 1.13)	1.35 (1.26, 1.44)	NA
		300 mg QD/ ritonavir 100 mg QD, d 8–17 (n=14)	0.97 (0.91, 1.04)	0.83 (0.77, 0.89)	NA
saquinavir[n] (soft gelatin capsules)	1200 mg QD, d 1–13 (n=7)	400 mg QD, d 7–13 (n=7)	4 39 (3.24, 5.95)	5.49 (4.04, 7.47)	6.86 (5.29, 8.91)
tenofovir[o]	300 mg QD, d 9–16 (n=33) and d 24–30 (n=33)	400 mg QD, d 2–16 (n=33)	1 14 (1.08, 1.20)	1.24 (1.21, 1.28)	1.22 (1.15, 1.30)
	300 mg QD, d 1–7 (pm) (n=14) d 25–34 (pm) (n=12)	300 mg QD/ritonavir 100 mg QD, d 25–34 (am) (n=12)[p]	1 34 (1 20, 1 51)	1 37 (1 30, 1.45)	1 29 (1 21, 1.36)
lamivudine + zidovudine	150 mg lamivudine + 300 mg zidovudine BID, d 1–12 (n=19)	400 mg QD, d 7–12 (n=19)	lamivudine: 1.04 (0.92, 1.16) zidovudine: 1.05 (0.88, 1.24) zidovudine glucuronide: 0.95 (0.88, 1.02)	lamivudine: 1.03 (0.98, 1.08) zidovudine: 1.05 (0.96, 1.14) zidovudine glucuronide: 1.00 (0.97, 1.03)	lamivudine: 1.12 (1.04, 1.21) zidovudine: 0.69 (0.57, 0.84) zidovudine glucuronide: 0.82 (0.62, 1.08)

Table 17: Drug Interactions: Pharmacokinetic Parameters for Coadministered Drugs in the Presence of REYATAZ[a]

Coadministered Drug	Coadministered Drug Dose/Schedule	REYATAZ Dose/Schedule	Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without REYATAZ; No Effect = 1.00		
			C_{max}	AUC	C_{min}

[a] Data provided are under fed conditions unless otherwise noted.

[b] All drugs were given under fasted conditions.

[c] 400 mg ddI EC and REYATAZ were administered together with food on Days 8 and 19.

[d] Upon further dose normalization of ethinyl estradiol 25 mcg with atazanavir relative to ethinyl estradiol 35 mcg without atazanavir, the ratio of geometric means (90% confidence intervals) for C_{max}, AUC, and C_{min} were 0.82 (0.73, 0.92), 1.06 (0.95, 1.17), and 1.35 (1.11, 1.63), respectively.

[e] Upon further dose normalization of ethinyl estradiol 35 mcg with atazanavir/ritonavir relative to ethinyl estradiol 25 mcg without atazanavir/ritonavir, the ratio of geometric means (90% confidence intervals) for C_{max}, AUC, and C_{min} were 1.17 (1.03, 1.34), 1.13 (1.05, 1.22), and 0.88 (0.77, 1.00), respectively.

[f] All subjects were on a 28 day lead-in period; one full cycle of Ortho Tri-Cyclen®. Ortho Tri-Cyclen® contains 35 mcg of ethinyl estradiol. Ortho Tri-Cyclen® LO contains 25 mcg of ethinyl estradiol. Results were dose normalized to an ethinyl estradiol dose of 35 mcg.

[g] 17-deacetyl norgestimate is the active component of norgestimate.

[h] (R)-methadone is the active isomer of methadone.

[i] Study was conducted in HIV-infected individuals.

[j] Subjects were treated with nevirapine prior to study entry.

[k] Omeprazole was used as a metabolic probe for CYP2C19. Omeprazole was given 2 hours after REYATAZ on Day 7; and was given alone 2 hours after a light meal on Day 20.

[l] Not the recommended therapeutic dose of atazanavir.

[m] Rosiglitazone used as a probe substrate for CYP2C8.

[n] The combination of atazanavir and saquinavir 1200 mg QD produced daily saquinavir exposures similar to the values produced by the standard therapeutic dosing of saquinavir at 1200 mg TID. However, the C_{max} is about 79% higher than that for the standard dosing of saquinavir (soft gelatin capsules) alone at 1200 mg TID.

[o] Note that similar results were observed in a study where administration of tenofovir and REYATAZ was separated by 12 hours.

[p] Administration of tenofovir and REYATAZ was temporally separated by 12 hours.

NA = not available.

12.4 Microbiology

Mechanism of Action

Atazanavir (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.

Antiviral Activity in Cell Culture

Atazanavir exhibits anti-HIV-1 activity with a mean 50% effective concentration (EC_{50}) in the absence of human serum of 2 to 5 nM against a variety of laboratory and clinical HIV-1 isolates grown in peripheral blood mononuclear cells, macrophages, CEM-SS cells, and MT-2 cells. ATV has activity against HIV-1 Group M subtype viruses A, B, C, D, AE, AG, F, G, and J isolates in cell culture. ATV has variable activity against HIV-2 isolates (1.9 to 32 nM), with EC_{50} values above the EC_{50} values of failure isolates. Two-drug combination antiviral activity studies with ATV showed no antagonism in cell culture with NNRTIs (delavirdine, efavirenz, and nevirapine), PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir), NRTIs (abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine, and zidovudine), the HIV-1 fusion inhibitor enfuvirtide, and two compounds used in the treatment of viral hepatitis, adefovir and ribavirin, without enhanced cytotoxicity.

Resistance

In Cell Culture: HIV-1 isolates with a decreased susceptibility to ATV have been selected in cell culture and obtained from patients treated with ATV or atazanavir/ritonavir (ATV/RTV). HIV-1 isolates with 93- to 183-fold reduced susceptibility to ATV from three different viral strains were selected in cell culture by 5 months. The substitutions in these HIV-1 viruses that contributed to ATV resistance include I50L, N88S, I84V, A71V, and M46I. Changes were also observed at the protease cleavage sites following drug selection. Recombinant viruses containing the I50L substitution without other major PI substitutions were growth impaired and displayed increased susceptibility in cell culture to other PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir). The I50L and I50V substitutions yielded selective resistance to ATV and amprenavir, respectively, and did not appear to be cross-resistant.

Clinical Studies of Treatment-Naive Patients: Comparison of Ritonavir-Boosted REYATAZ vs. Unboosted REYATAZ: Study AI424-089 compared REYATAZ 300 mg once daily with ritonavir

100 mg vs. REYATAZ 400 mg once daily when administered with lamivudine and extended-release stavudine in HIV-infected treatment-naive patients. A summary of the number of virologic failures and virologic failure isolates with ATV resistance in each arm is shown in Table 18.

Table 18: Summary of Virologic Failures[a] at Week 96 in Study AI424-089: Comparison of Ritonavir Boosted REYATAZ vs. Unboosted REYATAZ: Randomized Patients

	REYATAZ 300 mg + ritonavir 100 mg (n=95)	REYATAZ 400 mg (n=105)
Virologic Failure (≥50 copies/mL) at Week 96	15 (16%)	34 (32%)
Virologic Failure with Genotypes and Phenotypes Data	5	17
Virologic Failure Isolates with ATV-resistance at Week 96	0/5 (0%)[b]	4/17 (24%)[b]
Virologic Failure Isolates with I50L Emergence at Week 96[c]	0/5 (0%)[b]	2/17 (12%)[b]
Virologic Failure Isolates with Lamivudine Resistance at Week 96	2/5 (40%)[b]	11/17 (65%)[b]

[a] Virologic failure includes patients who were never suppressed through Week 96 and on study at Week 96, had virologic rebound or discontinued due to insufficient viral load response.

[b] Percentage of Virologic Failure Isolates with genotypic and phenotypic data.

[c] Mixture of I50I/L emerged in 2 other ATV 400 mg-treated patients. Neither isolate was phenotypically resistant to ATV.

Clinical Studies of Treatment-Naive Patients Receiving REYATAZ 300 mg With Ritonavir 100 mg: In Phase III study AI424-138, an as-treated genotypic and phenotypic analysis was conducted on samples from patients who experienced virologic failure (HIV-1 RNA ≥400 copies/mL) or discontinued before achieving suppression on ATV/RTV (n=39; 9%) and LPV/RTV (n=39; 9%) through 96 weeks of treatment. In the ATV/RTV arm, one of the virologic failure isolates had a 56-fold decrease in ATV susceptibility emerge on therapy with the development of PI resistance-associated substitutions L10F, V32I, K43T, M46I, A71I, G73S, I85I/V, and L90M. The NRTI resistance-associated substitution M184V also emerged on treatment in this isolate conferring emtricitabine resistance. Two ATV/RTV-virologic failure isolates had baseline phenotypic ATV resistance and IAS-defined major PI resistance-associated substitutions at baseline. The I50L substitution emerged on study in one of these failure isolates and was associated with a 17-fold decrease in ATV susceptibility from baseline and the other failure isolate with baseline ATV resistance and PI substitutions (M46M/I and I84I/V) had

additional IAS-defined major PI substitutions (V32I, M46I, and I84V) emerge on ATV treatment associated with a 3-fold decrease in ATV susceptibility from baseline. Five of the treatment failure isolates in the ATV/RTV arm developed phenotypic emtricitabine resistance with the emergence of either the M184I (n=1) or the M184V (n=4) substitution on therapy and none developed phenotypic tenofovir disoproxil resistance. In the LPV/RTV arm, one of the virologic failure patient isolates had a 69-fold decrease in LPV susceptibility emerge on therapy with the development of PI substitutions L10V, V11I, I54V, G73S, and V82A in addition to baseline PI substitutions L10L/I, V32I, I54I/V, A71I, G73G/S, V82V/A, L89V, and L90M. Six LPV/RTV virologic failure isolates developed the M184V substitution and phenotypic emtricitabine resistance and two developed phenotypic tenofovir disoproxil resistance.

Clinical Studies of Treatment-Naive Patients Receiving REYATAZ 400 mg Without Ritonavir: ATV-resistant clinical isolates from treatment-naive patients who experienced virologic failure on REYATAZ 400 mg treatment without ritonavir often developed an I50L substitution (after an average of 50 weeks of ATV therapy), often in combination with an A71V substitution, but also developed one or more other PI substitutions (eg, V32I, L33F, G73S, V82A, I85V, or N88S) with or without the I50L substitution. In treatment-naive patients, viral isolates that developed the I50L substitution, without other major PI substitutions, showed phenotypic resistance to ATV but retained in cell culture susceptibility to other PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir); however, there are no clinical data available to demonstrate the effect of the I50L substitution on the efficacy of subsequently administered PIs.

Clinical Studies of Treatment-Experienced Patients: In studies of treatment-experienced patients treated with ATV or ATV/RTV, most ATV-resistant isolates from patients who experienced virologic failure developed substitutions that were associated with resistance to multiple PIs and displayed decreased susceptibility to multiple PIs. The most common protease substitutions to develop in the viral isolates of patients who failed treatment with ATV 300 mg once daily and RTV 100 mg once daily (together with tenofovir and an NRTI) included V32I, L33F/V/I, E35D/G, M46I/L, I50L, F53L/V, I54V, A71V/T/I, G73S/T/C, V82A/T/L, I85V, and L89V/Q/M/T. Other substitutions that developed on ATV/RTV treatment including E34K/A/Q, G48V, I84V, N88S/D/T, and L90M occurred in less than 10% of patient isolates. Generally, if multiple PI resistance substitutions were present in the HIV-1 virus of the patient at baseline, ATV resistance developed through substitutions associated with resistance to other PIs and could include the development of the I50L substitution. The I50L substitution has been detected in treatment-experienced patients experiencing virologic failure after long-term treatment. Protease cleavage site changes also emerged on ATV treatment but their presence did not correlate with the level of ATV resistance.

Cross-Resistance

Cross-resistance among PIs has been observed. Baseline phenotypic and genotypic analyses of clinical isolates from ATV clinical trials of PI-experienced patients showed that isolates cross-resistant to multiple PIs were cross-resistant to ATV. Greater than 90% of the isolates with substitutions that included I84V or G48V were resistant to ATV. Greater than 60% of isolates containing L90M, G73S/T/C, A71V/T, I54V, M46I/L, or a change at V82 were resistant to ATV, and 38% of isolates containing a D30N substitution in addition to other changes were resistant to ATV. Isolates resistant to ATV were also cross-resistant to other PIs with >90% of the isolates resistant to indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir, and 80% resistant to amprenavir. In treatment-experienced patients, PI-resistant viral isolates that developed the I50L substitution in addition to other PI resistance-associated substitution were also cross-resistant to other PIs.

Baseline Genotype/Phenotype and Virologic Outcome Analyses

Genotypic and/or phenotypic analysis of baseline virus may aid in determining ATV susceptibility before initiation of ATV/RTV therapy. An association between virologic response at 48 weeks and the number and type of primary PI resistance-associated substitutions detected in baseline HIV-1 isolates from antiretroviral-experienced patients receiving ATV/RTV once daily or lopinavir (LPV)/RTV twice daily in Study AI424-045 is shown in Table 19.

Overall, both the number and type of baseline PI substitutions affected response rates in treatment-experienced patients. In the ATV/RTV group, patients had lower response rates when 3 or more baseline PI substitutions, including a substitution at position 36, 71, 77, 82, or 90, were present compared to patients with 1–2 PI substitutions, including one of these substitutions.

Table 19: HIV RNA Response by Number and Type of Baseline PI Substitution, Antiretroviral-Experienced Patients in Study AI424-045, As-Treated Analysis

	Virologic Response = HIV RNA <400 copies/mL[b]	
Number and Type of Baseline PI Substitutions[a]	**ATV/RTV (n=110)**	**LPV/RTV (n=113)**
3 or more primary PI substitutions including:[c]		
D30N	75% (6/8)	50% (3/6)
M36I/V	19% (3/16)	33% (6/18)

Table 19: HIV RNA Response by Number and Type of Baseline PI Substitution, Antiretroviral-Experienced Patients in Study AI424-045, As-Treated Analysis

M46I/L/T	24% (4/17)	23% (5/22)
I54V/L/T/M/A	31% (5/16)	31% (5/16)
A71V/T/I/G	34% (10/29)	39% (12/31)
G73S/A/C/T	14% (1/7)	38% (3/8)
V77I	47% (7/15)	44% (7/16)
V82A/F/T/S/I	29% (6/21)	27% (7/26)
I84V/A	11% (1/9)	33% (2/6)
N88D	63% (5/8)	67% (4/6)
L90M	10% (2/21)	44% (11/25)
Number of baseline primary PI substitutions[a]		
All patients, as-treated	58% (64/110)	59% (67/113)
0–2 PI substitutions	75% (50/67)	75% (50/67)
3–4 PI substitutions	41% (14/34)	43% (12/28)
5 or more PI substitutions	0% (0/9)	28% (5/18)

[a] Primary substitutions include any change at D30, V32, M36, M46, I47, G48, I50, I54, A71, G73, V77, V82, I84, N88, and L90.

[b] Results should be interpreted with caution because the subgroups were small.

[c] There were insufficient data (n<3) for PI substitutions V32I, I47V, G48V, I50V, and F53L.

The response rates of antiretroviral-experienced patients in Study AI424-045 were analyzed by baseline phenotype (shift in susceptibility in cell culture relative to reference, Table 20). The analyses are based on a select patient population with 62% of patients receiving an NNRTI-based regimen before study entry compared to 35% receiving a PI-based regimen. Additional data are needed to determine clinically relevant break points for REYATAZ.

Table 20: Baseline Phenotype by Outcome, Antiretroviral-Experienced Patients in Study AI424-045, As-Treated Analysis

Baseline Phenotype[a]	**Virologic Response = HIV RNA <400 copies/mL**[b] **ATV/RTV (n=111)**	**LPV/RTV (n=111)**
0–2	71% (55/78)	70% (56/80)
>2–5	53% (8/15)	44% (4/9)
>5–10	13% (1/8)	33% (3/9)
>10	10% (1/10)	23% (3/13)

[a] Fold change susceptibility in cell culture relative to the wild-type reference.

[b] Results should be interpreted with caution because the subgroups were small.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies in mice and rats were conducted with atazanavir. At the high dose in female mice, the incidence of benign hepatocellular adenomas was increased at systemic exposures 7.2-fold higher than those in humans at the recommended 400-mg clinical dose. There were no increases in the incidence of tumors in male mice at any dose in the study. In rats, no significant positive trends in the incidence of neoplasms occurred at systemic exposures up to 5.7-fold higher than those in humans at the recommended 400-mg clinical dose. The clinical relevance of the carcinogenic findings in female mice is unknown.

Atazanavir tested positive in an *in vitro* clastogenicity test using primary human lymphocytes, in the absence and presence of metabolic activation. Atazanavir tested negative in the *in vitro* Ames reverse-mutation assay, *in vivo* micronucleus and DNA repair tests in rats, and *in vivo* DNA damage test in rat duodenum (comet assay).

13.2 Reproductive Toxicology Studies

At the systemic drug exposure levels (AUC) equal to (in male rats) or two times (in female rats) those at the human clinical dose (400 mg once daily), atazanavir did not produce significant effects on mating, fertility, or early embryonic development.

14 CLINICAL STUDIES

14.1 Adult Patients Without Prior Antiretroviral Therapy

Study AI424-138: a 96-week study comparing the antiviral efficacy and safety of atazanavir/ritonavir with lopinavir/ritonavir, each in combination with fixed-dose tenofovir-emtricitabine in HIV-1 infected treatment naive subjects. Study AI424-138 is a 96-week open-label, randomized, multicenter study, comparing REYATAZ (300 mg once daily) with ritonavir (100 mg once daily) to lopinavir with ritonavir (400/100 mg twice daily), each in combination with fixed-dose tenofovir with emtricitabine (300/200 mg once daily), in 878 antiretroviral

treatment-naive treated patients. Patients had a mean age of 36 years (range: 19–72), 49% were Caucasian, 18% Black, 9% Asian, 23% Hispanic/Mestizo/mixed race, and 68% were male. The median baseline plasma CD4+ cell count was 204 cells/mm^3 (range: 2 to 810 cells/mm^3) and the mean baseline plasma HIV-1 RNA level was 4.94 $\log_{10}$ copies/mL (range: 2.60 to 5.88 $\log_{10}$ copies/mL). Treatment response and outcomes through Week 96 are presented in Table 21.

Table 21: Outcomes of Treatment Through Week 96 (Study AI424-138)

Outcome	REYATAZ 300 mg + ritonavir 100 mg (once daily) with tenofovir/emtricitabine (once daily)[a] (n=441) 96 Weeks	lopinavir 400 mg + ritonavir 100 mg (twice daily) with tenofovir/emtricitabine (once daily)[a] (n=437) 96 Weeks
Responder[b,c,d]	75%	68%
Virologic failure[e]	17%	19%
Rebound	8%	10%
Never suppressed through Week 96	9%	9%
Death	1%	1%
Discontinued due to adverse event	3%	5%
Discontinued for other reasons[f]	4%	7%

[a] As a fixed-dose combination: 300 mg tenofovir, 200 mg emtricitabine once daily.

[b] Patients achieved HIV RNA <50 copies/mL at Week 96. Roche Amplicor®, v1.5 ultra-sensitive assay.

[c] Pre-specified ITT analysis at Week 48 using as-randomized cohort: ATV/RTV 78% and LPV/RTV 76% [difference estimate: 1.7% (95% confidence interval: −3.8%, 7.1%)].

[d] Pre-specified ITT analysis at Week 96 using as-randomized cohort: ATV/RTV 74% and LPV/RTV 68% [difference estimate: 6.1% (95% confidence interval: 0.3%, 12.0%)].

[e] Includes viral rebound and failure to achieve confirmed HIV RNA <50 copies/mL through Week 96.

[f] Includes lost to follow-up, patient's withdrawal, noncompliance, protocol violation, and other reasons.

Through 96 weeks of therapy the proportion of responders among patients with high viral loads (ie, baseline HIV RNA ≥100,000 copies/mL) was comparable for the REYATAZ/ritonavir (165 of 223 patients, 74%) and lopinavir/ritonavir (148 of 222 patients, 67%) arms. At 96 weeks the median increase from baseline in CD4+ cell count was 261 cells/mm^3 for the REYATAZ/ritonavir arm and 273 cells/mm^3 for the lopinavir/ritonavir arm.

Study AI424-034: REYATAZ once daily compared to efavirenz once daily, each in combination with fixed-dose lamivudine + zidovudine twice daily. Study AI424-034 was a randomized, double-blind, multicenter trial comparing REYATAZ (400 mg once daily) to efavirenz (600 mg once daily), each in combination with a fixed-dose combination of lamivudine (3TC) (150 mg) and zidovudine (ZDV) (300 mg) given twice daily, in 810 antiretroviral treatment-naive patients. Patients had a mean age of 34 years (range: 18 to 73), 36% were Hispanic, 33% were Caucasian, and 65% were male. The mean baseline CD4+ cell count was 321 cells/mm^3 (range: 64 to 1424 cells/mm^3) and the mean baseline plasma HIV-1 RNA level was 4.8 log_{10} copies/mL (range: 2.2 to 5.9 log_{10} copies/mL). Treatment response and outcomes through Week 48 are presented in Table 22.

Table 22: Outcomes of Randomized Treatment Through Week 48 (Study AI424-034)

Outcome	REYATAZ 400 mg once daily + lamivudine + zidovudine[d] (n=405)	efavirenz 600 mg once daily + lamivudine + zidovudine[d] (n=405)
Responder[a]	67% (32%)	62% (37%)
Virologic failure[b]	20%	21%
Rebound	17%	16%
Never suppressed through Week 48	3%	5%
Death	–	<1%
Discontinued due to adverse event	5%	7%
Discontinued for other reasons[c]	8%	10%

[a] Patients achieved and maintained confirmed HIV RNA <400 copies/mL (<50 copies/mL) through Week 48. Roche Amplicor® HIV-1 Monitor™ Assay, test version 1.0 or 1.5 as geographically appropriate.
[b] Includes viral rebound and failure to achieve confirmed HIV RNA <400 copies/mL through Week 48.
[c] Includes lost to follow-up, patient's withdrawal, noncompliance, protocol violation, and other reasons.
[d] As a fixed-dose combination: 150 mg lamivudine, 300 mg zidovudine twice daily.

Through 48 weeks of therapy, the proportion of responders among patients with high viral loads (ie, baseline HIV RNA ≥100,000 copies/mL) was comparable for the REYATAZ and efavirenz arms. The mean increase from baseline in CD4+ cell count was 176 cells/mm^3 for the REYATAZ arm and 160 cells/mm^3 for the efavirenz arm.

Study AI424-008: REYATAZ 400 mg once daily compared to REYATAZ 600 mg once daily, and compared to nelfinavir 1250 mg twice daily, each in combination with stavudine and lamivudine twice daily. Study AI424-008 was a 48-week, randomized, multicenter trial, blinded to dose of REYATAZ, comparing REYATAZ at two dose levels (400 mg and 600 mg once daily) to nelfinavir (1250 mg twice daily), each in combination with stavudine (40 mg) and lamivudine (150 mg) given twice daily, in 467 antiretroviral treatment-naive patients. Patients had a mean age of 35 years (range: 18 to 69), 55% were Caucasian, and 63% were male. The mean baseline CD4+ cell count was 295 cells/mm^3 (range: 4 to 1003 cells/mm^3) and the mean baseline plasma HIV-1 RNA level was 4.7 $\log_{10}$ copies/mL (range: 1.8 to 5.9 $\log_{10}$ copies/mL). Treatment response and outcomes through Week 48 are presented in Table 23.

Table 23: Outcomes of Randomized Treatment Through Week 48 (Study AI424-008)

Outcome	REYATAZ 400 mg once daily + lamivudine + stavudine (n=181)	nelfinavir 1250 mg twice daily + lamivudine + stavudine (n=91)
Responder[a]	67% (33%)	59% (38%)
Virologic failure[b]	24%	27%
Rebound	14%	14%
Never suppressed through Week 48	10%	13%
Death	<1%	–
Discontinued due to adverse event	1%	3%
Discontinued for other reasons[c]	7%	10%

[a] Patients achieved and maintained confirmed HIV RNA <400 copies/mL (<50 copies/mL) through Week 48. Roche Amplicor® HIV-1 Monitor™ Assay, test version 1.0 or 1.5 as geographically appropriate.

[b] Includes viral rebound and failure to achieve confirmed HIV RNA <400 copies/mL through Week 48.

[c] Includes lost to follow-up, patient's withdrawal, noncompliance, protocol violation, and other reasons.

Through 48 weeks of therapy, the mean increase from baseline in CD4+ cell count was 234 cells/mm^3 for the REYATAZ 400-mg arm and 211 cells/mm^3 for the nelfinavir arm.

14.2 Adult Patients With Prior Antiretroviral Therapy

Study AI424-045: REYATAZ once daily + ritonavir once daily compared to REYATAZ once daily + saquinavir (soft gelatin capsules) once daily, and compared to lopinavir + ritonavir twice daily, each in combination with tenofovir + one NRTI. Study AI424-045 is an ongoing, randomized, multicenter trial comparing REYATAZ (300 mg once daily) with ritonavir (100 mg

once daily) to REYATAZ (400 mg once daily) with saquinavir soft gelatin capsules (1200 mg once daily), and to lopinavir + ritonavir (400/100 mg twice daily), each in combination with tenofovir and one NRTI, in 347 (of 358 randomized) patients who experienced virologic failure on HAART regimens containing PIs, NRTIs, and NNRTIs. The mean time of prior exposure to antiretrovirals was 139 weeks for PIs, 283 weeks for NRTIs, and 85 weeks for NNRTIs. The mean age was 41 years (range: 24 to 74); 60% were Caucasian, and 78% were male. The mean baseline CD4+ cell count was 338 cells/mm^3 (range: 14 to 1543 cells/mm^3) and the mean baseline plasma HIV-1 RNA level was 4.4 $\log_{10}$ copies/mL (range: 2.6 to 5.88 $\log_{10}$ copies/mL).

Treatment outcomes through Week 48 for the REYATAZ/ritonavir and lopinavir/ritonavir treatment arms are presented in Table 24. REYATAZ/ritonavir and lopinavir/ritonavir were similar for the primary efficacy outcome measure of time-averaged difference in change from baseline in HIV RNA level. Study AI424-045 was not large enough to reach a definitive conclusion that REYATAZ/ritonavir and lopinavir/ritonavir are equivalent on the secondary efficacy outcome measure of proportions below the HIV RNA lower limit of detection. [See *Clinical Pharmacology, Tables 19* and *20 (12.4)*.]

Table 24: Outcomes of Treatment Through Week 48 in Study AI424-045 (Patients with Prior Antiretroviral Experience)

Outcome	REYATAZ 300 mg + ritonavir 100 mg once daily + tenofovir + 1 NRTI (n=119)	lopinavir/ritonavir (400/100 mg) twice daily + tenofovir + 1 NRTI (n=118)	Difference[a] (REYATAZ-lopinavir/ritonavir) (CI)
HIV RNA Change from Baseline (log_{10} copies/mL)[b]	−1.58	−1.70	+0.12[c] (−0.17, 0.41)
CD4+ Change from Baseline (cells/mm^3)[d]	116	123	−7 (−67, 52)
Percent of Patients Responding[e]			
HIV RNA <400 copies/mL[b]	55%	57%	−2.2% (−14.8%, 10.5%)
HIV RNA <50 copies/mL[b]	38%	45%	−7.1% (−19.6%, 5.4%)

[a] Time-averaged difference through Week 48 for HIV RNA; Week 48 difference in HIV RNA percentages and CD4+ mean changes, REYATAZ/ritonavir vs lopinavir/ritonavir; CI = 97.5% confidence interval for change in HIV RNA; 95% confidence interval otherwise.

[b] Roche Amplicor® HIV-1 Monitor™ Assay, test version 1.5.

[c] Protocol-defined primary efficacy outcome measure.

[d] Based on patients with baseline and Week 48 CD4+ cell count measurements (REYATAZ/ritonavir, n=85; lopinavir/ritonavir, n=93).

[e] Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL (<50 copies/mL) through Week 48.

No patients in the REYATAZ/ritonavir treatment arm and three patients in the lopinavir/ritonavir treatment arm experienced a new-onset CDC Category C event during the study.

In Study AI424-045, the mean change from baseline in plasma HIV-1 RNA for REYATAZ 400 mg with saquinavir (n=115) was –1.55 log_{10} copies/mL, and the time-averaged difference in change in HIV-1 RNA levels versus lopinavir/ritonavir was 0.33. The corresponding mean increase in CD4+ cell count was 72 cells/mm^3. Through 48 weeks of treatment, the proportion of patients in this treatment arm with plasma HIV-1 RNA <400 (<50) copies/mL was 38% (26%). In this study, coadministration of REYATAZ and saquinavir did not provide adequate efficacy [see *Drug Interactions (7)*].

Study AI424-045 also compared changes from baseline in lipid values. [See *Adverse Reactions (6.1)*.]

Study AI424-043: Study AI424-043 was a randomized, open-label, multicenter trial comparing REYATAZ (400 mg once daily) to lopinavir/ritonavir (400/100 mg twice daily), each in

combination with two NRTIs, in 300 patients who experienced virologic failure to only one prior PI-containing regimen. Through 48 weeks, the proportion of patients with plasma HIV-1 RNA <400 (<50) copies/mL was 49% (35%) for patients randomized to REYATAZ (n=144) and 69% (53%) for patients randomized to lopinavir/ritonavir (n=146). The mean change from baseline was –1.59 $\log_{10}$ copies/mL in the REYATAZ treatment arm and –2.02 $\log_{10}$ copies/mL in the lopinavir/ritonavir arm. Based on the results of this study, REYATAZ without ritonavir is inferior to lopinavir/ritonavir in PI-experienced patients with prior virologic failure and is not recommended for such patients.

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.

16 HOW SUPPLIED/STORAGE AND HANDLING

REYATAZ® (atazanavir sulfate) Capsules are available in the following strengths and configurations of plastic bottles with child-resistant closures.

Product Strength*	Capsule Shell Color (cap/body)	Markings on Capsule (ink color)		Capsules per Bottle	NDC Number
		cap	body		
100 mg	blue/white	BMS 100 mg (white)	3623 (blue)	60	0003-3623-12
150 mg	blue/powder blue	BMS 150 mg (white)	3624 (blue)	60	0003-3624-12
200 mg	blue/blue	BMS 200 mg (white)	3631 (white)	60	0003-3631-12
300 mg	red/blue	BMS 300 mg (white)	3622 (white)	30	0003-3622-12
* atazanavir equivalent as atazanavir sulfate.					

REYATAZ (atazanavir sulfate) Capsules should be stored at 25° C (77° F); excursions permitted to 15–30° C (59–86° F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

A statement to patients and healthcare providers is included on the product's bottle label: **ALERT: Find out about medicines that should NOT be taken with REYATAZ**. FDA-Approved Patient Labeling is available for REYATAZ.

Patients should be informed that REYATAZ is not a cure for HIV infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease. Patients should be told that there are currently no data demonstrating that therapy with REYATAZ can reduce the risk of transmitting HIV to others through sexual contact.

17.1 Dosing Instructions

Patients should be told that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death. Patients should remain under the care of a physician while using REYATAZ. Patients should be advised to take REYATAZ with food every day and take other concomitant antiretroviral therapy as prescribed. REYATAZ must always be used in combination with other antiretroviral drugs. Patients should not alter the dose or discontinue therapy without consulting with their doctor. If a dose of REYATAZ is missed, patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped the patient should not double the next dose.

17.2 Drug Interactions

REYATAZ may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, nonprescription medication, or herbal products, particularly St. John's wort.

Patients receiving a PDE5 inhibitor and atazanavir should be advised that they may be at an increased risk of PDE5 inhibitor-associated adverse events including hypotension, visual changes, and prolonged penile erection, and should promptly report any symptoms to their doctor.

17.3 Cardiac Conduction Abnormalities

Patients should be informed that atazanavir may produce changes in the electrocardiogram (eg, PR prolongation). Patients should consult their physician if they are experiencing symptoms such as dizziness or lightheadedness.

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 (eg, Stevens-Johnson syndrome, 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, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, granulocytopenia, lymphadenopathy, and renal dysfunction) must discontinue REYATAZ and seek medical evaluation immediately.

17.5 Hyperbilirubinemia

Patients should be informed that asymptomatic elevations in indirect bilirubin have occurred in patients receiving REYATAZ. This may be accompanied by yellowing of the skin or whites of the eyes and alternative antiretroviral therapy may be considered if the patient has cosmetic concerns.

17.6 Fat Redistribution

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy including protease inhibitors and that the cause and long-term health effects of these conditions are not known at this time. It is unknown whether long-term use of REYATAZ will result in a lower incidence of lipodystrophy than with other protease inhibitors.

FDA-Approved Patient Labeling

Patient Information

REYATAZ® (RAY-ah-taz)

(generic name = **atazanavir sulfate**)

Capsules

ALERT: Find out about medicines that should NOT be taken with REYATAZ. Read the section "What important information should I know about taking REYATAZ with other medicines?"

Read the Patient Information that comes with REYATAZ before you start using it and each time you get a refill. There may be new information. This leaflet provides a summary about REYATAZ and does not include everything there is to know about your medicine. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is REYATAZ?

REYATAZ is a prescription medicine used with other anti-HIV medicines to treat people who are infected with the human immunodeficiency virus (HIV). HIV is the virus that causes acquired immune deficiency syndrome (AIDS). REYATAZ is a type of anti-HIV medicine called a protease inhibitor. HIV infection destroys CD4+ (T) cells, which are important to the immune system. The immune system helps fight infection. After a large number of (T) cells are destroyed, AIDS develops. REYATAZ helps to block HIV protease, an enzyme that is needed for the HIV virus to multiply. REYATAZ may lower the amount of HIV in your blood, help your body keep its supply of CD4+ (T) cells, and reduce the risk of death and illness associated with HIV.

Does REYATAZ cure HIV or AIDS?

REYATAZ does not cure HIV infection or AIDS. At present there is no cure for HIV infection. People taking REYATAZ may still get opportunistic infections or other conditions that happen with HIV infection. Opportunistic infections are infections that develop because the immune system is weak. Some of these conditions are pneumonia, herpes virus infections, and *Mycobacterium avium* complex (MAC) infections. **It is very important that you see your healthcare provider regularly while taking REYATAZ.**

REYATAZ does not lower your chance of passing HIV to other people through sexual contact, sharing needles, or being exposed to your blood. For your health and the health of others, it is important to always practice safer sex by using a latex or polyurethane condom or other barrier to lower the chance of sexual contact with semen, vaginal secretions, or blood. Never use or share dirty needles.

Who should not take REYATAZ?

Do not take REYATAZ if you:

- **are taking certain medicines.** (See "What important information should I know about taking REYATAZ with other medicines?") Serious life-threatening side effects or death may happen. Before you take REYATAZ, tell your healthcare provider about all medicines you are taking or planning to take. These include other prescription and nonprescription medicines, vitamins, and herbal supplements.
- **are allergic to REYATAZ or to any of its ingredients.** The active ingredient is atazanavir sulfate. See the end of this leaflet for a complete list of ingredients in REYATAZ. Tell your healthcare provider if you think you have had an allergic reaction to any of these ingredients.

What should I tell my healthcare provider before I take REYATAZ?

Tell your healthcare provider:

- **If you are pregnant or planning to become pregnant.** It is not known if REYATAZ can harm your unborn baby. Pregnant women have experienced serious side effects when taking REYATAZ with other HIV medicines called nucleoside analogues. You and your healthcare provider will need to decide if REYATAZ is right for you. If you use REYATAZ while you are pregnant, talk to your healthcare provider about the Antiretroviral Pregnancy Registry.
- **If you are breast-feeding.** You should not breast-feed if you are HIV-positive because of the chance of passing HIV to your baby. Also, it is not known if REYATAZ can pass into

your breast milk and if it can harm your baby. If you are a woman who has or will have a baby, talk with your healthcare provider about the best way to feed your baby.

- **If you have liver problems or are infected with the hepatitis B or C virus.** See "What are the possible side effects of REYATAZ?"
- **If you have end stage kidney disease** managed with hemodialysis.
- **If you have diabetes.** See "What are the possible side effects of REYATAZ?"
- **If you have hemophilia.** See "What are the possible side effects of REYATAZ?"
- **About all the medicines you take** including prescription and nonprescription medicines, vitamins, and herbal supplements. Keep a list of your medicines with you to show your healthcare provider. For more information, see "What important information should I know about taking REYATAZ with other medicines?" and "Who should not take REYATAZ?" Some medicines can cause serious side effects if taken with REYATAZ.

How should I take REYATAZ?

- **Take REYATAZ once every day exactly as instructed by your healthcare provider.** Your healthcare provider will prescribe the amount of REYATAZ that is right for you.
  - For adults who have never taken anti-HIV medicines before, the dose is 300 mg once daily with 100 mg of NORVIR® (ritonavir) once daily taken with food. For adults who are unable to tolerate ritonavir, 400 mg (two 200-mg capsules) once daily (without NORVIR®) taken with food is recommended.
  - For adults who have taken anti-HIV medicines in the past, the usual dose is 300 mg plus 100 mg of NORVIR® (ritonavir) once daily taken with food.
- Your dose will depend on your liver function and on the other anti-HIV medicines that you are taking. REYATAZ is always used with other anti-HIV medicines. If you are taking REYATAZ with SUSTIVA® (efavirenz) or with VIREAD® (tenofovir disoproxil fumarate), you should also be taking NORVIR® (ritonavir).
- **Always take REYATAZ with food** (a meal or snack) to help it work better. Swallow the capsules whole. **Do not open the capsules.** Take REYATAZ at the same time each day.
- **If you are taking antacids or didanosine (VIDEX® or VIDEX® EC)**, take REYATAZ 2 hours before or 1 hour after these medicines.
- **If you are taking medicines for indigestion**, **heartburn**, **or ulcers such as AXID® (nizatidine)**, **PEPCID AC® (famotidine)**, **TAGAMET® (cimetidine)**, **ZANTAC®**

(ranitidine), **AcipHex® (rabeprazole)**, **NEXIUM® (esomeprazole)**, **PREVACID® (lansoprazole)**, **PRILOSEC® (omeprazole), or PROTONIX® (pantoprazole)**, talk to your healthcare provider.

- **Do not change your dose or stop taking REYATAZ without first talking with your healthcare provider.** It is important to stay under a healthcare provider's care while taking REYATAZ.
- **When your supply of REYATAZ starts to run low**, get more from your healthcare provider or pharmacy. It is important not to run out of REYATAZ. The amount of HIV in your blood may increase if the medicine is stopped for even a short time.
- **If you miss a dose of REYATAZ**, take it as soon as possible and then take your next scheduled dose at its regular time. If, however, it is within 6 hours of your next dose, do not take the missed dose. Wait and take the next dose at the regular time. Do not double the next dose. **It is important that you do not miss any doses of REYATAZ or your other anti-HIV medicines.**
- **If you take more than the prescribed dose of REYATAZ**, call your healthcare provider or poison control center right away.

Can children take REYATAZ?

Dosing recommendations are available for children 6 years of age and older for REYATAZ Capsules. Dosing recommendations are not available for children from 3 months to less than 6 years of age. REYATAZ should not be used in babies under the age of 3 months.

What are the possible side effects of REYATAZ?

The following list of side effects is **not** complete. Report any new or continuing symptoms to your healthcare provider. If you have questions about side effects, ask your healthcare provider. Your healthcare provider may be able to help you manage these side effects.

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

- **yellowing of the skin or eyes.** These effects may be due to increases in bilirubin levels in the blood (bilirubin is made by the liver). Call your healthcare provider if your skin or the white part of your eyes turn yellow. Although these effects may not be damaging to your liver, skin, or eyes, it is important to tell your healthcare provider promptly if they occur.

- **a change in the way your heart beats (heart rhythm change).** Call your healthcare provider right away if you get dizzy or lightheaded. These could be symptoms of a heart problem.

- **diabetes and high blood sugar (hyperglycemia)** sometimes happen in patients taking protease inhibitor medicines like REYATAZ. Some patients had diabetes before taking protease inhibitors while others did not. Some patients may need changes in their diabetes medicine.

- **if you have liver disease** including hepatitis B or C, your liver disease may get worse when you take anti-HIV medicines like REYATAZ.
- **kidney stones** have been reported in patients taking REYATAZ. If you develop signs or symptoms of kidney stones (pain in your side, blood in your urine, pain when you urinate) tell your healthcare provider promptly.
- **some patients with hemophilia** have increased bleeding problems with protease inhibitors like REYATAZ.
- **changes in body fat.** These changes may include an increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the trunk. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known at this time.

Other common side effects of REYATAZ taken with other anti-HIV medicines include nausea; headache; stomach pain; vomiting; diarrhea; depression; fever; dizziness; trouble sleeping; numbness, tingling, or burning of hands or feet; and muscle pain.

Gallbladder disorders (which may include gallstones and gallbladder inflammation) have been reported in patients taking REYATAZ.

What important information should I know about taking REYATAZ with other medicines?

Do not take REYATAZ if you take the following medicines (not all brands may be listed; tell your healthcare provider about all the medicines you take). REYATAZ may cause serious, life-threatening side effects or death when used with these medicines.

- Ergot medicines: dihydroergotamine, ergonovine, ergotamine, and methylergonovine such as CAFERGOT®, MIGRANAL®, D.H.E. 45®, ergotrate maleate, METHERGINE®, and others (used for migraine headaches).
- ORAP® (pimozide, used for Tourette's disorder).
- PROPULSID® (cisapride, used for certain stomach problems).
- Triazolam, also known as HALCION® (used for insomnia).
- Midazolam, also known as VERSED® (used for sedation), when taken by mouth.

Do not take the following medicines with REYATAZ because of possible serious side effects:

- CAMPTOSAR® (irinotecan, used for cancer).
- CRIXIVAN® (indinavir, used for HIV infection). Both REYATAZ and CRIXIVAN sometimes cause increased levels of bilirubin in the blood.
- Cholesterol-lowering medicines MEVACOR® (lovastatin) or ZOCOR® (simvastatin).

Do not take the following medicines with REYATAZ because they may lower the amount of REYATAZ in your blood. This may lead to an increased HIV viral load. Resistance to REYATAZ or cross-resistance to other HIV medicines may develop:

- Rifampin (also known as RIMACTANE®, RIFADIN®, RIFATER®, or RIFAMATE®, used for tuberculosis).

- St. John's wort (*Hypericum perforatum*), an herbal product sold as a dietary supplement, or products containing St. John's wort.
- VIRAMUNE® (nevirapine, used for HIV infection).

Do not take the following medicine if you are taking REYATAZ and NORVIR® together:

- VFEND® (voriconazole).

The following medicines may require your healthcare provider to monitor your therapy more closely:

- CIALIS® (tadalafil), LEVITRA® (vardenafil), or VIAGRA® (sildenafil). REYATAZ may increase the chances of serious side effects that can happen with CIALIS, LEVITRA, or VIAGRA. Do not use CIALIS, LEVITRA, or VIAGRA while you are taking REYATAZ unless your healthcare provider tells you it is okay.
- LIPITOR® (atorvastatin) or CRESTOR® (rosuvastatin). There is an increased chance of serious side effects if you take REYATAZ with this cholesterol-lowering medicine.
- Medicines for abnormal heart rhythm: CORDARONE® (amiodarone), lidocaine, quinidine (also known as CARDIOQUIN®, QUINIDEX®, and others).
- VASCOR® (bepridil, used for chest pain).
- COUMADIN® (warfarin).
- Tricyclic antidepressants such as ELAVIL® (amitriptyline), NORPRAMIN® (desipramine), SINEQUAN® (doxepin), SURMONTIL® (trimipramine), TOFRANIL®(imipramine), or VIVACTIL® (protriptyline).
- Medicines to prevent organ transplant rejection: SANDIMMUNE® or NEORAL® (cyclosporin), RAPAMUNE® (sirolimus), or PROGRAF® (tacrolimus).
- The antidepressant trazodone (DESYREL® and others).
- Fluticasone propionate (ADVAIR®, FLONASE®, FLOVENT®), given by nose or inhaled to treat allergic symptoms or asthma. Your doctor may choose not to keep you on fluticasone, especially if you are also taking NORVIR®.

The following medicines may require a change in the dose or dose schedule of either REYATAZ or the other medicine:

- INVIRASE® (saquinavir).
- NORVIR® (ritonavir).
- SUSTIVA® (efavirenz).
- Antacids or buffered medicines.
- VIDEX® (didanosine).
- VIREAD® (tenofovir disoproxil fumarate).
- MYCOBUTIN® (rifabutin).
- Calcium channel blockers such as CARDIZEM® or TIAZAC® (diltiazem), COVERA-HS® or ISOPTIN SR® (verapamil) and others.
- BIAXIN® (clarithromycin).
- Medicines for indigestion, heartburn, or ulcers such as AXID® (nizatidine), PEPCID AC® (famotidine), TAGAMET® (cimetidine), or ZANTAC® (ranitidine).

Talk to your healthcare provider about choosing an effective method of contraception. REYATAZ may affect the safety and effectiveness of hormonal contraceptives such as birth control pills or the contraceptive patch. Hormonal contraceptives do not prevent the spread of HIV to others.

Remember:

1. **Know all the medicines you take.**
2. **Tell your healthcare provider about all the medicines you take.**
3. **Do not start a new medicine without talking to your healthcare provider.**

How should I store REYATAZ?

- Store REYATAZ Capsules at room temperature, 59° to 86° F (15° to 30° C). Do **not** store this medicine in a damp place such as a bathroom medicine cabinet or near the kitchen sink.
- Keep your medicine in a tightly closed container.

- Keep all medicines out of the reach of children and pets at all times. Do not keep medicine that is out of date or that you no longer need. Dispose of unused medicines through community take-back disposal programs when available or place REYATAZ in an unrecognizable, closed container in the household trash.

General information about REYATAZ

This medicine was prescribed for your particular condition. Do not use REYATAZ for another condition. Do not give REYATAZ to other people, even if they have the same symptoms you have. It may harm them. **Keep REYATAZ and all medicines out of the reach of children and pets.**

This summary does not include everything there is to know about REYATAZ. Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Remember no written summary can replace careful discussion with your healthcare provider. If you would like more information, talk with your healthcare provider or you can call 1-800-321-1335.

What are the ingredients in REYATAZ?

Active Ingredient: atazanavir sulfate

Inactive Ingredients: Crospovidone, lactose monohydrate (milk sugar), magnesium stearate, gelatin, FD&C Blue #2, and titanium dioxide.

US Patent Nos: 5,849,911 and 6,087,383

Bristol-Myers Squibb Company

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021567/S-019

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA 21-567
Submission Number	SE8
Submission Code	019
Letter Date	January 5, 2009
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Reviewer Name	Kirk M. Chan-Tack, M.D.
Review Completion Date	September 22, 2009
Established Name	Atazanavir (ATV)
Trade Name	Reyataz
Therapeutic Class	HIV Protease Inhibitor
Applicant	Bristol Myers Squibb
Priority Designation	S
Formulation	Capsule
Dosing Regimen	300 mg orally daily plus ritonavir (RTV) 100 mg daily
Indication	Treatment of HIV-1 infection
Intended Population	Treatment-naïve HIV-infected adults

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The 96-week efficacy and safety data presented in this supplement support the dosing regimen of atazanavir/ritonavir (ATV/RTV) 300/100 mg QD for treatment of HIV-1 infection in treatment-naïve adults.

FDA review of the 48-week data from Study 138 supported traditional approval of this regimen for treatment-naïve adults. In this submission, Study 138 is updated to include the 96-week efficacy and safety results for ATV/RTV 300/100 mg QD in treatment-naïve adults. Overall, the 96-week efficacy and safety data are consistent with the results previously obtained at Weeks 48 and 96.

In Study 138, ATV/RTV was non-inferior to lopinavir (LPV)/RTV in treatment-naïve HIV-infected adults. Review of the safety data submitted in this supplement did not identify any new toxicities with ATV/RTV. As expected, a higher incidence of hyperbilirubinemia was observed with ATV/RTV as a result of increased ATV concentrations. Overall, ATV/RTV-treated subjects had favorable lipid profiles compared to LPV/RTV at Weeks 48 and 96. The observed magnitude of dyslipidemia was less with ATV/RTV than LPV/RTV. Fewer subjects initiated lipid lowering therapy in the ATV/RTV group compared to the LPV/RTV group. However, this finding was not associated with other benefits such as a reduced incidence of lipodystrophy or cardiovascular disease. The observed toxicities did not outweigh the benefit of ATV/RTV as an option for treatment-naïve adults.

1.2 Risk Benefit Analysis

Use of ATV/RTV 300/100 mg QD in treatment-naïve HIV-infected adults is supported by safety, efficacy, pharmacokinetic, and microbiology data. Review of the 96-week safety data for Study 138 submitted in this supplement did not identify any new toxicities with use of ATV/RTV in treatment-naïve adults. Adverse events leading to discontinuation were overall low (ATV/RTV – 13, LPV/RTV – 22) through Week 96. The most common adverse events leading to study discontinuation in subjects receiving ATV/RTV were jaundice (n=3), nausea (n=2), abdominal distention (n=1), abdominal pain (n=1), rash (n=2), and increased transaminases (n=1). Over 96 weeks, hyperbilirubinemia was the only Grade 2-4 treatment-related AE (7.5% versus 0.2%) reported with higher frequency (≥ 5 % difference) in ATV/RTV recipients than LPV/RTV recipients.

Overall, safety results at Week 96 were similar to Week 48. Among other Grade 2-4 treatment-related AEs of interest, rash was slightly higher among ATV/RTV recipients compared to LPV/RTV recipients (3.2% versus 2.5%); however, diarrhea (2.5% versus 12.4%), hypertriglyceridemia (1.1% versus 5.0%), and hyperlipidemia (0% versus 1.6%) were reported

with a lower frequency in ATV/RTV recipients. The most common Grade 3–4 laboratory abnormalities reported among ATV/RTV recipients were elevation of total bilirubin (44.1%), total cholesterol (10.8%), creatine kinase (7.8%), and decreased neutrophils (4.8%). All other Grade 3–4 laboratory abnormalities, including transaminases (ALT – 2.5%, AST – 2.5%), occurred with a frequency of less than 3%.

Overall, efficacy results at Week 96 were similar to Week 48. Efficacy analyses showed ATV/RTV was, with high statistical confidence, no more than 10% worse than the comparator arm. Efficacy outcomes (proportion of subjects with HIV-RNA < 50 copies/mL at Week 96) for ATV/RTV were overall similar to LPV/RTV (75% versus 68%).

Microbiology data from Study 138 also support approval of ATV/RTV for treatment-naïve HIV-infected adults. Results demonstrated a comparable number of treatment failures in treatment-naïve patients treated with ATV/RTV and LPV/RTV, and overall findings were similar at Weeks 48 and 96.

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 new post-marketing concerns emerged during review of this supplement. As such, no new risk management activity is required.

1.4 Recommendations on Post Marketing Activities/Phase 4 Commitments

No additional post-marketing commitments are requested with this supplement. The following Phase 4 commitment is outstanding:

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

In NDA 21-567 SE5-015 (letter date: September 27, 2007), the Applicant submitted data for the capsule formulation in patients six years to 18 years of age. In that submission, the Applicant 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 the potential issue of neonatal and/or infant hyperbilirubinemia was previously granted. The clinical review team recommended granting the partial deferral pending the submission of the supplement for the powder formulation. From a preliminary review of the data from patients who received the powder formulation (to be formally submitted in the future), 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. On March 25, 2008, the review team recommended the following PREA requirement that was accepted by the Applicant:

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

2 Introduction and Regulatory Background

2.1 Product Information

Established Name: Atazanavir
Trade Name: Reyataz
Chemical: $C_{38}H_{52}N_6O_7 \cdot H_2SO_4$
Class: Protease Inhibitor
Formulation: Capsules (100 mg, 200 mg, 300 mg, (b) (4)
Dosage: 1) 300 mg daily and RTV 100 mg daily for treatment-naïve and treatment-experienced adults
2) 400 mg daily for treatment-naïve adults
Indication: In combination with other antiretroviral agents for the treatment of HIV-1 infection.

2.2 Tables of Currently Available Treatments for Proposed Indications

As of August 2009, 26 drugs are approved for the treatment of HIV-1 infection (this list does not include fixed dose combinations or different formulations). These drugs fall into six classes based on mechanism of action in the HIV life cycle: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion/entry inhibitors, CCR5 co-receptor inhibitors, and integrase inhibitors (Table 1).

Table 1: Currently Approved Antiretrovirals

Drug Class	Generic Name	Trade Name
NRTI*	Zidovudine	Retrovir®
	Didanosine	Videx®
	Stavudine	Zerit®
	Lamivudine	Epivir®
	Abacavir	Ziagen®
	Tenofovir	Viread®
	Emtricitabine	Emtriva®
	Zalcitabine*	Hivid®
NNRTI	Delavridine	Rescriptor®
	Nevirapine	Viramune®

	Efavirenz	Sustiva®
	Etravirine	Intelence®
PI	Indinavir	Crixivan®
	Ritonavir	Norvir®
	Saquinavir, hard gel	Invirase®
	Saquinavir, soft gel*	Fortovase®
	Nelfinavir	Viracept®
	Amprenavir*	Agenerase®
	Fosamprenavir	Lexiva®
	Atazanavir	Reyataz®
	Lopinavir/ritonavir fixed dose combination	Kaletra®
	Tipranavir	Aptivus®
	Darunavir	Prezista®
Fusion Inhibitor	Enfuvirtide	Fuzeon®
CCR5 Inhibitor	Maraviroc	Selzentry®
Integrase Inhibitor	Raltegravir	Isentress®

***Sale and distribution of zalcitabine (ddC, Hivid®) was discontinued on December 31, 2006. Sale and distribution of saquinavir soft gelatin capsules (SQV, Fortovase) was discontinued on February 15, 2006. Sale and distribution of amprenavir (AMP, Agenerase®) was discontinued on October 31, 2007 (Reference: Drug Discontinuation. Available at: http://www.fda.gov/CDER/Drug/shortages/default.htm#disc).**

The use of highly active therapy (HAART) has decreased the morbidity and mortality of HIV disease. Of PI-based regimens, atazanavir/ritonavir (ATV/RTV), lopinavir/ritonavir (LPV/RTV), and fosamprenavir/ritonavir (FPV/RTV) are listed as preferred options in the 2008 DHHS HIV-1 Adult Treatment Guidelines. These guidelines also state "treatment goals should be maximal and durable suppression of viral load, restoration and preservation of immunologic function, improvement of quality of life, and reduction of HIV-related morbidity and mortality"(Available at: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf. Accessed July 7, 2009). Obstacles in achieving these goals include drug side effects, drug intolerance, and drug resistance. Antiretroviral therapy is often associated with significant drug toxicities such as hepatotoxicity, hyperlipidemia, hypertriglyceridemia, rash, fat redistribution, hyperglycemia, pancreatitis, and lactic acidosis. When selecting an antiretroviral (ARV) regimen, clinicians must carefully consider potential side effects, especially when the possibility for overlapping toxicities exists.

2.3 Availability of Proposed Active Ingredient in the United States

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

2.4 Important Safety Issues With Consideration to Related Drugs

Class-related adverse events/laboratory abnormalities and potential for significant drug-drug interaction potential are common for the approved protease inhibitors (PIs). Ritonavir (RTV) has significant drug-drug interactions due to its potent inhibition of CYP3A4 metabolism. Several drug interaction studies have been recently included in previous label supplements.

The addition of RTV may also increase the magnitude of the interaction with ATV and other agents. RTV-containing regimens are known to adversely affect lipid profiles to varying degrees. While a favorable lipid profile was seen with ATV compared to nelfinavir (NFV), lopinavir/ritonavir (LPV/RTV) and efavirenz (EFV), 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, hepatotoxicity, rash, lipodystrophy, (b) (4) increased bleeding episodes in patients with hemophilia, and fat redistribution.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Study 138 of ATV/RTV in treatment-naïve patients began in November 2005 and was completed in June 2008. In November 2007, the Applicant submitted a pre-NDA package and questions for the FDA review team. FDA provided written comments that were accepted by the Applicant. In December 2007, the Applicant submitted the 48-week results from Study 138 as a supplemental NDA for ATV/RTV use in treatment-naïve adults, which received approval on September 30, 2008. The Applicant has now submitted the 96 week results from Study 138 to provide additional long-term safety and efficacy data for ATV/RTV in treatment-naïve adults.

2.6 Other Relevant Background Information

At this time, no additional information is available from regulatory actions in other countries.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

In light of the previously conducted inspections and relative lack of subject drop-outs and missing data, no DSI audits were requested by the review team.

3.2 Compliance with Good Clinical Practices

No problems with informed consent, specific study sites, or study conduct were identified. All studies were written to conform to accepted ethical standards and were reviewed by Institutional Review Boards overseeing each investigative site.

3.3 Financial Disclosures

Pursuant to 21 CFR 54.2(e), the financial certification statement provided by the Applicant was reviewed. The Applicant requested that investigators and sub-investigators from all studies contained in the sNDA disclose proprietary interest or significant equity as defined in the regulations. The Applicant has included a list of all investigators and sub-investigators who responded to their request on form 3454. The Applicant submitted updated financial disclosure information for review. The financial interest statements were acceptable, No new financial interests were reported.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

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

4.2 Clinical Microbiology

A censored dataset was used for the baseline resistance and outcome analyses. The analysis was as-treated and as such also included subjects who discontinued before achieving suppression after 4 weeks. Please refer to Dr. Lisa Naeger's FDA Microbiology review for a detailed analysis of the resistance data. A summary of the important microbiology issues raised in Dr. Naeger's review are presented below.

Study AI424138 was a 96-week study conducted to compare the proportion of subjects with HIV RNA <50 copies/mL (copies/mL) at Week 48 between ATV/RTV QD + tenofovir (TDF) and emtricitabine (FTC) versus LPV/RTV 400/100 mg BID + TDF and FTC treatment regimens in treatment-naïve subjects. Genotypic and phenotypic resistance profiles were determined for subjects who met the criteria for virologic failure through Week 96 (HIV RNA > 400 copies/mL). For the FDA analysis, virologic failures included 83 subjects (40 ATV/RTV; 43 LPV/RTV) who had a virologic rebound without resuppression, were never suppressed through Week 96 and on study at Week 96, discontinued due to insufficient viral load response before Week 96 or discontinued before achieving suppression after Week 4. Five subjects (0003-00246, 0065-00596, 0111-00736, 0115-00009, 0115-00014) were removed from the analysis

because they had viral loads ≤400 copies/mL; therefore, there were 39 virologic failures analyzed in both arms. Baseline resistance was comparable between both arms.

In an as-treated censored analysis, 7.9% and 8.8% of subjects had virologic failure through 48 weeks in the ATV/ RTV and LPV/ RTV arms, respectively. There were 10% and 12% subjects with virologic failure through 96 weeks in the ATV/RTV and LPV/RTV arms, respectively. Genotypes and phenotypes of the virologic failure subjects were analyzed for emergence of genotypic and phenotypic resistance through 96 weeks. Five of the 40 isolates in the ATV/RTV arm were phenotypically resistant to ATV (>2-fold change from reference) at failure. Two of these isolates were ATV resistant at baseline, while the other three had ATV resistance emerge on therapy.

Two ATV/RTV-Virologic Failure Isolates with Baseline ATV Resistance

The two baseline ATV-resistant isolates had IAS-defined major PI substitutions at baseline. The I50L substitution emerged on study in one of these subjects and was associated with a 17-fold decrease in ATV susceptibility from baseline. This subject isolate also had baseline RT substitutions M41L, D67G, M184V, T215Y and T219G which conferred baseline FTC and TDF resistance. The other failure isolate with baseline ATV resistance had additional IAS-defined major PI substitutions (V32I, M46I and I84V) emerge on ATV treatment associated with a 3-fold decrease in ATV susceptibility from baseline. This isolate had baseline RT substitutions M41L, T215Y, K103K/R and M184V, which conferred baseline FTC resistance, but not detectable TDF resistance.

Three ATV/RTV-Virologic Failure Isolates had Reduced ATV Susceptibility Emerge on Therapy

One ATV/RTV-virologic failure subject isolate developed the major IAS PI substitutions V32I, M46I, and L90M on ATV/RTV treatment as well as L10L/F, I15I/V, K20K/R, E35D, K43K/T, G73S, and I85I/V. These substitutions conferred a 56-fold decrease in ATV susceptibility from reference and a 71-fold reduction from baseline. The RT substitution M184V emerged on treatment conferring FTC resistance. The RT mixture substitutions K65K/R, K70K/E and L210L/W also emerged, but did not confer detectable TDF resistance. The other two subjects had no IAS-defined major PI mutations at baseline and did not have any PI or RT mutations emerge on treatment. The ATV phenotype for these two isolates was 2.11- and 2.14-fold and probably reflects the variability of the assay rather than true reduced ATV susceptibility.

(b) (4)

[redacted]

LPV/RTV-Virologic Failure Isolates

In the LPV/RTV arm, one virologic failure patient's isolates had a 69-fold decrease in LPV susceptibility emerge on therapy with the development of PI substitutions L10V, V11I, I54V, G73S, and V82A in addition to baseline PI substitutions V32I, I54I/V, V82A/V, L90M, L10I/L, A71I, G73S/G and L89V. Six of the LPV/r treatment failure isolates developed emtricitabine resistance with the emergence of the M184V substitution, one had both emtricitabine and TDF

resistance emerge on treatment and one additional virologic failure subject isolate had TDF resistance emerge on treatment.

Overall, the M184V substitution and emtricitabine resistance emerged on treatment in 1 ATV/RTV and 7 LPV/RTV virologic failure subjects. Phenotypic resistance to TDF emerged in 2 LPV/RTV virologic failure isolates and was present at baseline in one ATV/RTV virologic failure isolate. One treatment failure isolate in the ATV/RTV arm had ATV resistance emerge on therapy. Only one subject isolate with baseline ATV resistance and 3 major PI substitutions at baseline had the emergence of the I50L substitution. Cross-resistance to other PIs emerged in some treatment failure subject isolates treated with ATV/RTV. However, some of the failure subject isolates were cross-resistant at baseline.

4.3 Preclinical Pharmacology/Toxicology

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

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

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

4.4.2 Pharmacodynamics

Please see Section 6 for analyses of the viral load (VL) data. No additional pharmacodynamic data were provided in this submission.

4.4.3 Pharmacokinetics

This sNDA contained no new clinical pharmacology data. Please refer to the original FDA NDA review for additional information.

5 Sources of Clinical Data

This review is primarily based on data from one Phase 3 trial (Study 138) conducted by the Applicant. Data from the Applicant's postmarketing database, as well as the FDA's Adverse Events Reporting System (AERS), were also reviewed to evaluate safety.

5.1 Table of Clinical Studies

Table 2 outlines the study type, geographic location, numbers of subjects, and status for the clinical trial submitted in this supplement.

Table 2: Clinical Study AI424138

Study	Study Type	Country or Continent	Design	Dose and Duration	Total No. of Subjects/ARV experience	Status
Phase 3 Study - Treatment-Naïve						
Study 138	Pivotal safety and efficacy	North America, South America Europe, Africa, Asia, Australia	Open-label, randomized, active control	ATV/RTV 300/100mg QD vs LPV/RTV 400/100 mg BID NRTI backbone: TDF/FTC 300/200 mg QD Duration: 96 wks	441 (ATV/RTV) vs 437 (LPV/RTV) Treatment-naive HIV-1 infected adults with screening HIV RNA ≥ 5000 c/mL	Completed

ATV/RTV, atazanavir/ritonavir; LPV/RTV, lopinavir/ritonavir; FTC, emtricitabine; TDF, tenofovir

5.2 Review Strategy

Safety data review included case report tabulations and case report forms when applicable. FDA clinical and statistical reviewers collaborated extensively throughout the review process, and a number of the efficacy analyses in this review were performed by the FDA statistical reviewer. Additionally, there was significant interaction between the clinical and microbiology reviewers. FDA statistical and microbiology reviewer assessments are summarized in this document, but complete details of their findings are available in the respective discipline reviews.

5.3 Discussion of Individual Studies

Study 138 was a 96-week, randomized, open-label, multi-national study to investigate the safety and efficacy of atazanavir/ritonavir capsules (ATV/RTV, 300/100 mg QD) compared to lopinavir/ritonavir capsules (LPV/RTV, 400/100 mg BID), both in combination with fixed-dose tenofovir/emtricitabine tablets (TDF/FTC, 300/200 mg QD), in treatment-naïve HIV-infected adults. Randomization was stratified for HIV-RNA (<100,000 copies/mL and > 100,000 copies/mL) and geographic region.

STUDY PERIOD:
Study Initiation Date: 18-November-2005
Study Completion Date: Completed
Database lock for this report: 23-June-2008

Key inclusion criteria:

- HIV-positive
- VL >5000 copies/mL
- Treatment-naïve
- Male and female patients who were ≥18 years old

Patients could have any CD4+ cell count.

Key exclusion criteria:
Pre-existing renal disease (defined as calculated creatinine clearance < 60 mL/min)

Study Treatments
ATV/RTV Group:
• ATV: 2 x 150 mg capsules once daily with food (meal or snack)
• RTV: 1 x 100 mg capsule once daily with food (meal or snack)
• TDF/FTC: 1 x 300/200 mg tablet once daily with food (meal or snack)

LPV/RTV Group:
• LPV/RTV: 3 x 133/33.3 mg capsules twice daily with food (meal or snack)
• TDF/FTC: 1 x 300/200 mg tablet once daily with food (meal or snack)

OBJECTIVES:
Primary Objectives:

- To compare the proportion of subjects with HIV-RNA < 50 copies/mL at Week 48 between ATV/RTV (300/100 mg QD) and LPV/RTV (400/100 mg BID), each given with TDF/FTC (300/200 mg QD).

Secondary Objectives:

- Proportion of subjects with HIV-RNA < 50 copies/mL at Week 96.
- Proportion of subjects with HIV-RNA < 400 copies/mL at Week 96.
- Time to loss of virologic response (defined as the earliest of virologic rebound, discontinuation, never responded or never treated).
- Changes in $\log_{10}$ HIV-RNA from baseline through Week 96.
- Changes in absolute CD4 count from baseline through Week 96.
- Frequency of adverse events (AEs), serious adverse events (SAEs), discontinuations due to AEs, and laboratory abnormalities.
- Changes in fasting lipids from baseline through Week 96, and proportions of subjects with NCEP-specified categories of fasting lipids from baseline through Week 96.
- Changes in fasting glucose and insulin from baseline through Week 96.
- Phenotypic/genotypic resistance testing of isolates from subjects with virologic failure.

Statistical Issues – please refer to the original FDA statistical NDA review for additional details
1) Sample Size and Power
According to the Applicant, a target sample size of 882 randomized subjects provides 90% power to demonstrate that ATV/RTV/TDF/FTC is non-inferior to the LPV/RTV/TDF/FTC, as

assessed by the proportion of subjects with HIV-RNA < 50 copies/mL at Week 48, assuming the following:

- A 2-sided 95% confidence interval (CI)
- A lower acceptance limit of -10%
- 70% of subjects on both ATV/RTV and LPV/RTV regimens have been on study therapy through Week 48 with HIV-RNA < 50 copies/mL at Week 48

A response rate of 60% for each treatment regimen at Week 96 will provide 85% power to establish non-inferiority, assuming a 2-sided 95% CI and a lower acceptance limit of -10%.

2) Statistical Analyses

The primary study endpoint was the proportion of subjects with HIV-RNA < 50 copies/mL at Week 48. The primary analysis was to demonstrate non-inferiority of ATV/RTV compared to LPV/RTV with respect to the proportion of subjects with HIV-RNA < 50 copies/mL at Week 48. Using a margin of 10% to assess non-inferiority, and assuming a response rate of 60% in each treatment arm, the Applicant calculated that the number of subjects enrolled would provide approximately 90% power to test this hypothesis at the 2.5% significance level. If the 95% confidence interval was above -10%, the Applicant would conclude ATV/RTV was non-inferior to LPV/RTV.

In Study 138, confidence intervals for the difference between ATV/RTV and LPV/RTV were computed using stratification by baseline HIV-RNA and continent. Efficacy relative to imputed placebo was inferred if 2-sided 95% lower bound for the difference was greater than -10%. The primary analysis used non-completers as failures. Treatment regimens were compared using the difference in proportions (ATV/RTV-LPV/RTV) and 95% confidence interval (CI) based on a stratified normal approximation.

6 Review of Efficacy

Efficacy Summary

The efficacy analyses conducted in this review were the proportion of subjects achieving HIV-RNA < 50 and < 400 copies/mL at Week 96. Additionally, the proportion of patients achieving HIV-RNA < 50 and < 400 copies/mL using the time to loss of virologic response (TLOVR) algorithm was also evaluated. Both analyses are presented in this review. Based on efficacy analyses conducted in this review, the label will be updated with the proportion of patients achieving HIV-RNA < 50 copies/mL at Week 96. This analysis is included in other ARVs labels for studies with 96-week results.

Using as-treated cohort for efficacy analyses, proportion of subjects with HIV-RNA < 50 copies/mL at Week 96 was 68% (303/443) for ATV/RTV versus 63% (278/440) for LPV/RTV. Week 96 efficacy results were overall similar to Week 48 (proportion of subjects with HIV-RNA < 50 copies/mL: ATV/RTV – 78%, LPV/RTV – 77%). Table 6 describes the TLOVR results for HIV RNA < 50 and < 400 copies/mL in treatment-naïve patients.

CD4 cell counts were obtained at several time-points throughout the study period. The median increase in absolute CD4 count from baseline to Week 96 was 261 cells/mm^3 and 200 cells/mm^3 for ATV/RTV and LPV/RTV respectively (see Tables 5 and 6). Overall, primary and secondary efficacy analyses suggest ATV/RTV is non-inferior to LPV/RTV for treatment-naïve HIV-infected adults. The efficacy outcomes at Week 48 and Week 96 are overall similar.

6.1 Indication

Reyataz (atazanavir sulfate) is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.

6.1.1 Methods

Week 96 efficacy data for Study 138 were reviewed in this submission. This included review of the datasets, clinical study reports, and case report tabulations. Efficacy analyses were based on the intent-to-treat (ITT) population and included proportion of patients achieving HIV-RNA < 50 and < 400 copies/mL at Week 96. The analysis was also conducted using the TLOVR algorithm.

For a detailed review of efficacy, please refer to Dr. Tom Hammerstrom's FDA Statistical review.

6.1.2 Demographics

Baseline demographics were evenly matched between the treatment groups and were unchanged from the Week 48 data (Table 3).

Table 3: Subject baseline characteristics (as-randomized)

	ATV/RTV (n=440)	LPV/RTV (n=443)	Total (n=883)
Median age (range), years	34 (19-72)	36 (19-71)	35 (19-72)
Gender			
Male, n (%)	302 (68.6)	304 (68.6)	606 (68.6)
Female, n (%)	138 (31.4)	139 (31.4)	277 (31.4)
Race/Ethnicity			
Caucasian, n (%)	207 (47.0)	221 (49.9)	428 (48.4)
Black, n (%)	83 (18.9)	80 (18.1)	163 (18.5)
Asian, n (%)	42 (9.5)	41 (9.3)	83 (9.4)
Hispanic/Latino, n (%)	7 (1.6)	6 (1.4)	13 (1.5)
Mestizo, n (%)	72 (16.4)	68 (15.3)	140 (15.9)
Mixed, n (%)	29 (6.6)	27 (6.2)	56 (6.3)
CDC Class C AIDS, n (%)	19 (4.3)	24 (5.4)	43 (4.9)
Median (range) baseline CD4+, cells/mm^3	205 (2-794)	204 (4-810)	205 (2-810)
CD4+ distribution, cells/mm^3			
<50, n (%)	58 (13.2)	48 (10.8)	106 (12.0)
50 – < 100, n (%)	45 (10.2)	29 (6.5)	74 (8.4)
100 – < 200, n (%)	106 (24.1)	134 (30.2)	240 (27.2)
200 – < 350, n (%)	157 (35.7)	164 (37.0)	321 (36.4)
350 – < 500, n (%)	53 (12.0)	50 (11.3)	103 (11.7)
≥ 500, n (%)	12 (2.7)	14 (3.2)	26 (2.9)
Missing, n (%)	9 (2.0)	4 (0.9)	13 (1.5)
Median (range) baseline HIV-RNA, copies/mL	5.01 (2.60-5.88)	4.96 (3.32-5.88)	4.98 (2.60-5.88)
HIV-RNA distribution, copies/mL			
<30, 000, n (%)	97 (22.0)	100 (22.6)	197 (22.3)
30, 000 – < 100,000, n (%)	118 (26.8)	135 (30.5)	253 (28.7)
100, 000 – < 500,000, n (%)	172 (39.1)	164 (37.0)	336 (38.0)
≥ 500,000, n (%)	53 (12.0)	44 (9.9)	97 (11.0)
Missing, n (%)	0	0	0
HIV subtype B, n (%)	280 (63.7)	276 (62.3)	556 (63.0)
HIV subtype C, n (%)	73 (16.6)	65 (14.7)	118 (13.4)
HIV subtype AE, n (%)	28 (6.4)	28 (6.3)	56 (6.3)
Hepatitis B surface antigen (HBsAg)			
Positive, n (%)	24 (5.5)	20 (4.5)	44 (5.0)
Negative, n (%)	415 (94.3)	422 (95.3)	837 (94.8)

Missing, n (%)	1 (0.2)	1 (0.2)	2 (0.2)
Hepatitis C antibody (HCV-Ab)			
Positive, n (%)	40 (9.1)	33 (7.5)	73 (8.3)
Negative, n (%)	399 (90.7)	409 (92.3)	808 (91.5)
Missing, n (%)	1 (0.2)	1 (0.2)	2 (0.2)
HBsAg and/or HCV-Ab*			
Positive, n (%)	61 (13.9)	51 (11.5)	112 (12.7)
Negative, n (%)	378 (85.9)	391 (88.3)	769 (87.1)
Missing, n (%)	1 (0.2)	1 (0.2)	2 (0.2)

*Five subjects (ATV/RTV – 3 subjects, LPV/RTV – 2 subjects) were infected with both hepatitis B and C.
Source: December 21, 2007 submission, Tables S.3.2A and S.3.2B (SCS Appendix).

Reviewer Comment
Similar to Study 034 (ATV 400 mg QD in treatment-naïve adults), Study 138 provides good representation of women (277/883, 31%) and Blacks (163/883, 18%). The other baseline demographics, clinical, immunologic, and virologic characteristics are similar to other recent treatment-naïve studies.

6.1.3 Patient Disposition

A total of 883 treatment-naive subjects were randomized in Study 138: 440 to ATV/RTV and 443 to LPV/RTV. All subjects received TDF/FTC QD. Two subjects in the ATV/RTV group and 3 in the LPV/RTV group were never treated. Three subjects (7-8, 115-5, and 116-4) were randomized to LPV/RTV but were treated with ATV/RTV. These three subjects were analyzed as-randomized on LPV/RTV in all efficacy analyses, but as-treated on ATV/RTV in all safety analyses. Consequently, in safety analyses, there were 441 subjects in the ATV/RTV group (440 subjects randomized minus 2 subjects who never treated plus 3 subjects given ATV/RTV instead of LPV/RTV) and 437 subjects in the LPV/RTV group (443 subjects randomized minus 3 subjects who never treated minus 3 subjects given ATV/RTV instead of LPV/RTV).

The proportion of subjects who discontinued by Week 48 was 9.6% and 13.9% on ATV/RTV and LPV/RTV, respectively. The proportion of subjects who discontinued by Week 96 was 9.6% and 13.9% on ATV/RTV and LPV/RTV, respectively (Table 4).

Table 4: Subject disposition at Week 48 and Week 96 (as-randomized)

	ATV/RTV		LPV/RTV		Total	
Subjects randomized, n (%)	440		443		883	
Subjects treated, n (%)	438 (99.5)		440* (99.3)		878 (99.4)	
	Week 48	Week 96	Week 48	Week 96	Week 48	Week 96
Discontinued, n (%)	42 (9.6)	77 (17.5)	61 (13.9)	96 (21.7)	103 (11.7)	173 (19.6)
Adverse event, n (%)	11 (2.5)	13 (3.0)	15 (3.4)	22 (5.0)	26 (2.9)	35 (4.0)
Death, n (%)	6 (1.4)	6 (1.4)	6 (1.4)	6 (1.4)	12 (1.4)	12 (1.4)
Lack of efficacy, n (%)	5 (1.1)	16 (3.6)	8 (1.8)	10 (2.3)	13 (1.5)	26 (2.9)
Non-adherence, n (%)	6 (1.4)	14 (3.2)	9 (2.0)	16 (3.6)	15 (1.5)	30 (3.4)
Loss to follow-up, n (%)	6 (1.4)	12 (2.7)	6 (1.4)	12 (2.7)	12 (1.4)	24 (2.7)
Consent withdrawn, n (%)	4 (0.9)	5 (1.1)	13 (2.9)	18 (4.1)	17 (1.9)	23 (2.6)

Pregnancy, n (%)	3 (0.7)	8 (1.8)	4 (0.9)	7 (1.6)	7 (0.8)	15 (1.7)
No longer meets study criteria, n (%)	1 (0.2)	2 (0.5)	0 (0.0)	3 (0.7)	1 (0.1)	5 (0.6)
Other protocol violation, n (%)	1 (0.2)	1 (0.2)	2 (0.4)	2 (0.4)	3 (0.3)	3 (0.3)

*Three subjects were randomized to LPV/RTV but were treated with ATV/RTV.
For efficacy analyses (as-randomized cohort): ATV/RTV 440, LPV/RTV 443.
For safety analyses (as-treated cohort): ATV/RTV 441 (440-2+3), LPV/RTV 437 (443-3-3).
Source: December 21, 2007 submission, January 5, 2009 submission.

Reviewer Comment
Overall, both regimens are tolerable over 48 and 96 weeks. Discontinuation rates were lower for ATV/RTV than LPV/RTV at both Weeks 48 and 96. Discontinuations due to adverse events were also lower for ATV/RTV than LPV/RTV at both Weeks 48 and 96.

6.1.4 Analysis of Primary Endpoint

Similar to Week 48, ATV/RTV appears to be non-inferior to LPV/RTV for treatment-naïve HIV-infected adults based on the proportion of subjects with HIV-RNA < 50 copies/mL at Week 96, using the Confirmed Virologic Response (CVR) Non-Completer = Failure CVR (NC = F; intention-to-treat [ITT]) response definition. Using as-treated cohort for efficacy analyses, FDA analyses showed that the proportion of subjects with HIV-RNA < 50 copies/mL at Week 48 was 78% (346/443) for ATV/RTV versus 77% (339/440) for LPV/RTV (difference estimate 1.1 [95% confidence interval (CI)]: -4.4, 6.6). The lower confidence limit of the difference estimate was greater than the boundary of -10%, indicating non-inferiority of ATV/RTV to LPV/RTV. Using as-treated cohort for efficacy analyses, FDA analyses showed that the proportion of subjects with HIV-RNA < 50 copies/mL at Week 96 was 75% (330/443) for ATV/RTV versus 68% (298/440) for LPV/RTV (difference estimate 6.8 [95% confidence interval (CI)]: 0.8, 12.7).

Treatment response and outcomes through Week 96 are presented in Table 5. As discussed with the Applicant, efficacy analyses were based on the following snapshot rule, which requires that the last HIV-RNA measurement in the week 90-102 window to be <50 copies/mL; and counts as a failure any subject with no HIV-RNA measurement in the window.

Table 5: Outcomes of Treatment Through Week 96 (Study AI424-138)

Outcome	REYATAZ 300 mg + ritonavir 100 mg (once daily) with tenofovir/emtricitabine (once daily)[a] (n=441) 96 Weeks	lopinavir 400 mg + ritonavir 100 mg (twice daily) with tenofovir/emtricitabine (once daily)[a] (n=437) 96 Weeks
Responder[b,c,d]	75%	68%
Virologic failure[e]	17%	19%
Rebound	8%	10%
Never suppressed through Week 96	9%	9%
Death	1%	≤1%
Discontinued due to adverse event	3%	5%
Discontinued for other reasons[f]	4%	7%

[a] As a fixed-dose combination: 300 mg tenofovir, 200 mg emtricitabine once daily.

[b] Patients achieved HIV RNA <50 copies/mL at Week 96. Roche Amplicor®, v1.5 ultra-sensitive assay.

[c] Pre-specified ITT analysis at Week 48 using as-randomized cohort: ATV/RTV 78% and LPV/RTV 76% [difference estimate: 1.7% (95% confidence interval: ⁻3.8%, 7.1%)].

[d] Pre-specified ITT analysis at Week 96 using as-randomized cohort: ATV/RTV 74% and LPV/RTV 68% [difference estimate: 6.1% (95% confidence interval: 0.3%, 12.0%)].

[e] Includes viral rebound and failure to achieve confirmed HIV RNA <50 copies/mL through Week 96.

[f] Includes lost to follow-up, patient's withdrawal, noncompliance, protocol violation, and other reasons.

Source: Applicant

6.1.5 Analysis of Secondary Endpoints(s)

As shown in Table 6, ATV/RTV appears similar to LPV/RTV for multiple secondary efficacy endpoints.

Table 6: Week 96 efficacy outcomes (as-randomized)

Efficacy endpoint	ATV/r (n=440)	LPV/r (n=443)	Difference estimate (95% CI)
HIV-RNA <50 copies/mL (CVR, NC=F)	327/440 (74.3)	302/443 (68.2)	6.1 (0.3, 12.0)
HIV-RNA <50 copies/mL, (CVR, NC=M)	327/360 (90.8)	302/340 (88.8)	1.8 (-2.6, 6.3)
HIV-RNA <50 copies/mL, (TLOVR)	308/440 (70.0)	281/443 (63.4)	6.6 (0.4, 12.7)
HIV-RNA <50 copies/mL, (VR-OC)	326/365 (89.3)	302/345 (87.5)	1.6 (-3.1, 6.2)
HIV-RNA <400 copies/mL (CVR, NC=F)	350/440 (79.5)	330/443 (74.5)	5.1 (-0.4, 10.6)
HIV-RNA <400 copies/mL, (CVR, NC=M)	350/360 (97.2)	330/340 (97.1)	0.2 (-2.7, 3.0)
HIV-RNA <400 copies/mL, (TLOVR)	345/440 (78.4)	321/443 (72.4)	6.0 (0.3, 11.6)
HIV-RNA <400 copies/mL, (VR-OC)	353/365 (96.7)	331/345 (95.9)	-1.7 (-2.3, 3.8)

Mean HIV-RNA change from baseline (log_{10} copies/mL)	-3.21	-3.19	N/A
Median CD4 change from baseline (cells/mm^3)	+261	+273	N/A

CVR=Confirmed Virologic Response, NC=Non-Completer, F=Failure, M=Missing
TLOVR=time to loss of virologic response, VR-OC=Virologic Response-Observed Cases

Mean HIV-RNA changes from baseline to Week 48 were -3.09 log_{10} copies/mL and -3.13 log_{10} copies/mL for ATV/RTV and LPV/RTV, respectively. Mean HIV-RNA changes from baseline to Week 96 were -3.21 log_{10} copies/mL and -3.19 log_{10} copies/mL for ATV/RTV and LPV/RTV, respectively.

Median increases in CD4 counts from baseline to Week 48 were also comparable at Week 48 (ATV/RTV – 191 cells/mm^3, LPV/RTV – 200 cells/mm^3) and Week 96 (ATV/RTV – 261 cells/mm^3, LPV/RTV – 273 cells/mm^3), respectively.

Reviewer Comment
In multiple secondary endpoint analyses, ATV/RTV appears to be non-inferior to LPV/RTV for treatment-naïve HIV-infected adults. Efficacy results are overall consistent at Week 48 and Week 96, respectively.

6.1.6 Other Endpoints

Please refer to Dr. Naeger's FDA microbiology review for analyses of other endpoints.

6.1.7 Subpopulations

As detailed in Dr. Hammerstrom's review and highlighted in Table 7, ATV/RTV appeared to be similarly effective to LPV/RTV for both sexes, white and black races, at all levels studied for age, baseline HIV RNA, baseline CD4 count, HBV/HCV co-infection, and HIV duration and stage. Overall findings were similar at Week 48 and Week 96.

Table 7: HIV-RNA <50 copies/mL (CVR, NC=F) at Week 96 by subpopulations (as-treated)

Subgroup	ATV/RTV (n=443)	LPV/RTV (n=440)
Overall study population	306/443 (69)	276/440 (63)
Baseline HIV-RNA <100,000 copies/mL	154/220 (70)	143/215 (67)
Baseline HIV-RNA >100,000 copies/mL	152/223 (68)	133/225 (59)
Baseline CD4 <50 cells/mm^3	49/68 (72)	27/51 (53)
Baseline CD4 50 - 100 cells/mm^3	31/45 (69)	20/29 (69)
Baseline CD4 100 - 200 cells/mm^3	66/106 (62)	85/134 (63)
Baseline CD4 ≥ 200 cells/mm^3	160/224 (71)	144/226 (64)

Baseline HBV and/or HCV positive	41/61 (67)	28/51 (55)
Baseline HBV and/or HCV negative	264/381 (69)	247/388 (64)
Male	219/305 (72)	196/301 (65)
Female	87/138 (63)	80/139 (58)
Asian	37/43 (86)	33/40 (83)
Black	54/85 (64)	46/78 (59)
Other	74/108 (69)	64/101 (63)
Caucasian	141/207 (68)	133/221 (60)
Age (stratified by quartile)		
<29	66/106 (62)	48/91 (53)
29-35	93/124 (75)	68/111 (61)
35-43	79/113 (70)	87/121 (72)
≥43	68/100 (68)	73/117 (62)

"Other" includes Asian, Hispanic/Latino, Mestizo, Mixed.
Source: FDA Statistical Review

Reviewer Comment
In Table 7, FDA statistical analyses are based on the following snapshot rule, which requires all HIV-RNA measurements in the week 90-102 window to be <50 copies/mL; and counts as a failure any subject with no HIV-RNA measurement in the window. If there are no such measurements, both the last HIV-RNA measurement before week 90 and the first HIV-RNA measurement after week 102 must be <50 copies/mL.

From a clinical perspective, it is suggested to base FDA analyses on the following snapshot rule, which requires that the last HIV-RNA measurement in the week 90-102 window to be <50 copies/mL; and counts as a failure any subject with no HIV-RNA measurement in the window (Table 8). FDA clinical reviewers consider this definition of the snapshot rule to be more reflective of actual clinical practice. Overall, efficacy outcomes are consistent as long as the same definition of snapshot rule is applied to both treatment groups.

Table 8: HIV-RNA <50 copies/mL (CVR, NC=F) at Week 96 (as-treated)

	ATV (n=443)		LPV (n=440)	
FDA_RESULT	N	%	N	%
SUCCESS	330	75%	298	68%
VIROLOGIC FAILURE	78	18%	86	20%
REBOUND	38	9%	44	10%
NEVER_SUPPRESSED	40	9%	42	10%
DEATH	6	1%	6	1%
Discontinued due to AE	13	3%	22	5%

Loss to Follow-Up	16	4%	28	6%

Source: FDA Statistical Review (using the following snapshot rule, which requires that the last observation in the week 90-102 window to be <50; and counts as a failure any subject with no HIV-RNA in the window)

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Based on the overall similarity between the Week 48 and 96 efficacy results for Study 138, this reviewer agrees with the Applicant's proposal to include Week 96 efficacy data for ATV/RTV 300/100 mg QD for treatment-naïve HIV-infected adults in the ATV label.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.1.10 Additional Efficacy Issues/Analyses

Not applicable.

7 Review of Safety

Summary of Safety Results and Conclusions

The safety analysis in Study 138 provides 96-week safety data for treatment-naïve adults who received ATV/RTV 300/100 mg QD. Overall the adverse event profile for ATV/RTV in treatment-naïve adults was similar at Week 48 and Week 96. No new toxicities were observed.

Through 48 weeks, 12 on-treatment deaths (ATV/RTV – 6, LPV/RTV – 6) were reported. No additional deaths were reported from Week 48 to Week 96.

The case narratives and case report forms the all deaths were previously reviewed in detail. In both treatment groups, analysis of demographic information of subjects who died on-treatment revealed a more advanced subgroup of patients relative to all subjects enrolled in Study 138. Most patients who died had lower CD4 counts (baseline and last available) and higher HIV-RNA levels (baseline and last available) than those who survived. Causes of on-treatment death among ATV/RTV recipients included renal failure with urosepsis (1), cholangitis with hepatorenal syndrome and multi-organ failure (1), acute respiratory failure (1), cardiac arrest (1), cerebral toxoplasmosis (1), and car accident (1). Causes of on-treatment death among LPV/RTV recipients included Kaposi's sarcoma (1), pneumonia (1), gastrointestinal bleeding (1), mesenteric artery thrombosis and septic shock (1), and cardiac arrest (1). Most cases had underlying comorbidities that could have contributed to death. For deaths due to AIDS-defining conditions (ATV/RTV – 1, LPV/RTV – 1), there was no evidence to suggest immune reconstitution inflammatory syndrome. No temporal relationship was identified between study

drug and adverse events leading to death. Based on these data, no deaths were considered related to study treatment by this reviewer.

Twenty six subjects (ATV/RTV – 11, LPV/RTV – 15) discontinued due to toxicity through Week 48. From Week 48 to Week 96, nine additional subjects (ATV/RTV – 2, LPV/RTV – 7) discontinued due to toxicity. Overall, thirty five subjects (ATV/RTV – 13, LPV/RTV – 22) discontinued due to toxicity through Week 96.

At Week 96, the most common adverse event leading to study discontinuation in subjects receiving ATV/RTV is jaundice (ATV/RTV – 3, LPV/RTV – zero). The most common adverse event leading to study discontinuation in subjects receiving LPV/RTV is diarrhea (ATV/RTV – zero, LPV/RTV – 7). Otherwise, a similar profile of adverse events leading to study discontinuation was observed in both treatment groups. Other important adverse events associated with discontinuation were nausea (ATV/RTV – 2, LPV/RTV – 2), rash (ATV/RTV – 2, LPV/RTV – 3), and increased transaminases (ATV/RTV – 1 subject, LPV/RTV – zero subjects).

The overall distribution of SAEs was generally similar in both treatment groups at Week 48 and Week 96. Over 48 weeks, serious adverse events (SAEs) were reported in 51 subjects (11.6%) receiving ATV/RTV and 42 subjects (9.6%) receiving LPV/RTV. From Week 48 to Week 96, SAEs were reported in 20 additional subjects (ATV/RTV – 12, LPV/RTV – 8). Overall through 96 weeks, SAEs were reported in 63 subjects (14.2%) receiving ATV/RTV and 50 subjects (11.4%) receiving LPV/RTV.

The adverse event profile was similar at Week 48 and Week 96. Through Week 48, Grade 2-4 AEs (regardless of causality) were reported in 251 subjects (56.9%) in the ATV/RTV treatment group and 259 subjects (59.2%) in the LPV/RTV treatment group. From Week 48 to Week 96, Grade 2-4 AEs (regardless of causality) were reported in 31 additional subjects in the ATV/RTV treatment group and 25 additional subjects in the LPV/RTV treatment group. Through Week 96, Grade 2-4 AEs (regardless of causality) were reported in 282 subjects (63.9%) in the ATV/RTV treatment group and 284 subjects (64.9%) in the LPV/RTV treatment group.

Through Week 48, the most common Grade 2–4 adverse events (≥5%, regardless of causality) reported with ATV/RTV were hyperbilirubinemia (5.9%) and diarrhea (5.4%). Other Grade 2-4 AEs (regardless of causality) of interest were jaundice/scleral icterus (4.5%), nausea (4.7%), and rash (4.8%).

Through Week 96, the most common Grade 2–4 adverse events (≥5%, regardless of causality) reported with ATV/RTV were hyperbilirubinemia (7.5%) and diarrhea (6.8%). Other Grade 2-4 AEs (regardless of causality) of interest were jaundice/scleral icterus (5.2%), nausea (5.2%), and rash (5.2%).

Hyperbilirubinemia was the only Grade 2-4 treatment-related AE (Week 48: 5.9% and 0%; Week 96: 7.5% and 0.2%) reported with a higher frequency (≥ 5 % difference) in the ATV/RTV group than the LPV/RTV group. Of note, reporting hyperbilirubinemia as an AE is not always

consistent from investigator to investigator, particularly in the context of a multi-center, multi-national study. Due to lack of standardized criteria for defining hyperbilirubinemia, this term is not included in the adverse event section of the label. Laboratory evaluations of total bilirubin provide an objective assessment of this issue and bilirubin data are displayed in the laboratory abnormalities section of the label.

Through Week 96, diarrhea was the only Grade 2-4 treatment-related AE (2.5% and 12.4%) reported with a lower frequency (≥ 5 % difference) in the ATV/RTV group than the LPV/RTV group. Grade 2-4 treatment-related hypertriglyceridemia was 5.0% in the LPV/RTV group compared to 1.1% in the ATV/RTV group. Also, Grade 2-4 treatment-related hyperlipidemia was reported in 7 subjects (1.6%) in the LPV/RTV group compared to zero subjects in the ATV/RTV group. The incidence of Grade 2-4 treatment-related rash AEs was slightly higher in the ATV/RTV group compared to the LPV/RTV group (3.2% and 2.3%, respectively).

The profile of laboratory abnormalities was similar at Week 48 and Week 96. Through Week 96, the most common Grade 3–4 laboratory abnormalities reported among ATV/RTV recipients were elevation of total bilirubin (44.1%), total cholesterol (10.8%), creatine kinase (7.8%), and decreased neutrophils (4.8%). The most common Grade 3–4 laboratory abnormalities reported in the LPV/RTV group were elevation of cholesterol (25.2%), creatine kinase (6.5%), triglycerides (4.2%), and prothrombin time (5.6%). All other Grade 3–4 laboratory abnormalities, including transaminases (ALT – 2.5%, AST – 2.5%), occurred with a frequency of less than 3%.

Reviewer Comment
The Applicant's common AE frequencies were overall similar to the review team's analyses. This reviewer also agrees with the Applicant's assessments of causality of adverse events.

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

Pivotal data
The safety results from Study 138 were reviewed, which included review of the datasets, clinical study reports, the case report tabulations, and selected case report forms. The Applicant used the 48-week safety and efficacy results in the label for traditional approval since 48 weeks was the primary endpoint in Study 138. For traditional approval, FDA analysis of key safety signals was performed using 48-week safety data. This submission provides updated 96-week safety results for inclusion in the label. Therefore, FDA analysis of key safety signals was performed using 96-week safety data. In the safety analyses, all percentages reflect the adverse events, serious adverse events, and laboratory abnormalities reported through Week 96 on the total number of subjects exposed to the treatment groups (ATV/RTV – 441 subjects, LPV/RTV – 437 subjects).

7.1.2 Adequacy of Data

The data from Study 138 were overall adequate to evaluate safety, tolerability, pharmacokinetics, and efficacy of ATV/RTV for treatment-naïve HIV-infected adults.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

Not applicable, since this submission contained one trial.

7.2 Adequacy of Safety Assessments

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

In Study 138, ATV/RTV exposure at appropriate doses and duration in the target population was overall adequate. The median duration on study treatment was 96 weeks for both ATV/RTV and LPV/RTV respectively.

Table 9: Treatment exposure to trial medication in Study 138

	Treatment groups / Number (%) of patients	
	ATV/RTV	LPV/RTV
Total treated	441 (100.0)	437 (100.0)
Mean (weeks)	87.1	83.8
SD (weeks)	24.2	27.0
Median (weeks)	96.0	96.0
Minimum (weeks)	0.1	0.1
Maximum (weeks)	107.7	109.0

Through Week 48, substitutions for TDF/FTC with other NRTIs were uncommon in both treatment arms:

- ATV/RTV (n=1): Subject 35-286
- LPV/RTV (n=3): Subjects 16-690, 18-591 and 18-629

From Week 48 to Week 96, two additional subjects (36-508, 150-806) in the LPV/RTV arm underwent NRTI substitution.

Overall through Week 96, substitutions for TDF/FTC with other NRTIs were uncommon in both treatment arms (ATV/RTV – 1 subject, LPV/RTV – 5 subjects).

For the ATV/RTV group (n=441), one subject (35-286) switched from TDF/FTC to zidovudine/lamivudine (ZDV/3TC). For the LPV/RTV group (n=437), one subject (16-690) switched from TDF/FTC to abacavir/lamivudine (ABC/3TC), two subjects (36-508 and 150-806)

switched from TDF/FTC to zidovudine/lamivudine (ZDV/3TC), and two subjects (18-591 and 18-629) switched from TDF/FTC to stavudine/lamivudine (d4T/3TC).

For one subject (16-690, LPV/RTV treatment group), NRTI switch was made due to pregnancy. For the other 4 subjects (ATV/RTV – 1 subject, LPV/RTV – 3 subjects), NRTI switches were made due to decline in renal function with TDF.

Reviewer Comment
Through Week 96, substitutions for TDF/FTC with other NRTIs due to decline in renal function were uncommon in both treatment arms (ATV/RTV – 1 subject, LPV/RTV – 4 subjects).

7.2.2 Explorations for Dose Response

Not applicable, since only one dose of ATV/RTV was used in Study 138

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

The extent and frequency of routine clinical testing was appropriate for Study 138. Subjects were monitored at Screening (Day -30), Baseline (Day 1), and Weeks 2, 4, 12, 24, 36, 48, 60, 72, 84, 96, or Early Termination.

7.2.5 Metabolic, Clearance, and Interaction Workup

Adequate study of metabolism, clearance and drug-drug interactions for atazanavir was previously performed and reviewed by FDA.

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

Adverse events observed with PIs include new onset diabetes, hyperglycemia, hepatotoxicity, rash, lipodystrophy, hypertriglyceridemia, hypercholesterolemia, hemolytic anemia, increased bleeding episodes in patients with hemophilia, and fat redistribution. In Study 138, these clinical concerns were included in the safety monitoring plan and safety data analyses. Of note, Study 138 was planned for 96 weeks and was completed prior to submission of this supplement. Toxicities such as rash, gastrointestinal toxicities, glucose abnormalities, lipid abnormalities are likely to occur within the first 48 and/or 96 weeks. Longer-term toxicities (such as lipodystrophy, fat redistribution) could develop with additional follow-up.

7.3 Major Safety Results

7.3.1 Deaths

When conducting analyses of deaths in Study 138, this reviewer applied the following criteria:

1. Any subject who died prior to taking any study drug was considered a pretreatment death.
2. Any subject who died while on-treatment or within 30 days of discontinuing study drug was considered an "on-treatment" death.
3. Any subject who died > 30 days after discontinuing study drug was considered a "post-treatment" death.

Thirteen deaths were reported in Study 138 at the time of database lock (June 23, 2008).

- Pre-treatment: 1 death (due to pneumonia)
- On-treatment: 12 deaths (ATV/RTV – 6, LPV/RTV – 6)
- Post-treatment: zero deaths

The case narratives and case report forms were reviewed in detail. Most cases had underlying comorbidities that could have contributed to death. In both treatment groups, analysis of baseline information of subjects who died on-treatment revealed that they had more advanced HIV disease relative to all subjects enrolled in Study 138. Most patients who died had lower CD4 counts (baseline and last available) and higher HIV-RNA levels (baseline and last available) than those who survived. Select demographic data of the subjects who died as compared to all subjects are displayed in the following table.

Table 10: Demographics of subjects who died in Study 138 (database cut-off: June 23, 2008)

	On-Tx Deaths ATVRTV	Overall ATVRTV group	On-Tx Deaths LPVRTV	Overall LPV/RTV group
Number of subjects	6	441	6	437
Median age, years	44	34	46.5	36
Median baseline CD4+, cells/mm^3	98.5	205	22	204
Median baseline VL, copies/mL	5.51	5.01	5.49	4.96

Source: December 21, 2007 submission and January 5, 2009 submission, FDA analysis deaths datasets.

The following table summarizes the causes of on-treatment deaths at the time of database lock. Among patients who died on-treatment, duration of treatment with ATV/RTV ranged from 12 to 332 days; duration of treatment with LPV/RTV ranged from 6 to 317 days. No temporal relationship was identified between study drug and adverse events leading to death.

Table 11: On-treatment deaths and number of days of treatment with study drug (database cut-off: June 23, 2008)

Cause of on-treatment death	ATV/RTV (n=6)		LPV/RTV (n=6)	
	Number of on-treatment deaths	Number of days of ATV/RTV treatment	Number of on-treatment deaths	Number of days of LPV/RTV treatment
Renal failure (with urosepsis)	1	37	0	N/A
Cholangitis (with hepatorenal syndrome and multi-organ failure)	1	204	0	N/A
Acute respiratory failure	1	25	0	N/A
Car accident	1	332	0	N/A
Cerebral toxoplasmosis	1	12	0	N/A
Cardiac arrest	1	99	1	283
Kaposi's sarcoma	0	N/A	1	121
Pneumonia	0	N/A	1	39
Gastrointestinal bleeding	0	N/A	1	6
Mesenteric artery thrombosis (with septic shock)	0	N/A	1	317
Multi-organ failure	0	N/A	1	12

Source: December 21, 2007 submission and January 5, 2009 submission, FDA analysis deaths datasets. N/A, not applicable.

Evaluation for immune reconstitution inflammatory syndrome (IRIS)
Two patients died due to opportunistic infections or AIDS-defining illnesses. Their narratives were evaluated to assess if these AIDS-defining illnesses occurred due to immune reconstitution inflammatory syndrome (IRIS):

- Subject 64-248 (ATV/RTV group) died on study day 13 from transtentorial herniation due to cerebral toxoplasmosis. The patient received ATV/RTV for 12 days. Baseline CD4 count was 138 cells/mm^3 and baseline HIV-RNA was 554,000 copies/mL. No CD4 or HIV-RNA was obtained at the time of death.
- Subject 110-794 (LPV/RTV group) died on study day 122 from Kaposi's sarcoma with pulmonary involvement. The subject received LPV/RTV for 121 days. Baseline CD4 count was zero cells/mm^3 and baseline HIV-RNA was 396,000 copies/mL. Last available CD4 was zero cells/mm^3 (Day 84) and HIV-RNA was 1150 copies/mL (Day 111).

Reviewer Comment
Based on the available information, it does not appear either of these cases was due to IRIS.

Assessment of Causality
One death on LPV/RTV was considered possibly related to study medication by investigators. A 56 year-old female (subject 040-911) presented with severe abdominal pain (Day 317). Antiretrovirals were discontinued on Day 317. Her symptoms worsened despite medical management and she underwent exploratory laparotomy (Day 321). Intra-operative findings included mesenteric artery thrombosis and ischemic bowel; patient had enterectomy and

hemicolectomy to remove necrotic bowel. She developed lactic acidosis and septic shock and died on Day 325. No autopsy was reported.

All other deaths in both treatment groups were considered by the investigators to be unrelated to ATV/RTV or LPV/RTV.

Reviewer Comment
After reviewing the case report form for subject 040-911, this reviewer does not consider this death related to study medication.

In summary, the reported causes of death observed in Study 138 were generally similar to those observed in other studies of HIV-infected patients. No deaths were reported from Week 48 to Week 96.

7.3.2 Nonfatal Serious Adverse Events

Through Week 48 of Study 138, a total of 51 patients (11.6%) in the ATV/RTV arm reported serious adverse events (SAEs). A total of 42 patients (9.6%) in the LPV/RTV arm reported SAEs.

From Week 48 to Week 96, SAEs were reported in 20 additional subjects (ATV/RTV – 12, LPV/RTV – 8).

Overall through 96 weeks, SAEs were reported in 63 subjects (14.2%) receiving ATV/RTV and 50 subjects (11.4%) receiving LPV/RTV (Table 12).

The overall distribution of SAEs at Week 48 and Week 96 was generally similar in both treatment groups. At Week 96, the highest percentage of patients with SAEs occurred in the following MedDRA System Organ Classes (MSOCs):

- Infections and Infestations (ATV/RTV 5.9%, LPV/RTV 4.1%)
- Gastrointestinal Disorders (ATV/RTV 1.7%, LPV/RTV 2.3%)
- General Disorders and Administration Site Conditions (ATV/RTV 0.5%, LPV/RTV 1.4%)
- Injury, Poisoning and Procedural Complications (ATV/RTV 1.3%, LPV/RTV 1.4%)
- Neoplasms Benign, Malignant and Unspecified -including cysts and polyps (ATV/RTV 1.1%, LPV/RTV 1.4%)
- Metabolism and Nutrition Disorders (ATV/RTV 0.5%, LPV/RTV 1.1%)
- Musculoskeletal and Connective Tissue Disorders (ATV/RTV 0.5%, LPV/RTV 1.1%)
- Psychiatric Disorders (ATV/RTV 1.3%, LPV/RTV 0.2%)

All other SAEs occurred in $\leq$ 1% of each of the remaining MSOCs for both treatment groups.

- Hepatobiliary Disorders (ATV/RTV 0.9%, LPV/RTV 0.2%)
- Investigations (ATV/RTV 0.7%, LPV/RTV 0.9%)

- Blood and Lymphatic Disorders (ATV/RTV 0.5%, LPV/RTV 0.7%)
- Immune System Disorders (ATV/RTV 0.5%, LPV/RTV 0.2%)
- Nervous System Disorders (ATV/RTV 0.5%, LPV/RTV 0.5%)
- Renal and Urinary Disorders (ATV/RTV 0.2%, LPV/RTV 0.7%)
- Respiratory, Thoracic and Mediastinal Disorders (ATV/RTV 0.2%, LPV/RTV 0.7%)
- Skin and Subcutaneous Disorders (ATV/RTV 0.2%, LPV/RTV 0.2%)
- Cardiac Disorders (ATV/RTV 0.2%, LPV/RTV 0.2%)

Other SAEs of interest included rash (ATV/RTV 0.2%, LPV/RTV 0.2%); acute renal failure (ATV/RTV 0.2%, LPV/RTV 0.0%); hyperlipidemia (ATV/RTV 0.0%, LPV/RTV 0.2%), and pancreatitis (ATV/RTV 0.0%, LPV/RTV 0.2%).

There were no SAE reports of jaundice, ocular icterus, hyperbilirubinemia, new onset diabetes, hyperglycemia, lipodystrophy, hypertriglyceridemia, hypercholesterolemia, hemolytic anemia, or fat redistribution.

The majority of SAE reports were considered by study investigators to be unrelated to study drugs.

Through Week 48, study investigators considered 3 SAEs (0.7%) in the ATV/RTV arm and 9 SAEs (2.0%) in the LPV/RTV arm to be possibly related to study drug. In the ATV/RTV arm, study-drug related SAEs included vomiting (1), cholecystitis (1), and Fanconi syndrome (1). In the LPV/RTV arm, the most common study-drug related SAEs were gastrointestinal toxicities (diarrhea – 3) and renal toxicities (proteinuria – 1, decreased creatinine clearance – 2).

From Week 48 to Week 96, study investigators considered 2 additional SAEs in the ATV/RTV arm (hyperlactatemia, Grade 4 hepatic enzyme elevations) and 2 additional SAEs in the LPV/RTV arm (diarrhea, hyperlipidemia) to be possibly related to study drug.

Overall through Week 96, study investigators considered 5 SAEs (1.1%) in the ATV/RTV arm and 11 SAEs (2.5%) in the LPV/RTV arm to be possibly related to study drug.

Reviewer Comment
The case report forms and narratives were reviewed for all SAEs. This reviewer agrees with the Applicant's assessment of causality.

Renal SAEs
Over 96 weeks, there were four renal SAEs (Fanconi syndrome – 1, proteinuria – 1, decreased creatinine clearance – 2) considered possibly related to TDF. One renal SAE (Fanconi syndrome) occurred in the ATV/RTV group; the other 3 renal SAE occurred among LPV/RTV recipients

- Fanconi syndrome (subject 35-286) was reported after 28 days of ATV/RTV/TDF/FTC, and study drugs were discontinued at that time.

- Grade 3 proteinuria (subject 115-9) was reported after 86 days of LPV/RTV/TDF/FTC; study drugs were discontinued on Day 100.
- Decreased creatinine clearance was reported in subject 18-591 after 170 days of LPV/RTV/TDF/FTC, and study drugs were interrupted at that time. After renal function improved to normal values; antiretrovirals (LPV/RTV and d4T/3TC instead of TDF/FTC) were resumed on study day 227.
- Decreased creatinine clearance was reported in subject 18-629 after 127 days of LPV/RTV/TDF/FTC. Of note, the subject received trimethoprim-sulfamethoxazole for treatment of pneumocystis pneumonia (study days 20-34) and quadruple-drug therapy for pulmonary tuberculosis (these medications were initiated on study day 34 and ongoing when decreased creatinine clearance was reported). Study drugs were interrupted from days 133 to 161. After renal function improved to normal values; antiretrovirals (LPV/RTV and d4T/3TC instead of TDF/FTC) were resumed on study day 162.

Reviewer Comment
Both ATV and LPV increase TDF concentrations. Higher TDF concentrations could potentiate TDF-associated adverse events, including renal disorders. These four renal SAEs could have resulted from increased TDF exposures due to drug-interaction between TDF and the respective PI. Of note, no renal SAEs were reported from Week 48 to Week 96.

Table 12: Summary of SAEs experienced by ≥ 0.5% of patients in Study 138, regardless of causality (Week 48 and Week 96)

Preferred Term	ATV/RTV (n=441)		LPV/RTV (n=437)	
	N (%)		N (%)	
	Week 48	Week 96	Week 48	Week 96
Total # of subjects with ≥ 1 serious AE, n (%)	51 (11.6)	63 (14.2)	42 (9.6)	50 (11.4)
Pneumonia[a]	5 (1.1)	5 (1.1)	5 (1.1)	5 (1.1)
Tuberculosis	3 (0.7)	4 (0.9)	3 (0.7)	4 (0.9)
Cryptococcal meningitis	2 (0.5)	2 (0.5)	0 (0.0)	0 (0.0)
Appendicitis	2 (0.5)	2 (0.5)	0 (0.0)	0 (0.0)
Diarrhea	2 (0.5)	3 (0.7)	6 (1.4)	6 (1.4)
Vomiting	1 (0.2)	1 (0.2)	2 (0.5)	2 (0.5)
Pyrexia	1 (0.2)	1 (0.2)	3 (0.7)	3 (0.7)
Weight decreased	1 (0.2)	1 (0.2)	3 (0.7)	3 (0.7)
Dehydration	1 (0.2)	1 (0.2)	3 (0.7)	3 (0.7)
Cholecystitis[b]	2 (0.5)	2 (0.5)	1 (0.2)	1 (0.2)
Cholangitis[b]	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Cholelithiasis[b]	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Cholestasis[b]	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Hepatorenal syndrome[b]	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Ascites[b]	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Pancreatitis	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Nausea	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Mesenteric artery thrombosis	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Gastrointestinal bleeding	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Pneumocystis pneumonia	0 (0.0)	0 (0.0)	3 (0.7)	3 (0.7)

Kaposi's sarcoma	1 (0.2)	1 (0.2)	2 (0.5)	2 (0.5)
Thrombocytopenia	2 (0.5)	2 (0.5)	0 (0.0)	0 (0.0)
Renal failure	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Fanconi's syndrome	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Proteinuria	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Decreased creatinine clearance	0 (0.0)	0 (0.0)	2 (0.5)	2 (0.5)
Drug eruption	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Dermatitis, allergic	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Respiratory failure	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Multi-organ failure	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Drug Hypersensitivity[c]	2 (0.5)	2 (0.5)	0 (0.0)	0 (0.0)
Suicide attempt	2 (0.5)	2 (0.5)	1 (0.2)	1 (0.2)
Osteonecrosis	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Rhabomyolysis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)

[a]Includes PT pneumonia, pneumonia pneumococcal, pneumonia streptococcal, lung infection pseudomonal.
[b]All occurred in the same patient.
[c]Not related to ATV/RTV (hypersensitivity reaction to silicone injection [1] and opioids [1], respectively)

Similar to Week 48, no new safety signals were apparent in this treatment-naïve population receiving ATV/RTV or LPV/RTV through Week 96. Fewer subjects in the ATV/RTV group reported gastrointestinal SAEs compared to LPV/RTV. Rash, hepatotoxicity, and pancreatitis were uncommon in both treatment groups. Overall, rates of other SAEs were generally comparable between treatment groups.

7.3.3 Dropouts and/or Discontinuations

Through Week 48 of Study 138, a total of 11 subjects (2.5%) in the ATV/RTV arm reported adverse events (AEs) leading to study discontinuation. A total of 15 subjects (3.4%) in the LPV/RTV arm reported AEs leading to study discontinuation.

From Week 48 to Week 96, 9 additional subjects (ATV/RTV – 2 subjects, LPV/RTV – 7 subjects) discontinued due to toxicity.

Through Week 96, a total of 35 subjects (ATV/RTV – 13 subjects [2.9%], LPV/RTV – 22 subjects [5%]) discontinued due to toxicity through Week 96. The adverse event profile was similar at Week 48 and Week 96. At Week 96, the most common adverse event leading to study discontinuation in subjects receiving ATV/RTV was jaundice (ATV/RTV – 3 subjects, LPV/RTV – zero subjects). The most common adverse event leading to study discontinuation in subjects receiving LPV/RTV was diarrhea (ATV/RTV – zero subjects, LPV/RTV – 7 subjects). Otherwise, a similar profile of adverse events leading to study discontinuation was observed in both treatment groups. Other important adverse events associated with dropouts included nausea (ATV/RTV – 2 subjects, LPV/RTV – 2 subjects), rash (ATV/RTV – 2 subjects, LPV/RTV – 3 subjects), and increased transaminases (ATV/RTV – 1 subject, LPV/RTV – zero subjects).

A summary of 48- and 96-week data for AEs of interest that led to study drug discontinuation is presented in Table 13. These adverse events were highlighted since they comprise some of the key safety issues for ATV/RTV.

Table 13: Selected Adverse Events Leading to Discontinuation of Study Drugs in >0.5% patients in either group (Week 48 and Week 96 – Study 138)

SOC, High Level Term, Preferred Term	ATV/RTV (n=441)		LPV/RTV (n=437)	
	N (%)		N (%)	
	Week 48	Week 96	Week 48	Week 96
Total # of subjects with AE leading to treatment discontinuation, n (%)	11 (2.5)	13 (2.9)	15 (3.4)	22 (5.0)
Gastrointestinal disorders	3 (0.7)	5 (1.1)	4 (0.9)	7 (1.6)
Nausea	2* (0.5)	2* (0.5)	2 (0.5)	2 (0.5)
Vomiting	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)
Diarrhea	0 (0.0)	0 (0.0)	4 (0.9)	7 (1.6)
Abdominal distention	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Abdominal pain	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Gastroesophageal reflux disease	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Pancreatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatobiliary disorders	3 (0.7)	3 (0.7)	0 (0.0)	0 (0.0)
Jaundice	3* (0.7)	3* (0.7)	0 (0.0)	0 (0.0)
Heptomegaly	1* (0.2)	1* (0.2)	0 (0.0)	0 (0.0)
Hyperbilirubinemia	1* (0.2)	1* (0.2)	0 (0.0)	0 (0.0)
Skin and subcutaneous disorders	2 (0.5)	2 (0.5)	3 (0.7)	3 (0.7)
Rash	1 (0.2)	1 (0.2)	2 (0.5)	2 (0.5)
Rash, generalized	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Lipodystrophy, acquired	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Skin discoloration	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Investigations – Transaminases increased	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Metabolism and nutrition – Hyperlipidemia	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.5)
Infections and Infestations	2 (0.5)	2 (0.5)	3 (0.7)	3 (0.7)
Tuberculosis	1 (0.2)	1 (0.2)	2 (0.5)	2 (0.5)
Cerebral toxoplasmosis	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Furuncles	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
General Disorders and Administration Site Conditions	2 (0.5)	2 (0.5)	0 (0.0)	0 (0.0)
Multi-organ failure	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Asthenia	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Neoplasms (benign, malignant, unspecified)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.5)

Kaposi's sarcoma	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Lipoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Other AEs of interest				
Congenital, Familial and Genetic Disorders – Fanconi's syndrome	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Cardiac Disorders – Hypertrophic Cardiomyopathy	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Immune System Disorders – Hypersensitivity	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Renal and Urinary Disorders – Proteinuria	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Musculoskeletal and Connective Tissue Disorders – Rhabdomyolysis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Psychiatric Disorders – Major depression	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Nervous System Disorders – Dizziness	1* (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Blood and Lymphatic Disorders – Thrombocytopenia	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)

*Subject 86-981 had history of hepatitis A, and was also co-infected with hepatitis C at baseline. Baseline ALT = 127 U/L (normal, 0-47 U/L), baseline AST = 90 U/L (normal, U/L), baseline total bilirubin = 0.3 mg/dL (normal, 0-1.1 mg/dL). On Day 28, maximum ALT = 224 U/L (Grade 2), maximum AST = 165 U/L (Grade 2), maximum total bilirubin = 3.7 mg/dL (Grade 3) were observed. Subject reported nausea and dizziness (Day 6), hyperbilirubinemia (Day 32), and jaundice, asthenia, and hepatomegaly – all on Day 34. Study medication was discontinued on Day 34 due to these AEs. No treatment was required. The events resolved on Day 53 (19 to 47 days after onset). Study medication was not resumed and the subject did not complete the study.

Source: January 5, 2009 submission, FDA analysis adverse events dataset

Over 96 weeks, no new safety signals were apparent in this treatment-naïve population receiving ATV/RTV or LPV/RTV. Discontinuations due to jaundice were reported in the ATV/RTV group (3 subjects) but not in the LPV/RTV group. Discontinuations due to diarrhea were reported in the LPV/RTV group (7 subjects) but not in the ATV/RTV group. Rash, hepatotoxicity, and hyperlipidemia were uncommon causes for study drug discontinuation in either treatment group. There were no study drug discontinuations due to pancreatitis. Overall, rates of other AEs leading to study drug discontinuation were generally comparable between treatment groups.

7.3.4 Significant Adverse Events

HIV-related opportunistic infections and other AIDS-defining illnesses

Over 48 weeks, new AIDS-defining events were reported in 15 subjects (3.4%) receiving ATV/RTV and 17 subjects (3.9%) receiving LPV/RTV, respectively. From Week 48 to 96, there were 3 additional AIDS-defining events (pulmonary tuberculosis – 2, tuberculosis – 1) reported in subjects receiving ATV/RTV. Through 96 weeks, new AIDS-defining events were reported in 18 subjects (4.1%) receiving ATV/RTV and 17 subjects (3.9%) receiving LPV/RTV, respectively. These AIDS-defining events are shown in Table 14.

Table 14: New CDC Class C AIDS-Defining Events (all grades, regardless of causality) – Week 96

System Organ Class	ATV/RTV (n=441)	LPV/RTV (n=437)
Preferred Term	N (%)	N (%)

Total # of subjects with AE, n (%)	18 (4.1)	17 (3.9)
Infections and Infestations	13 (2.9)	13 (3.0)
Cerebral toxoplasmosis	2 (0.5)	1 (0.2)
Cryptococcal meningitis	2 (0.5)	0 (0.0)
Pulmonary tuberculosis	4 (0.9)*	2 (0.5)
Disseminated tuberculosis	0 (0.0)	1 (0.2)
Tuberculosis	1 (0.0)*	1 (0.2)
Atypical myocbacterial lymphadenitis	1 (0.2)	0 (0.0)
Mycobacterial avium complex infection	0 (0.0)	1 (0.2)
Candidiasis	1 (0.2)	1 (0.2)
Esophageal candidiasis	1 (0.2)	2 (0.5)
Oral candidiasis	0 (0.0)	1 (0.2)
Isosporiasis	1 (0.2)	0 (0.0)
Pneumocystis jiroveci pneumonia	0 (0.0)	2 (0.5)
Cytomegalovirus chorioretinitis	0 (0.0)	1 (0.2)
Neoplasms, benign, malignant, and unspecified	5 (1.1)	4 (0.9)
Kaposi's sarcoma	4 (0.9)	3 (0.7)
Diffuse large B-cell lymphoma	1 (0.2)	0 (0.0)
Cervical carcinoma	0 (0.0)	1 (0.2)

*From Week 48 to 96, 2 subjects developed pulmonary tuberculosis and 1 subject developed tuberculosis. All other AIDS-defining events occurred during the first 48 weeks.
Source: January 5, 2009 submission, FDA analysis adverse events dataset; Appendix 6.6A, 6.6B, 6.6C (SCS)

Overall, no new safety issues regarding development of AIDS-defining events were observed through 48 or 96 weeks in Study 138.

Renal toxicity adverse events
Since TDF concentrations are increased in the presence of ATV and LPV, renal toxicity adverse events were reviewed in detail. Through Week 48 and Week 96, renal toxicity adverse events were uncommon in both treatment groups.

Through Week 48, renal toxicity AEs (all grades, all causality) were reported in 11 subjects (2.5%) in the ATV/RTV group compared to 9 subjects (1.8%) in the LPV/RTV group.

Through Week 96, renal toxicity AEs (all grades, all causality) were reported in 16 subjects (3.6%) in the ATV/RTV group compared to 19 subjects (4.3%) in the LPV/RTV group.

Most events were Grade 1. The overall profile of renal toxicity adverse events was generally similar between treatment groups, with the exception of increased proteinuria in the LPV/RTV group (Table 15).

Table 15: Renal toxicity adverse events (all grades, all causality) – Week 48

System Organ	ATV/RTV (n=441)	LPV/RTV (n=437)

Class, Preferred term	Week 48		Week 96		Week 48		Week 96	
	Grade 1-4 N (%)	Grade 2-4 N (%)	Grade 1-4 N (%)	Grade 2-4 N (%)	Grade 1-4 N (%)	Grade 2-4 N (%)	Grade 1-4 N (%)	Grade 2-4 N (%)
Any renal adverse event	11 (2.5)	4 (0.9)	16 (3.6)	6 (1.4)	9 (2.1)	6 (1.4)	19 (4.3)	9 (2.1)
Renal and Urinary Disorders	10 (2.3)	3 (0.7)	15 (3.4)	5 (1.1)	9 (2.1)	6 (1.4)	19 (4.3)	9 (2.1)
Dysuria	3 (0.7)	0 (0.0)	4 (0.9)	0 (0.0)	2 (0.5)	1 (0.2)	5 (1.1)	2 (0.5)
Nephrolithiasis	2 (0.5)	0 (0.0)	2 (0.5)	0 (0.0)	1 (0.2)	1 (0.2)	2 (0.5)	2 (0.5)
Renal failure	2 (0.5)	2 (0.5)	2 (0.5)	2 (0.5)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Albuminuria	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Proteinuria	1 (0.2)	1 (0.2)	2 (0.5)	2 (0.5)	2 (0.5)	1 (0.2)	6 (1.4)	3 (0.7)
Renal colic	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal pain	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hematuria	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.5)	0 (0.0)
Nephritis	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nephropathy toxic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	2 (0.5)	2 (0.5)	2 (0.5)
Congenital, Familial and Genetic Disorders	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fanconi's syndrome	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: January 5, 2009 submission, FDA analysis adverse events dataset

Over 96 weeks, renal toxicity adverse events occurred with an incidence of < 1%, with the exception of proteinuria (1.4%) in the LPV/RTV group (Table 15). Most events were considered not related to study drugs. One subject (15-111) in the ATV/RTV group died from renal failure with urosepsis; this event was considered not related to study drugs by the investigator. Of note, this subject had baseline creatinine clearance of 63 mL/min; although this met Study 138 eligibility criteria (>60 mL/min), this subject's baseline creatinine clearance was lower than the normal reference range (> 80 mL/min; *Clin Infect Dis*. 2005; 40:1559–1585).

One subject in each treatment group discontinued study drugs due to a renal adverse event [Fanconi's syndrome (subject 35-286) – ATV/RTV; Grade 3 proteinuria (subject 115-9) – LPV/RTV]. Both adverse events were considered possibly related to TDF. Please refer to Section 7.3.2 for additional details and refer to Section 7.4.2 for a discussion of renal laboratory parameters.

7.3.5 Submission Specific Primary Safety Concerns

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

Jaundice/Hyperbilirubinemia/Ocular icterus

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. Clinical manifestations of hyperbilirubinemia include jaundice and ocular icterus. 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 trials, reports of Grade 2-4 clinical jaundice in treatment-naive patients treated with ATV alone was 7%, and was 9% for treatment-experienced patients treated with ATV/RTV.

Of note, reporting hyperbilirubinemia as an AE is not always consistent from investigator to investigator, particularly in the context of a multi-center, multi-national study. Laboratory evaluations of total bilirubin provide an objective assessment of this issue. Please refer to Section 7.4.2 for detailed analyses of bilirubin elevations.

Through Week 48 and Week 96, AEs of jaundice, hyperbilirubinemia, and ocular icterus (all grades, regardless of causality) were more common with ATV/RTV than LPV/RTV (Table 16).

Table 16: Jaundice, hyperbilirubinemia, ocular icterus (all causality) – Week 48 and Week 96

Preferred term	ATV/RTV (n=441)		LPV/RTV (n=437)	
	Week 48	Week 96	Week 48	Week 96
	N (%)	N (%)	N (%)	N (%)
Jaundice				
Grade 1-4	69 (15.6)	83 (18.8)	2 (0.5)	2 (0.5)
Grade 2-4	16 (3.6)	18 (4.1)	0 (0.0)	0 (0.0)
Grade 3-4	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Hyperbilirubinemia				
Grade 1-4	42 (9.5)	64 (14.5)	1 (0.2)	5 (1.1)
Grade 2-4	26 (5.9)	44 (10.0)	1 (0.2)	2 (0.5)
Grade 3-4	13 (2.9)	19 (4.3)	0 (0.0)	0 (0.0)
Ocular icterus				
Grade 1-4	38 (8.6)	43 (9.8)	0 (0.0)	0 (0.0)
Grade 2-4	4 (0.9)	4 (0.9)	0 (0.0)	0 (0.0)
Grade 3-4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 17 shows investigator assessed treatment-related AEs of jaundice, hyperbilirubinemia, and ocular icterus. As expected, these AEs were more common with ATV/RTV than LPV/RTV at Week 48 and Week 96.

Table 17: Treatment-related* jaundice, hyperbilirubinemia, ocular icterus – Week 48 and Week 96

Preferred term	ATV/RTV (n=441)		LPV/RTV (n=437)	
	Week 48	Week 96	Week 48	Week 96
	N (%)	N (%)	N (%)	N (%)
Jaundice				

Grade 1-4	67 (15.2)	80 (18.1)	1 (0.2)	1 (0.2)
Grade 2-4	16 (3.6)	18 (4.1)	0 (0.0)	0 (0.0)
Grade 3-4	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Hyperbilirubinemia				
Grade 1-4	42 (9.5)	51 (11.6)	0 (0.0)	2 (0.5)
Grade 2-4	26 (5.9)	33 (7.5)	0 (0.0)	1 (0.2)
Grade 3-4	13 (2.9)	19 (4.3)	0 (0.0)	0 (0.0)
Ocular icterus				
Grade 1-4	37 (8.4)	41 (9.3)	0 (0.0)	0 (0.0)
Grade 2-4	4 (0.9)	4 (0.9)	0 (0.0)	0 (0.0)
Grade 3-4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

*Investigator assessment.

Overall, Grade 3-4 jaundice, hyperbilirubinemia, and ocular icterus were relatively uncommon at Week 48 and Week 96. Discontinuations due to jaundice/hyperbilirubinemia were reported in the ATV/RTV group (3 subjects – all during the first 48 weeks) but not in the LPV/RTV group.

Rash

In controlled clinical trials in adults, rash (all grades, regardless of causality) occurred in 20% of patients treated with ATV. The median time to onset of rash was 7.3 weeks after initiation of ATV and the median duration of rash was 1.4 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 (b) (4) . Hypersensitivity reactions such as Stevens-Johnson syndrome, erythema multiforme, and toxic skin eruptions have also been reported in patients receiving ATV.

FDA analyses used a wider range of preferred terms than the Applicant in the evaluation of rash (Tables 18 and 19). Consequently, FDA analyses show slightly higher numbers than the applicant's analyses. However, overall trends are similar between FDA and Applicant analyses. Table 18 shows rash events (all grades, all causality) reported over 48 weeks. Most rash events were Grade 1.

Table 18: Grade 1-4 Rash and Grade 2-4 Rash (all causality) – Week 48 and Week 96

Preferred term	ATV/RTV (n=441)				LPV/RTV (n=437)			
	Week 48		Week 96		Week 48		Week 96	
	Grade 1-4 N (%)	Grade 2-4 N (%)	Grade 1-4 N (%)	Grade 2-4 N (%)	Grade 1-4 N (%)	Grade 2-4 N (%)	Grade 1-4 N (%)	Grade 2-4 N (%)
Rash	25 (5.7)	13 (2.9)	27 (6.1)	13 (2.9)	15 (3.4)	7 (1.6)	19 (4.3)	7 (1.6)
Pruritus	14 (3.1)	0 (0.0)	15 (3.4)	0 (0.0)	14 (3.2)	7 (1.6)	14 (3.2)	7 (1.6)
Rash generalized	5 (1.1)	2 (0.5)	5 (1.1)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Pruritus generalized	3 (0.7)	0 (0.0)	3 (0.7)	0 (0.0)	3 (0.7)	1 (0.2)	3 (0.7)	1 (0.2)
Rash papular	4 (0.9)	0 (0.0)	5 (1.1)	0 (0.0)	8 (1.8)	2 (0.5)	11 (2.5)	3 (0.7)
Dermatitis	6 (1.4)	2 (0.5)	8 (1.8)	3 (0.7)	6 (1.4)	0 (0.0)	8 (1.8)	0 (0.0)
Dermatitis allergic	5 (1.1)	2 (0.5)	7 (1.6)	3 (0.7)	11 (2.5)	5 (1.1)	12 (2.7)	6 (1.4)
Dermatosis	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Prurigo	3 (0.7)	1 (0.2)	3 (0.7)	1 (0.2)	3 (0.7)	1 (0.2)	3 (0.7)	1 (0.2)
Rash erythematous	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.5)	1 (0.2)	2 (0.5)	1 (0.2)
Rash maculo-papular	2 (0.5)	1 (0.2)	3 (0.7)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rash pruritic	3 (0.7)	0 (0.0)	4 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Rash vesicular	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urticaria localized	0 (0.0)	0 (0.0)	3 (0.7)	0 (0.0)	1 (0.2)	1 (0.2)	5 (1.1)	1 (0.2)
Urticaria papular	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)
Photosensitivity reaction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	2 (0.5)
Skin discoloration	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	1 (0.2)
Skin disorder	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin exfoliation	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin fissure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Skin lesion	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.9)	1 (0.2)
Total	71 (16.1)	21 (4.8)	90 (20.4)	23 (5.2)	63 (14.4)	25 (5.7)	89 (20.4)	32 (7.3)

Source: January 5, 2009 submission, FDA analysis adverse events dataset

Table 19 shows investigator assessed treatment-related skin reactions. At Week 48, there were 36 treatment-related skin reactions ATV/RTV group compared to 22 treatment-related skin reactions in the LPV/RTV group. At Week 96, there were 37 treatment-related skin reactions ATV/RTV group compared to 29 treatment-related skin reactions in the LPV/RTV group. The majority of skin reactions in both treatment groups were Grade 1.

Table 19: Grade 1-4 Rash and Grade 2-4 Rash (treatment-related*) – Week 48 and Week 96

Preferred term	ATV/RTV (n=441)				LPV/RTV (n=437)			
	Week 48		Week 96		Week 48		Week 96	
	Grade 1-4 N (%)	Grade 2-4 N (%)	Grade 1-4 N (%)	Grade 2-4 N (%)	Grade 1-4 N (%)	Grade 2-4 N (%)	Grade 1-4 N (%)	Grade 2-4 N (%)
Rash	16 (3.6)	10 (2.3)	16 (3.6)	10 (2.3)	6 (1.4)	3 (0.7)	9 (2.1)	3 (0.7)
Pruritus	6 (1.4)	0 (0.0)	6 (1.4)	0 (0.0)	4 (0.9)	1 (0.2)	4 (0.9)	1 (0.2)
Rash generalized	4 (0.9)	2 (0.5)	4 (0.9)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pruritus generalized	2 (0.5)	0 (0.0)	2 (0.5)	0 (0.0)	2 (0.5)	1 (0.2)	2 (0.5)	1 (0.2)
Rash papular	2 (0.5)	0 (0.0)	2 (0.5)	0 (0.0)	4 (0.9)	1 (0.2)	4 (0.9)	1 (0.2)
Dermatitis	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
Dermatitis allergic	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Prurigo	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.5)	1 (0.2)	2 (0.5)	1 (0.2)
Rash erythematous	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Rash maculo-papular	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rash pruritic	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Skin disorder	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin discoloration	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Skin lesion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)

Urticaria localized	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Total	36 (8.2)	14 (3.2)	37 (8.4)	14 (3.2)	22 (5.0)	10 (2.3)	29 (6.6)	10 (2.3)

*Investigator assessment.
Source: January 5, 2009 submission, FDA analysis adverse events dataset

Through 48 and 96 weeks, moderate-to-severe rash adverse events were uncommon in both treatment groups. Four subjects (ATV/RTV – 2 subjects, LPV/RTV – 2 subjects) discontinued study drugs due to rash; these discontinuations all occurred during the first 48 weeks. The overall profile of rash adverse events was generally similar between treatment groups.

Nephrolithiasis, Hyperglycemia, and Fat Redistribution
These types of adverse events, especially fat redistribution, are typically seen with prolonged antiretroviral treatment. Given the relatively short duration of treatment and follow-up in Study 138, the isolated occurrences of these AEs were not unexpected. Higher rates of nephrolithiasis, hyperglycemia, and fat redistribution are possible with longer durations of therapy. Overall, no new submission-specific safety signals were observed through 96 weeks in Study 138.

Nephrolithiasis
Through 48 weeks, nephrolithiasis (all grades, regardless of causality) was uncommon in both treatment groups (ATV/RTV – 2 subjects, LPV/RTV – 1 subject). From Week 48 to Week 96, one additional subject in the LPV/RTV group reported nephrolithiasis. Overall through 96 weeks, there were 4 reports of nephrolithiasis (ATV/RTV – 2 subjects, LPV/RTV – 2 subjects).

In the ATV/RTV group, one event was considered not related to study drug since this was a pre-existing condition; the other event was considered possibly related to study drug. In the LPV/RTV group, both events were considered not related to study drug. All 4 adverse events were considered non-serious. No data on crystal analysis were available for any subject. In the ATV/RTV group, both events were Grade 1; in the LPV/RTV group, both events were Grade 2. Study treatments were continued in all 4 subjects. There were no study drug discontinuations due to nephrolithiasis.

Hyperglycemia
Over 48 weeks, hyperglycemia (all grades, regardless of causality) was reported in zero subjects in the ATV/RTV group compared to 3 subjects in the LPV/RTV group. From Week 48 to Week 96, two additional subjects reported hyperglycemia (ATV/RTV – 1 subject, LPV/RTV – 1 subject). Overall through 96 weeks, there were 5 reports of hyperglycemia (ATV/RTV – 1 subjects, LPV/RTV – 4 subjects). In the ATV/RTV group, the event was Grade 1; in the LPV/RTV group, there were two Grade 1 events and two Grade 2 events.

Fat Redistribution
Over 48 weeks, fat redistribution (all grades, regardless of causality) was reported in one subject in the ATV/RTV treatment group and 3 subjects in the LPV/RTV treatment group (Grade 1 – 2 subjects, Grade 2 – 1 subject). There were no additional reports of fat redistribution from Week 48 to Week 96.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

All adverse events (Grade 1-4)
All causality
In Study 138, the adverse event profile for ATV/RTV in treatment-naïve adults was similar to ATV/RTV in treatment-experienced adults. Through Week 48, adverse events (all grades, regardless of causality) were reported in 400 subjects (90.7%) in the ATV/RTV treatment group and 399 subjects (91.3%) in the LPV/RTV treatment group. Through Week 96, AEs (all grades, regardless of causality) were reported in 417 subjects (94.5%) in the ATV/RTV treatment group and 408 subjects (93.4%) in the LPV/RTV treatment group (Table 20).

Similar to Week 48, the most commonly reported AEs at Week 96 (all grades, regardless of causality, ≥ 5% incidence) were diarrhea, nausea, abdominal pain, vomiting, headache, dizziness, back pain, nasopharyngitis, upper respiratory tract infection, and rash (Table 20). With few exceptions, the incidence of AEs was similar between ATV/RTV and LPV/RTV treatment groups. Diarrhea, nausea, vomiting, and hypertriglyceridemia were reported more frequently in the LPV/RTV group compared to the ATV/RTV group. Jaundice, hyperbilirubinema, and ocular icterus were reported more frequently in the ATV/RTV group compared to the LPV/RTV group. Jaundice, hyperbilirubinemia, and ocular icterus were more common (≥ 5% difference) on ATV/RTV than LPV/RTV. Diarrhea and nausea were less common (≥ 5% difference) on ATV/RTV than LPV/RTV.

At Week 48, renal toxicity was 2% in each treatment group; at Week 96, renal toxicity was reported in 3.6% of ATV/RTV recipients compared to 4.3% of LPV/RTV recipients. Please refer to Section 7.3.2 and Section 7.3.4 for additional details.

Table 20: AEs (all grades, regardless of causality) and ≥ 5% difference between treatment groups – Week 48 and Week 96

Preferred Term	ATV/RTV (n=441)		LPV/RTV (n=437)	
	Week 48	Week 96	Week 48	Week 96
	N (%)	N (%)	N (%)	N (%)
Total # of subjects with AE, n (%)	400 (90.7)	417 (94.5)	399 (91.3)	408 (93.4)
Nausea	70 (15.9)	73 (16.6)	101 (23.1)	103 (23.6)
Diarrhea	92 (20.9)	109 (24.7)	231 (52.9)	237 (54.2)
Vomiting	28 (6.3)	34 (7.7)	47 (10.8)	49 (11.2)
Hyperbilirubinemia	42 (9.5)	64 (14.5)	1 (0.2)	5 (1.1)
Jaundice	69 (15.6)	83 (18.8)	2 (0.5)	2 (0.5)
Ocular icterus	38 (8.6)	43 (9.8)	0 (0.0)	0 (0.0)

Rash**	71 (16.1)	90 (20.4)	63 (14.4)	89 (20.4)
Hypertriglyceridemia	13 (0.7)	19 (4.3)	37 (4.1)	48 (11.0)
Hyperlipidemia	1 (0.2)	11 (2.5)	4 (0.9)	11 (2.5)

**Refer to Tables 17 and 18 for list of preferred terms used in FDA analysis for rash.
Since these AEs are commonly associated with antiretrovirals, rash, vomiting, and hypertriglyceridemia were included in this table.
Source: January 5, 2009 submission, FDA analysis adverse events dataset

Treatment-related (investigator assessment)
Through 48 weeks, treatment-related AEs (all grades) were reported in 270 subjects (61.2%) in the ATV/RTV treatment group and 307 subjects (70.3%) in the LPV/RTV treatment group.

Through 96 weeks, treatment-related AEs (all grades) were reported in 289 subjects (65.5%) in the ATV/RTV treatment group and 317 subjects (72.5%) in the LPV/RTV treatment group.

At Weeks 48 and 96, treatment-related AEs (all grades) reported with a higher frequency (≥ 5% difference) in the ATV/RTV treatment group than the LPV/RTV treatment group were jaundice (Week 48: 15.2% versus 0.2%; Week 96: 18.1% versus 0.2%), hyperbilirubinemia (Week 48: 9.5% versus 0%; Week 96: 11.6% versus 0.5%), and ocular icterus (Week 48: 8.4% versus 0%; Week 96: 9.3% versus 0%).

Table 21: Treatment-related* AEs (all grades) and ≥ 5% difference between treatment groups – Week 48 and Week 96

Preferred Term	ATV/RTV (n=441)		LPV/RTV (n=437)	
	Week 48	Week 96	Week 48	Week 96
	N (%)	N (%)	N (%)	N (%)
Total # of subjects with AE, n (%)	270 (61.2)	289 (65.5)	307 (70.3)	317 (72.5)
Nausea	65 (14.7)	68 (15.4)	95 (21.7)	95 (21.7)
Diarrhea	49 (11.1)	53 (12.0)	202 (46.2)	205 (46.9)
Vomiting	17 (3.9)	20 (4.5)	29 (6.6)	29 (6.6)
Hyperbilirubinemia	42 (9.5)	51 (11.6)	0 (0.0)	2 (0.5)
Jaundice	67 (15.2)	80 (18.1)	1 (0.2)	1 (0.2)
Ocular icterus	37 (8.4)	41 (9.3)	0 (0.0)	0 (0.0)
Rash**	36 (8.2)	37 (8.4)	22 (5.0)	29 (6.6)
Hypertriglyceridemia	10 (2.3)	16 (3.6)	37 (8.5)	47 (10.8)

*Investigator assessment.
**Refer to Tables 17 and 18 for list of preferred terms used in FDA analysis for rash.
Due to its clinical significance, ocular icterus was included in this table.
Source: January 5, 2009 submission, FDA analysis adverse events dataset, and Appendix 2.1.1D (SCS)

Grade 2-4 adverse events
All causality
Through Week 48, Grade 2-4 AEs (regardless of causality) were reported in 251 subjects (56.9%) in the ATV/RTV treatment group and 259 subjects (59.2%) in the LPV/RTV treatment group.

From Week 48 to Week 96, Grade 2-4 AEs (regardless of causality) were reported in 31 additional subjects in the ATV/RTV treatment group and 25 additional subjects in the LPV/RTV treatment group.

Through Week 96, Grade 2-4 AEs (regardless of causality) were reported in 282 subjects (63.9%) in the ATV/RTV treatment group and 284 subjects (64.9%) in the LPV/RTV treatment group. Hyperbilirubinemia was the only Grade 2-4 AE reported with a higher frequency (≥ 5 % difference) in the ATV/RTV group (7.5%) than the LPV/RTV group (0.5%). Diarrhea was the only Grade 2-4 AE reported with a lower frequency (≥ 5 % difference) in the ATV/RTV group (6.8%) than the LPV/RTV group (16.7%).

Treatment-related (investigator assessment)
Through Week 48, Grade 2-4 treatment-related AEs were reported in 115 subjects (26.1%) in the ATV/RTV treatment group and 129 subjects (29.5%) in the LPV/RTV treatment group.

From Week 48 to Week 96, Grade 2-4 treatment-related AEs were reported in 18 additional subjects in the ATV/RTV treatment group and 11 additional subjects in the LPV/RTV treatment group.

Through Week 96, Grade 2-4 treatment-related AEs were reported in 133 subjects (30.2%) in the ATV/RTV treatment group and 140 subjects (32.0%) in the LPV/RTV treatment group.

Table 22 shows treatment-emergent AEs (Grades 2-4) observed in ≥ 2% of patients in either treatment group at Week 48 and Week 96, respectively. The most frequently occurring AEs were related to the gastrointestinal and hepatobiliary systems.

Table 22: Grade 2-4 treatment-related* AEs observed in ≥ 2% of patients in either treatment group at Week 48 and Week 96

Preferred Term	ATV/RTV (n=441)		LPV/RTV (n=437)	
	Week 48	Week 96	Week 48	Week 96
	N (%)	N (%)	N (%)	N (%)
Total # of subjects with Grade 2-4 Treatment-Related AE, n (%)	115 (26.1)	133 (30.2)	129 (29.5)	140 (32.0)
Nausea	17 (3.9)	18 (4.1)	33 (7.6)	33 (7.6)
Diarrhea	10 (2.3)	11 (2.5)	50 (11.4)	54 (12.4)

Hyperbilirubinemia	26 (5.9)	33 (7.5)	0 (0.0)	1 (0.2)
Jaundice	16 (3.6)	18 (4.1)	0 (0.0)	0 (0.0)
Ocular icterus	4 (0.9)	4 (0.9)	0 (0.0)	0 (0.0)
Rash**	14 (3.2)	14 (3.2)	10 (2.3)	10 (2.3)
Hypertriglyceridemia	3 (0.7)	5 (1.1)	18 (4.1)	22 (5.0)

*Investigator assessment.
**Refer to Tables 17 and 18 for list of preferred terms used in FDA analysis for rash.
Source: January 5, 2009 submission, FDA analysis adverse events dataset, and Table 2.1.1.3 (SCS)

Hepatobiliary AEs: Hyperbilirubinemia was the only Grade 2-4 treatment-related AE (Week 48: 5.9% and 0%; Week 96: 7.5% and 0.2%) reported with a higher frequency (≥ 5 % difference) in the ATV/RTV group than the LPV/RTV group. Please refer to Section 7.3.5 for additional discussion.

Gastrointestinal AEs: Diarrhea was the only Grade 2-4 treatment-related AE (Week 48: 2.3% and 11.4%; Week 96: 2.5% and 12.4%) reported with a lower frequency (≥ 5 % difference) in the ATV/RTV group than the LPV/RTV group.

Metabolic and nutrition AEs: Grade 2-4 treatment-related hypertriglyceridemia was 4.1% in the LPV/RTV group compared to 0.7% in the ATV/RTV group at Week 48. Overall trends were similar at Week 96 (LPV/RTV – 5%, ATV/RTV – 1.1%).

At Week 96, Grade 2-4 treatment-related hyperlipidemia was reported in 7 subjects (1.6%) in the LPV/RTV group compared to zero subjects in the ATV/RTV group. Of note, these reports all occurred during the first 48 weeks of Study 138.

Rash AEs: The incidence of Grade 2-4 treatment-related rash AEs was slightly higher in the ATV/RTV group compared to the LPV/RTV group (3.2% and 2.3%, respectively). These reports all occurred during the first 48 weeks of Study 138. Please refer to Section 7.3.4 for additional discussion.

Grade 3-4 adverse events
All causality
Through Week 48, Grade 3-4 AEs (regardless of causality) were reported in 72 subjects (16.3%) in the ATV/RTV treatment group and 63 subjects (14.4%) in the LPV/RTV treatment group.

From Week 48 to Week 96, Grade 3-4 AEs (regardless of causality) were reported in 19 additional subjects in the ATV/RTV treatment group and 7 additional subjects in the LPV/RTV treatment group. In the ATV/RTV group, 7 of the new reports were due to hyperbilirubinemia.

Through Week 96, Grade 3-4 AEs (regardless of causality) were reported in 91 subjects (20.6%) in the ATV/RTV treatment group and 70 subjects (16.0%) in the LPV/RTV treatment group.

Reviewer Comment
Similar to Week 48, the majority of AEs at Week 96 were mild (Grade 1) to moderate (Grade 2). Overall, no new safety signals were identified through 96 weeks in Study 138.

7.4.2 Laboratory Findings

As a class effect, ATV/RTV and other protease inhibitors can cause abnormalities in liver function tests, lipids, and glucose. ATV also causes hyperbilirubinemia, primarily elevated indirect (unconjugated) bilirubin, due to inhibition of UDP-glucuronosyl transferase (UGT).

As per study protocol, hematologic, chemistry, lipid, urinalyses, and pregnancy tests for female subjects were collected at all visits for safety laboratory analyses. Hepatitis serologies were performed at screening to determine the patient's baseline hepatitis status. For subjects with negative baseline hepatitis serologies, these laboratory assessments were also obtained at Week 48 and Week 96/Early Termination.

The Applicant and the FDA analyzed laboratory test results for all subjects in Study 138 who had both a baseline and an on-treatment or final laboratory measurement. The following table presents treatment-emergent laboratory values occurring in $\geq$ 2% of subjects in either treatment group. Bilirubin elevations were the most commonly reported laboratory abnormalities among patients receiving ATV/RTV. Cholesterol and triglyceride elevations were the most commonly reported laboratory abnormalities among patients receiving LPV/RTV. ALT elevations were comparable between treatment arms, while AST elevations were more commonly reported among ATV/RTV recipients than LPV/RTV recipients.

Table 23: Selected Treatment Emergent Laboratory Abnormalities of Grades 3-4 in $\geq$ 2% of Subjects in Either Treatment Group – Week 48 and Week 96

Laboratory parameter	ATV/RTV(n=441)		LPV/RTV(n=437)	
	Grade 3-4, N (%)		Grade 3-4, N (%)	
	Week 48	Week 96	Week 48	Week 96
ALT	8/435 (1.8)	11/435 (2.5)	6/431 (1.4)	7/431 (1.6)
AST	9/435 (2.1)	11/435 (2.5)	2/430 (0.5)	5/430 (1.2)
Total bilirubin	146/435 (33.6)	192/435 (44.1)	1/431 (0.2)	1/431 (0.2)
Cholesterol	30/434 (6.9)	47/434 (10.8)	77/428 (18.0)	108/428 (25.2)
Triglycerides	2/434 (0.5)	3/434 (0.7)	15/428 (3.5)	18/428 (4.2)
Creatine kinase	22/435 (5.1)	34/435 (7.8)	20/430 (4.7)	28/430 (6.5)
Neutrophils	14/434 (3.2)	21/434 (4.8)	3/431 (0.7)	7/431 (1.6)
Prothrombin time	6/435 (1.4)	9/435 (2.1)	16/431 (3.7)	24/431 (5.6)

Overall laboratory findings were similar at Week 48 and Week 96. The majority of laboratory abnormalities were Grade 1/2. As expected, subjects with abnormal baseline values were more

predisposed to developing Grade 3/4 laboratory abnormalities compared to subjects with normal baseline values.

Table 24: Selected Grade 3/4 laboratory values in ≥ 2% of Subjects in Either Treatment Group – Week 48 and Week 96 (stratified by baseline value)

Laboratory parameter	Baseline	ATV/RTV(n=441)		LPV/RTV(n=437)	
		Week 48	Week 96	Week 48	Week 96
		N (%)	N (%)	N (%)	N (%)
ALT	Total	8/435 (1.8)	11/435 (2.5)	6/431 (1.4)	7/431 (1.6)
	Normal	4/372 (1.1)	6/372 (1.6)	4/379 (1.1)	4/379 (1.1)
	Abnormal	4/63 (6.3)	5/63 (7.9)	2/52 (3.8)	3/52 (5.8)
AST	Total	9/435 (2.1)	11/435 (2.5)	2/430 (0.5)	5/430 (1.2)
	Normal	4/357 (1.1)	6/357 (1.7)	2/371 (0.5)	5/371 (1.3)
	Abnormal	5/78 (6.4)	5/78 (6.4)	0/59 (0.0)	0/59 (0.0)
Total bilirubin	Total	146/435 (33.6)	192/435 (44.1)	1/431 (0.2)	1/431 (0.2)
	Normal	144/433 (33.2)	190/433 (43.8)	1/430 (0.2)	1/430 (0.2)
	Abnormal	2/2 (100.0)	2/2 (100.0)	0/1 (0.0)	0/1 (0.0)
Cholesterol	Total	30/434 (6.9)	47/434 (10.8)	77/428 (18.0)*	108/428 (25.2)
	Normal	16/393 (4.1)	29/393 (7.4)	53/389 (13.6)	82/389 (21.1)
	Abnormal	13/34 (38.3)	17/34 (50.0)	23/32 (71.9)	25/32 (78.1)
	Missing	1/7 (14.3)	1/7 (14.3)	1/7 (14.3)	1/7 (14.3)
Triglycerides	Total	2/434 (0.5)	3/434 (0.7)	15/428 (3.5)	18/428 (4.2)
	Normal	2/397 (0.5)	2/397 (0.5)	7/392 (1.8)	9/392 (2.3)
	Abnormal	0/30 (0.0)	1/30 (3.3)	8/29 (27.6)	8/29 (27.6)
	Missing	0/7 (0.0)	0/7 (0.0)	0/7 (0.0)	1/7 (14.3)
Creatine kinase	Total	22/435 (5.1)	34/435 (7.8)	20/430 (4.7)	28/430 (6.5)
	Normal	18/416 (4.3)	26/416 (6.3)	15/408 (3.7)	23/408 (5.6)
	Abnormal	4/19 (21.1)	8/19 (42.1)	5/22 (22.7)	5/22 (22.7)
Neutrophils	Total	14/434 (3.2)	21/434 (4.8)	3/431 (0.7)	7/431 (1.6)
	Normal	7/391 (1.8)	12/391 (3.1)	3/397 (0.8)	5/397 (1.3)
	Abnormal	7/42 (16.7)	9/42 (21.4)	0/34 (0.0)	2/34 (5.9)
	Missing	0/1 (0.0)	0/1 (0.0)	0/0 (0.0)	0/0 (0.0)
Prothrombin time	Total	6/435 (1.4)	9/435 (2.1)	16/431 (3.7)	24/431 (5.6)
	Normal	4/379 (1.1)	6/379 (1.6)	8/371 (2.2)	15/371 (4.0)

	Abnormal	2/56 (3.6)	3/56 (5.4)	8/60 (13.3)	9/60 (15.0)

Source: January 5, 2009 submission.

*Of note, in the KALETRA label, Week 48 data from Study 863 in 326 treatment-naïve subjects (LPV/RTV capsules 400/100 mg BID, given with stavudine and lamivudine) reported the following rates of Grade 3/4 treatment-emergent laboratory values:

- ALT – 4%
- AST – 2%
- Cholesterol – 9%
- Triglycerides – 9%
- Neutrophils – 1%

Reviewer Comment
As discussed during review of Week 48 data, the reasons for different rates of Grade 3/4 cholesterol observed among treatment-naïve subjects receiving LPV/RTV in Study 138 (18%) and Study 863 (9%) are unclear. In Study 138, fasting lipids were measured; however, laboratory measurements were performed without regard to fasting in Study 863. Also, it seems unlikely the different background NRTIs could account entirely for these observed differences in cholesterol abnormalities.

In Study 138, more Grade 3/4 laboratory abnormalities in neutrophils (<750 cells/mm^3) were reported in ATV/RTV recipients than LPV/RTV recipients. These findings were observed at both Week 48 (ATV/RTV – 14 subjects, LPV/RTV – 3 subjects) and Week 96 (ATV/RTV – 21 subjects, LPV/RTV – 7 subjects). This difference could be partially attributed to the number of subjects with abnormal baseline neutrophil counts (Week 48: ATV/RTV – 7 subjects, LPV/RTV – zero subjects; Week 96: ATV/RTV – 9 subjects, LPV/RTV – 2 subjects). For subjects with normal baseline neutrophil counts, Grade 3/4 laboratory abnormalities in neutrophils were reported in 3.1% of ATV/RTV recipients (12/391) compared to 1.3% of LPV/RTV recipients (5/397) at Week 96.

Similar to Week 48, subjects with Grade 3/4 laboratory abnormalities in neutrophils at Week 96 were clinically asymptomatic and these laboratory abnormalities generally appeared to be isolated values with no clinical significance. This observation appears to be supported by other data from System Organ Class "Infections and Infestations" showing overall rates of adverse events, serious adverse events, and adverse events leading to study drug discontinuation were comparable between treatment groups:

- Infections and Infestations (Week 48)
    - All grades: ATV/RTV – 243/441 [55.1%], LPV/RTV – 247/437 [56.5%]
    - Grades 2-4: ATV/RTV – 109/441 [24.7%], LPV/RTV – 126/437 [28.8%]
    - Serious adverse events: ATV/RTV – 20/441 [4.5%], LPV/RTV – 16/437 [3.7%]
    - Adverse events leading to study drug discontinuation: ATV/RTV – 1/441 [0.2%], LPV/RTV – 3/437 [0.7%]

- Infections and Infestations (Week 96)

- All grades: ATV/RTV – 292/441 [66.2%], LPV/RTV – 283/437 [64.8%]
- Grades 2-4: ATV/RTV – 150/441 [34.0%], LPV/RTV – 156/437 [35.7%]
- Serious adverse events: ATV/RTV – 26/441 [5.9%], LPV/RTV – 18/437 [4.1%]
- Adverse events leading to study drug discontinuation: ATV/RTV – 2/441 [0.5%], LPV/RTV – 3/437 [0.7%]

Similar to Week 48, overall number of subjects reporting Grade 3/4 laboratory abnormalities at Week 96 was low in both treatment groups for renal parameters, hematologic parameters, amylase, lipase, and glucose.

Table 25: Selected Grade 3/4 laboratory abnormalities occurring in < 2% of Subjects in Either Treatment Group – Week 48 and Week 96

Laboratory parameter	ATV/RTV(n=441)		LPV/RTV(n=437)	
	Week 48	Week 96	Week 48	Week 96
	N (%)	N (%)	N (%)	N (%)
BUN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Creatinine*	1 (0.2)	1 (0.2)	1 (0.2)	2 (0.5)
Proteinuria†	3 (0.7)	5 (1.1)	1 (0.2)	6 (1.4)
Amylase	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lipase	6 (1.4)	9 (2.0)	6 (1.4)	9 (2.1)
Hyperglycemia	1 (0.2)	3 (0.7)	1 (0.2)	2 (0.5)
WBC	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Hemoglobin	2 (0.5)	3 (0.7)	6 (1.4)	7 (1.6)
Platelets	5 (1.1)	5 (1.1)	1 (0.2)	1 (0.2)

Overall, no new pattern of laboratory abnormalities appears evident from review of the datasets and supporting documents. FDA analysis of the laboratory data concurs with the Applicant's overall analysis.

Liver function abnormalities

Similar to Week 48, relatively few subjects experienced Grade 3/4 ALT and/or AST through Week 96. As shown in Table 24, Grade 3/4 ALT occurred in 11 of 435 (2.5%) subjects in the ATV/RTV group and 7 of 431 (1.6%) of subjects in the LPV/RTV group, respectively. Grade 3/4 AST occurred in 11 of 435 (2.5%) subjects in the ATV/RTV group and 5 of 430 (1.2%) subjects in the LPV/RTV group, respectively.

Liver function abnormalities in Patients Co-Infected with Hepatitis B and/or C

In Study 138, there were 111 subjects (ATV/RTV – 60 subjects, LPV/RTV – 51 subjects) with hepatitis B and/or C co-infection who received at least one dose of study treatment. In the

LPV/RTV group, only 50 subjects were evaluable for ALT/AST; one subject discontinued study therapy before the Week 4 visit and had no on-treatment ALT/AST data.

Table 26: AST/ALT and Total Bilirubin (Grade 3 to 4) Abnormalities in Subjects Co-infected with Hepatitis B (HBV) and/or Hepatitis C (HCV) – Week 96

Laboratory parameter	Baseline	ATV/RTV(n=441)		LPV/RTV(n=437)	
		Co-infected N=60 (%)	Not Co-infected N=381 (%)	Co-infected N=51 (%)	Not Co-infected N=386 (%)
ALT	Total	6/60 (10.0)	5/375 (1.3)	4/50* (8.0)	3/381 (0.8)
	Normal	4/45 (8.9)	2/327 (0.6)	1/37 (2.7)	3/342 (0.9)
	Abnormal	2/15 (13.3)	3/48 (6.3)	3/13 (23.1)	0/39 (0)
AST	Total	6/60 (10.0)	5/375 (1.3)	0/50 (0)	5/380 (1.3)
	Normal	3/36 (8.3)	3/321 (0.9)	0/35 (0)	5/336 (1.5)
	Abnormal	3/24 (12.5)	2/54 (3.7)	0/15 (0)	0/44 (0)
Total bilirubin	Total	29/60 (48.3)	163/375 (43.5)	0/50 (0)	3/381 (0.8)
	Normal	28/59 (47.5)	162/374 (43.3)	0/50 (0)	3/380 (0.8)
	Abnormal	1/1 (100)	1/1 (100)	0/0 (0)	0/1 (0)

*One subject discontinued study therapy before the Week 4 visit and had no on-treatment ALT/AST data.
ALT and AST: Grade 3 (> 5-10 x ULN), Grade 4 (> 10 x ULN)
Total bilirubin: Grade 3 (2.6-5.0 x ULN), Grade 4 (> 5.0 x ULN)

In this subpopulation of hepatitis B and/or C co-infected subjects:

- Week 48: Grade 3/4 ALT (> 5x ULN) occurred in 5 of 60 (8.3%) subjects in the ATV/RTV group and 3 of 50 (6.0%) of subjects in the LPV/RTV group, respectively. Grade 3/4 AST (> 5x ULN) occurred in 5 of 60 (8.3%) subjects in the ATV/RTV group and zero subjects in the LPV/RTV group, respectively.

- Week 96: Grade 3/4 ALT (> 5x ULN) occurred in 6 of 60 (10.0%) subjects in the ATV/RTV group and 4 of 50 (8.0%) of subjects in the LPV/RTV group (Table 26). Grade 3/4 AST (> 5x ULN) occurred in 6 of 60 (10.0%) subjects in the ATV/RTV group and zero subjects in the LPV/RTV group.

Reviewer Comment
Overall, the incidence of Grade 3/4 ALT in co-infected subjects was comparable between treatment groups at Weeks 48 and 96.

The incidence of Grade 3/4 AST in co-infected subjects was higher for ATV/RTV recipients than LPV/RTV recipients. This observation was expected since only 5 subjects (all not co-infected) reported Grade 3/4 AST in the LPV/RTV group through 48 weeks.

Similar to data with other ARVs, the incidence of Grade 3/4 ALT/AST reported in the ATV/RTV group was greater in co-infected subjects than those who were not co-infected. Co-infected subjects also reported higher incidence of abnormal bilirubin (all grades) compared to subjects who were not co-infected. Of note, only one co-infected subject (86-981) discontinued the study due to these hepatic laboratory abnormalities (please refer to Section 7.3.3).

Potential Hy's Law cases

Additionally, concomitant increases in ALT/AST and total bilirubin were evaluated. The FDA Guidance on Premarketing evaluation of Drug-Induced Liver Injury (DILI) also discusses Hy's Law as "the single clearest marker for a potential for severe DILI." Hy's Law is summarized as:

1) Evidence of hepatocellular injury in the population (ALT or AST > 3x ULN), and
2) Total Bilirubin (TBL) > 2x ULN without notable increase Alkaline Phosphatase (<2x ULN), and
3) No other explanation (liver disease or other drug).

Within Grade 3/4 ALT/AST values, an analysis was performed to compare the frequency of ATV/RTV versus LPV/RTV patients with laboratory abnormalities that could be suggestive of a Hy's Law case. This analysis is confounded by the potential for ATV/RTV to cause bilirubin elevations. In the ATV/RTV treatment group, three subjects (86-981, 14-106, and 145-428) had concurrent abnormalities in ALT/AST and total bilirubin. The case report forms and narratives were reviewed in detail to determine the presence or absence of clinical symptoms and other potential etiologies for hepatotoxicity. Each case has at least one confounder (co-morbidity, concurrent medication) that could contribute to hepatotoxicity. Please refer to Section 7.3.3 (Table 13) for a detailed discussion of Subject 86-981 (confounders included history of hepatitis A, co-infection with hepatitis C, and elevated baseline ALT and AST). The clinical information for subjects 14-106 and 145-428 is summarized below:

- Subject 14-106 (baseline HBV positive, HCV negative)
  - Laboratory values are shown in Table 27:
    - ALT was Grade 2 (screening and baseline), decreased to Grade 1 (Week 4), then increased to Grade 3 (Week 12), reached a maximum value of Grade 4 (Week 24), and declined gradually to Grade 1 (Week 48).
    - AST was Grade 1 (screening and baseline), increased to Grade 2 (Week 12 – Week 28), reached a maximum value of Grade 3 (Week 30), and declined gradually to normal range by Week 48.
    - Total bilirubin was normal at screening and baseline, increased to Grade 4 (Week 4), and ranged from Grade 2-4 until the database lock. Week 48 (Day 337) bilirubin was Grade 2.
    - Day 85 (Week 12) was the first timepoint when subject reported concurrent ALT, AST, total bilirubin abnormalities that could be suggestive of a Hy's Law case (by laboratory criteria).
  - Subject reported the following AEs:
    - Grade 1 jaundice (considered related to ATV/RTV) was reported at Day 7 and resolved 8 days later.
    - Subject was hospitalized for acute cholecystitis at Day 114 (this event was considered not related to study medication). Ultrasound revealed distended gallbladder and circumferentially thickened wall. On Day 127, subject underwent laparoscopic cholecystectomy and symptoms resolved on Day 129 (15 days after onset).
  - Study medications were continued throughout.

Table 27: ALT, AST, and total bilirubin for Subject 14-106

Study day	ALT (IU/L)	AST (IU/L)	Total Bilirubin (mg/dL)
-14 (screening)	111 (Grade 2)	77 (Grade 1)	0.4
1 (baseline)	151 (Grade 2)	87 (Grade 1)	0.6
29	80 (Grade 1)	39	6.5 (Grade 4)
85	**363 (Grade 3)**	**134 (Grade 2)**	**4.6 (Grade 3)**
169	421 (Grade 4)	188 (Grade 2)	2.3 (Grade 2)
178	407 (Grade 4)	171 (Grade 2)	3.5 (Grade 3)
190	485 (Grade 4)	198 (Grade 2)	4.5 (Grade 3)
206	442 (Grade 4)	235 (Grade 3)	2.9 (Grade 2)
230	298 (Grade 3)	134 (Grade 2)	4.5 (Grade 3)
248	236 (Grade 3)	113 (Grade 2)	4.3 (Grade 3)
317	142 (Grade 2)	68 (Grade 1)	6.3 (Grade 4)
337	87 (Grade 1)	40	3.0 (Grade 2)
421	48	23	4.2 (Grade 3)

ALT and AST: Grade 1 (> 1.25-2.5 x ULN), Grade 2 (> 2.5-5 x ULN), Grade 3 (> 5-10 x ULN), Grade 4 (> 10 x ULN)
Total bilirubin: Grade 1 (> 1.1-1.5 x ULN), Grade 2 (1.6-2.5 x ULN), Grade 3 (2.6-5.0 x ULN), Grade 4 (> 5.0 x ULN)

- Subject 145-428 (baseline HBV negative, HCV negative)
  - Subject had a single Grade 2 ALT and Grade 4 AST on Day 337; the elevated transaminases returned to Grade 1 within one week while continuing on study drug. Prior to Day 337, ALT ranged from normal to Grade 1, and AST values were all normal.
  - Total bilirubin was normal at screening and baseline, increased to Grade 3 (Week 4), and ranged from Grade 2-3 until the database lock. Week 48 (Day 337) bilirubin was Grade 2.
  - Week 48, subject reported concurrent Grade 2 ALT, Grade 4 AST, and Grade 3 total bilirubin.
  - Week 49, subject reported concurrent Grade 1 ALT, Grade 4 AST, and Grade 3 total bilirubin, respectively.
  - Subject did not report hyperbilirubinemia, jaundice, or ocular icterus.
  - Subject reported the following AEs:
    - Day 2: Grade 1 nausea, diarrhea, fatigue, dizziness
    - Day 25: Grade 1 diarrhea
    - Day 158: Grade 2 diarrhea
  - Study medications were continued throughout.

Table 28: ALT, AST, and total bilirubin for Subject 145-428

Study day	ALT (IU/L)	AST (IU/L)	Total Bilirubin (mg/dL)
-23 (screening)	49	31	0.7
1 (baseline)	100 (Grade 1)	36	0.5
29	31	21	3.5 (Grade 3)
36	52	31	4.2 (Grade 3)
90	29	21	2.5 (Grade 2)
168	32	23	4.1 (Grade 3)
253	31	23	3.8 (Grade 3)
337	**201 (Grade 2)**	**508 (Grade 4)**	**3.6 (Grade 2)**
345	65 (Grade 1)	53 (Grade 1)	3.7 (Grade 3)

ALT and AST: Grade 1 (> 1.25-2.5 x ULN), Grade 2 (> 2.5-5 x ULN), Grade 3 (> 5-10 x ULN), Grade 4 (> 10 x ULN)
Total bilirubin: Grade 1 (> 1.1-1.5 x ULN), Grade 2 (1.6-2.5 x ULN), Grade 3 (2.6-5.0 x ULN), Grade 4 (> 5.0 x ULN)

Therefore, neither of these cases matches the definition of a Hy's Law case as outlined in the Guidance on Premarketing evaluation of Drug-Induced Liver Injury (DILI). Of note, these cases were reported during the first 48 weeks of Study 138.

No subjects in the LPV/RTV treatment group had concurrent abnormalities in ALT/AST and total bilirubin that could be suggestive of a Hy's Law case by laboratory criteria.

Renal function abnormalities

- At Week 48, Grade 1-4 creatinine abnormalities were reported for 7 subjects (1.6%) in the ATV/RTV group compared to 14 subjects (3.2%) in the LPV/RTV group. At Week 96, Grade 1-4 creatinine abnormalities were reported for 16 subjects (3.7%) in the ATV/RTV group compared to 27 subjects (6.3%) in the LPV/RTV group.

- At Week 48, Grade 3/4 creatinine elevations were reported in one subject in each treatment group. At Week 96, one additional subject in the LPV/RTV group reported Grade 3/4 creatinine elevation (Table 25).

- At Week 48, Grade 3/4 proteinuria was reported in three subjects (0.7%) in the ATV/RTV group compared to one subject (0.2%) in the LPV/RTV group. At Week 96, Grade 3/4 proteinuria was reported in 5 subjects (1.1%) in the ATV/RTV group compared to 6 subjects (1.4%) in the LPV/RTV group (Table 25).

- Mean changes in serum creatinine from baseline to Week 48 and Week 96 respectively were not clinically significant in either treatment group:
    - Mean serum creatinine in the ATV/RTV group was 0.84 mg/dL (Q1, Q3: 0.7, 1.0) at baseline, 0.89 mg/dL (Q1, Q3: 0.76, 1.0) at Week 48, and 0.90 mg/dL (Q1, Q3: 0.76, 1.0) at Week 96.
    - Mean serum creatinine in the LPV/RTV group was 0.87 mg/dL (Q1, Q3: 0.7, 1.0) at baseline, 0.89 mg/dL (Q1, Q3: 0.78, 1.0) at Week 48, and 0.90 mg/dL (Q1, Q3: 0.80, 1.0) at Week 96.

- Mean changes in creatinine clearance (CrCl) from baseline to Week 48 and Week 96 respectively were not clinically significant in either treatment group:
    - Mean creatinine clearance in the ATV/RTV group was 114 mL/min (Q1, Q3: 95, 129) at baseline, 113 mL/min (Q1, Q3: 93, 129) at Week 48, and 113 mL/min (Q1, Q3: 94, 128) at Week 96.
    - Mean creatinine clearance in the LPV/RTV group was 110 mL/min (Q1, Q3: 91, 126) at baseline, 110 mL/min (Q1, Q3: 90, 125) at Week 48, and 108 mL/min (Q1, Q3: 88, 126) at Week 96.

- Changes from baseline CrCl (calculated Cockroft-Gault formula) are shown below:

Table 29: Decreases in CrCl from baseline to Week 24, 48, and 96 respectively

Time-point	CrCl decrease from baseline	ATV/RTV (n=441)	LPV/RTV (n=437)
		N (%)	N (%)
Week 24	> 50%	1/419 (0.2)	2/410 (0.5)
	≥ 25-50%	20/419 (4.8)	16/410 (3.9)
	> 0-25%	220/419 (52.5)	216/410 (52.7)
	0%	178/419 (42.5)	176/410 (42.9)
Week 48	> 50%	0/398 (0.0)	0/374 (0.0)
	≥ 25-50%	16/398 (4.0)	17/374 (4.5)
	> 0-25%	186/398 (46.7)	173/374 (46.3)
	0%	196/398 (49.3)	184/374 (49.2)
Week 96	> 50%	0/366 (0.0)	2/340 (0.6)
	≥ 25-50%	8/366 (2.2)	8/340 (2.4)
	> 0-25%	182/366 (49.7)	172/340 (50.6)
	0%	176/366 (48.1)	158/340 (46.5)

Normal creatinine clearance > 80 mL/min (*Clin Infect Dis.* 2005; 40:1559–1585)

No subject reported persistent > 50% reduction from baseline in CrCl at Week 48. From Week 48 to Week 96, two subjects on LPV/RTV had > 50% reduction from baseline in CrCl and no subjects on ATV/RTV had a > 50% reduction.

Sixteen (4%) and seventeen (4.5%) of subjects reported ≥ 25% to < 50% reduction in CrCl at Week 48 on ATV/RTV and LPV/RTV respectively. Eight subjects (2%) on both regimens reported ≥ 25% to < 50% reduction in CrCl at Week 96.

As discussed in Section 7.2.1, substitution of TDF/FTC due to decline in renal function was uncommon through Week 48 (ATV/RTV – 1 subject, LPV/RTV – 2 subjects) and Week 96 (ATV/RTV – 1 subject, LPV/RTV – 4 subjects), respectively.

Reviewer Comment
Renal toxicities were uncommon in both treatment groups at Week 48 and Week 96. Mean changes in serum creatinine from baseline to Week 48 and Week 96 were not clinically significant in either treatment group. Mean changes in creatinine clearance (CrCl) from baseline to Week 48 and Week 96 were not clinically significant in either treatment group. Although a subset of subjects in both treatment groups experienced ≥25% to <50% reduction in CrCl at Week 48, few patients required substitution of TDF/FTC due to decline in renal function. Of note, Study 138 excluded subjects with pre-existing renal disease, defined as calculated creatinine clearance < 60 mL/min. In clinical practice, patients with underlying renal disease (regardless of cause) should be carefully monitored for development of any renal abnormalities or worsening of renal function (Guidelines for the Management of Chronic Kidney Disease in HIV-Infected Patients: Recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. 2005; 40:1559–1585).

Fasting Lipids
Lipid abnormalities are a class effect associated with PIs. ATV is associated with lower rates of lipid abnormalities than other PIs (Metabolic issues associated with protease inhibitors. *J Acquir Immune Defic Syndr*. 2007; 45 Suppl 1:S19–26). Diagnosis and management of this potential long-term toxicity is an important issue for HIV-infected patients and clinicians (Guidelines for the evaluation and management of dyslipidemia in HIV-infected adults receiving antiretroviral therapy: recommendations of the HIV Medical Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group. *Clin Infect Dis*. 2003; 37:613–627).

Based on Study 138 (Table 30), ATV/RTV appears to be associated with lower rates of clinically significant lipid abnormalities than LPV/RTV:

- Fewer subjects developed hyperlipidemia in the ATV/RTV arm compared to the LPV/RTV arm through 48 weeks (Grade 1-4: 28.1% versus 46.5%; Grade 3/4: 6.9% versus 18.0%) and 96 weeks (Grade 1-4: 35.9% versus 55.1%; Grade 3/4: 10.8% versus 25.2%) respectively.

- The number of subjects using lipid lowering agents in the ATV/RTV group was 5 (1.1%) at baseline, 10 (2.3%) at Week 48, and 14 (3.2%) at Week 96.

- The number of subjects using lipid lowering agents in the LPV/RTV group was 5 (1.1%) at baseline, 33 (7.6%) at Week 48, and 43 (9.8%) at Week 96.

- Through 48 weeks, 5 subjects in the ATV/RTV group and 28 subjects in the LPV/RTV group initiated lipid-lowering therapy.

- From Week 48 to Week 96, 4 additional subjects in the ATV/RTV group and 10 additional subjects in the LPV/RTV group initiated lipid-lowering therapy.

- Through 96 weeks, 9 subjects in the ATV/RTV group and 38 subjects in the LPV/RTV group initiated lipid-lowering therapy.

- Mean change from baseline in fasting total cholesterol was lower with ATV/RTV than LPV/RTV (13% versus 25% – see Table 30):
    - Mean total cholesterol values in the ATV/RTV group were 149 mg/dL (Q1, Q3: 124, 170) at baseline, 169 mg/dL (Q1, Q3: 141, 191) at Week 48, and 169 mg/dL (Q1, Q3: 143, 189) at Week 96.
    - Mean total cholesterol values in the LPV/RTV group were 150 mg/dL (Q1, Q3: 125, 170) at baseline, 187 mg/dL (Q1, Q3: 158, 212) at Week 48, and 186 mg/dL (Q1, Q3: 157, 212) at Week 96.

- More LPV/RTV recipients than ATV/RTV recipients shifted at least one higher National Cholesterol Education Program (NCEP) category by Week 96 for total cholesterol (ATV/RTV – 16%, LPV/RTV –29%) and LDL cholesterol (ATV/RTV – 32%, LPV/RTV – 40%).

- Through 48 and 96 weeks, no subjects discontinued ATV/RTV due to hyperlipidemia.

- Through 48 weeks, one subject discontinued LPV/RTV due to hyperlipidemia. From Week 48 to Weeks 96, one additional subject discontinued LPV/RTV due to hyperlipidemia. Through 96 weeks, two subjects discontinued LPV/RTV due to hyperlipidemia.

Triglycerides

- Fewer subjects developed hypertriglyceridemia in the ATV/RTV arm compared to the LPV/RTV arm through 48 weeks (Grade 1-4: 20.2% versus 44.2%, respectively; Grade 3/4: 0.5% versus 3.5%, respectively) and 96 weeks (Grade 1-4: 25.1% versus 49.5%, respectively; Grade 3/4: 0.7% versus 4.2%, respectively).

- Mean change from baseline in fasting triglycerides was lower with ATV/RTV than LPV/RTV (15% versus 52% – see Table 30):
    - Mean triglyceride values in the ATV/RTV group were 126 mg/dL (Q1, Q3: 80, 146) at baseline, 145 mg/dL (Q1, Q3: 88, 176) at Week 48, and 140 mg/dL (Q1, Q3: 88, 169) at Week 96.
    - Mean triglyceride values in the LPV/RTV group were 129 mg/dL (Q1, Q3: 80, 156) at baseline, 194 mg/dL (Q1, Q3: 117, 230) at Week 48, and 184 mg/dL (Q1, Q3: 115, 230) at Week 96.

- More LPV/RTV recipients than ATV/RTV recipients shifted into higher NCEP categories by Week 96 for triglycerides (ATV/RTV – 23%, LPV/RTV – 49%).

- Through 48 weeks and 96 weeks, no subjects discontinued ATV/RTV or LPV/RTV due to hypertriglyceridemia.

Table 30: Mean Change from Baseline (BL) in Fasting Lipids – Week 48 and Week 96

	ATV/RTV[a,b]					LPV/RTV[b,c]				
	BL	Week 48		Week 96		BL	Week 48		Week 96	
	mg/dL (n=428[e])	mg/dL (n=372[e])	Δ[d] (n=372[e])	mg/dL (n=342[e])	Δ[d] (n=342[e])	mg/dL (n=424[e])	mg/dL (n=335[e])	Δ[d] (n=335[e])	mg/dL (n=291[e])	Δ[d] (n=291[e])
LDL-Cholesterol[f]	92	105	+14%	105	+14%	93	111	+19%	110	+17%
HDL-Cholesterol[f]	37	46	+29%	44	+21%	36	48	+37%	46	+29%
Total Cholesterol[f]	149	169	+13%	169	+13%	150	187	+25%	186	+25%
Triglycerides[f]	126	145	+15%	140	+13%	129	194	+52%	184	+50%

a REYATAZ 300 mg with ritonavir 100 mg once daily with the fixed-dose combination: 300 mg tenofovir, 200 mg emtricitabine once daily

b Values obtained after initiation of serum lipid-reducing agents were not included in these analyses At baseline, serum lipid-reducing agents were used in 1% in the lopinavir/ritonavir treatment arm and 1% in the REYATAZ/ritonavir arm Through Week 48, serum lipid-reducing agents were used in 8% in the lopinavir/ritonavir treatment arm and 2% in the REYATAZ/ritonavir arm Through Week 96, serum lipid-reducing agents were used in 10% in the lopinavir/ritonavir treatment arm and 3% in the REYATAZ/ritonavir arm

c Lopinavir 400 mg with ritonavir 100 mg twice daily with the fixed-dose combination 300 mg tenofovir, 200 mg emtricitabine once daily

d The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 48 or Week 96 values and is not a simple difference of the baseline and Week 48 or Week 96 mean values, respectively

e Number of patients with LDL-cholesterol measured

f Fasting

Source: Applicant

Reviewer Comment
Similar to Week 48, the Week 96 findings provide additional data suggesting ATV/RTV affects lipids less than LPV/RTV. However, any other positive clinical impact of this finding, such as reduced incidence of lipodystrophy or cardiovascular disease, has not yet been demonstrated.

Overall, no new safety signals were evident from review of laboratory abnormalities in treatment-naïve subjects receiving ATV/RTV or LPV/RTV through 96 weeks. Safety findings were overall similar at Week 48 and Week 96.

7.4.3 Vital Signs

Vital sign data were reviewed and no clinically significant changes were noted.

7.4.4 Electrocardiograms (ECGs)

Collection of ECGs was not required in Study 138. There were no episodes of PR interval or QT prolongation reported as AEs. Of note, subjects with known cardiac abnormalities were excluded from Study 138.

7.4.5 Special Safety Studies

No special safety studies were submitted or considered necessary by this reviewer.

7.4.6 Immunogenicity

No immunogenicity studies were submitted or considered necessary by this reviewer.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not applicable as the same dose was used for all subjects.

7.5.2 Time Dependency for Adverse Events

Similar to other PIs, higher rates of some adverse events (such as fat redistribution, nephrolithiasis, and hyperglycemia) and laboratory abnormalities (cholesterol and triglyceride) could occur with prolonged use of ATV/RTV compared to the number of these AEs reported during 96 weeks.

Please refer to section 7.3.5 for additional details.

7.5.3 Drug-Demographic Interactions

The Applicant analyzed AEs by age, gender, race and geographic location in Study 138. Overall findings were similar at Week 48 and Week 96.

Age
In the ATV/RTV group (median age 34, range 19-72), 429 subjects (97.5%) were between 18-55 years old. There were 9 subjects (2%) ages 56-64, and 2 subjects (0.5%) were 65 or older.

In the LPV/RTV group (median age 36, range 19-71), 424 subjects (95.7%) were between 18-55 years old LPV/RTV. There were 16 subjects (3.6%) ages 56-64, and 3 subjects (0.7%) were 65 or older.

Reviewer Comment

Overall, subgroup analyses of clinical AEs by age did not detect significant differences between treatment groups. Analyses were limited by small numbers of patients ages 56 or older in either treatment group. Insufficient numbers of subjects age 65 and older were enrolled in Study 138 to determine whether this population responds differently from younger subjects.

Gender
The majority of subjects in Study 138 were male (68.6%). There were 303 males and 138 females receiving ATV/RTV and 298 males and 139 females receiving LPV/RTV. The overall frequency of AEs (all grades, regardless of causality) was similar within each of the treatment groups, with both male and female patients receiving ATV/RTV having a slightly lower percentage of AEs compared with the LPV/RTV patients. Overall trends were similar at Week 48 and Week 96.

At Week 96, the frequency of AEs (all grades, regardless of causality) by treatment and gender for ATV/RTV were: males 93.1%, females 97.8%; and for LPV/RTV were: males 89.6%, females 95.0%.

Comparing the ATV/RTV males and ATV/RTV females, the following AEs (all grades, regardless of causality) were observed to have a Preferred Term (PT) difference of ≥5%:
• Nausea: females 23.9%; males 13.2%
• Vomiting: females 11.6%; males 5.9%
• Diarrhea: females 20.3%; males 26.7%
Of note, anemia was reported in 5.8% of females, compared to 2.0% of males.

Comparing the LPV/RTV males and LPV/RTV females, the following AEs (all grades, regardless of causality) were observed to have PT difference of ≥5%:
• Nausea: females 33.8%; males 18.8%
• Vomiting: females 17.3%; males 8.4%
Of note, diarrhea was reported in 53.2% of females, compared to 54.7% of males. Anemia was reported in 5.8% of females, compared to 1.3% of males.

Comparing the ATV/RTV males and LPV/RTV males, the following AE (all grades, regardless of causality) was observed to have PT difference of ≥5%:
• Nausea: ATV/RTV 13.2%; LPV/RTV 18.8%
• Diarrhea: ATV/RTV 26.7%; LPV/RTV 54.7%
Of note, vomiting was reported in 5.9% of males receiving ATV/RTV, compared to 8.4% of males receiving LPV/RTV.

Comparing the ATV/RTV females and LPV/RTV females, the following AEs (all grades, regardless of causality) were observed to have PT difference of ≥5%:
• Nausea: ATV/RTV 23.9%; LPV/RTV 33.8%
• Vomiting: ATV/RTV 11.6%; LPV/RTV 17.3%
• Diarrhea: ATV/RTV 20.3%; LPV/RTV 53.2%

Race
Similar to Week 48, the overall frequency of AEs (all grades, regardless of causality) by race was similar within each of the treatment groups at Week 96.

Table 31: Frequency of AEs (all grades, regardless of causality) stratified by race and treatment group – Week 96 (as-treated)

Race/Ethnicity	ATV/RTV (n=441)		LPV/RTV (n=437)	
	Total	Number with AE	Total	Number with AE
Caucasian, n (%)	207 (47.0)	194/207 (93.7)	221 (50.6)	201/221 (91.0)
Black, n (%)	85 (19.3)	81/85 (95.3)	77 (17.6)	76/77 (98.7)
Asian, n (%)	42 (9.5)	39/42 (92.9)	40 (9.2)	39/40 (97.5)
Other, n (%)	107* (24.3)	103/107 (96.3)	99† (22.7)	92/99 (92.9)

*Other: Hispanic/Latino – 7, Mestizo – 72, Mixed – 28
†Other: Hispanic/Latino – 6, Mestizo – 68, Mixed – 25

A few differences in AEs stratified by race were observed and these are summarized below. These differences were overall similar at Week 48 and Week 96.

Through Week 96 in the ATV/RTV group:
• Incidence of jaundice and hyperbilirubinemia (all grades, regardless of causality) was highest in Asians (38% and 40%, respectively), compared to Other (29% and 19%, respectively), Caucasians (16% and 4%, respectively), and Blacks (2% and 6%, respectively).
- Incidence of treatment-related Grade 2-4 jaundice (as assessed by investigators): Caucasians (7%), Asians (5%), Other (2%), Blacks (0%).
- Incidence of treatment-related Grade 2-4 hyperbilirubinemia (as assessed by investigators): Asians (29%), Other (9%), Blacks (6%), Caucasians (3%).

• Incidence of ocular icterus (all grades, regardless of causality) was highest in Other races (27%), compared to Caucasians (5%), Blacks (4%), and Asians (2%).
• Blacks had the lowest incidence of nausea (6%) compared with Caucasians (20%), Asians (17%), and Other (19%).

Through Week 96 in the LPV/RTV group:
• Incidence of nausea (all grades, regardless of causality) was highest in Asians (38%) compared to Other, Caucasian, and Blacks (31%, 20%, 17%, respectively).
• Incidence of hypertriglyceridemia (all grades, regardless of causality) was highest in Asians (23%) compared to Other, Caucasian, and Blacks (19%, 9%, 0%, respectively).
• Incidence of hyperlipidemia (all grades, regardless of causality) was highest in Asians (10%) compared to Other, Caucasian, and Blacks (0%, 3%, 1%, respectively).
• Incidence of treatment-related Grade 2-4 diarrhea was highest in Caucasians (15%) compared to Other (12%), Asians (10%), and Blacks (5%).
• Incidence of treatment-related Grade 2-4 nausea was highest in Other (11%) compared to Asians (8%), Caucasians (8%), and Blacks (3%).
• Incidence of treatment-related Grade 2-4 hypertriglyceridemia was highest in Other (10%) compared to Asians (8%), Caucasians (4%), and Blacks (0%).

• Incidence of treatment-related Grade 2-4 hyperlipidemia was highest in Asians (3%) compared to Caucasians (2%), Other (0%), and Blacks (0%).

Reviewer Comment
Subgroup analyses were limited by small numbers for some races, such as Asians and Hispanics. At Week 48 and Week 96 respectively, high rates of jaundice and hyperbilirubinemia (all grades, regardless of causality) were observed among Asians receiving ATV/RTV (42 subjects) relative to Caucasians, Blacks, and Other races. The clinical significance of this observation is not fully characterized at this time. The incidence of severe neonatal hyperbilirubinemia is higher in Asians than in whites (Textbook of Neonatology, 3rd Edition. Churchill- Livingston, Edinburgh, pp 715–732). However, review of the literature did not identify adult data regarding incidence of hyperbilirubinemia among different races. As discussed during the clinical review of the Week 48 data, reporting hyperbilirubinemia as an AE is not always consistent from investigator to investigator, particularly in the context of a multi-center, multi-national study. Laboratory evaluations of total bilirubin provide an objective assessment of this issue. Evaluation of laboratory values for total bilirubin (rather than those reported as clinical AEs) did not show any substantial differences in ethnicity or geography at Week 48 or Week 96. Overall rates of Grade 3-4 total bilirubin elevations at Week 96 were generally similar for different ethnic groups (Asians 55%, Caucasians 43%, Blacks 33%, 'Other' 50%) and different continents (Asia 58%, Europe 38%, North America 49%, South America 44%, Africa 38%). Based on these additional analyses and delineation of possible reporting differences between hyperbilirubinemia as an AE versus total bilirubin laboratory measurements, there does not appear to be a clinically significant difference in these events.

7.5.4 Drug-Disease Interactions

In general, comparable results were seen at Week 48 and Week 96 for baseline HBV and/or HCV not co-infected and co-infected subjects within regimens.

Through Week 96 in the ATV/RTV group, frequency of hyperbilirubinemia (all grades, regardless of causality) was 10% and 22% for not co-infected and co-infected subjects respectively. No other PTs with differences ≥5% were reported. For example, frequency of jaundice was 19% and 18% for not co-infected and co-infected subjects, respectively.

Please refer to Section 7.4.2 and Table 25 for additional details regarding liver function abnormalities. Similar to data with other antiretroviral drugs, the incidence of abnormal ALT or AST was greater in subjects who were co-infected with hepatitis B or C than in those who were not co-infected when compared within each regimen. Additionally, in the ATV/RTV group, co-infected subjects reported a higher incidence of abnormal bilirubin (all grades) compared to subjects who were not co-infected.

Through Week 96 in the LPV/RTV group, the frequencies of diarrhea (53% vs 63%), vomiting (11% vs 16%), upper respiratory infection (11% vs 22%), pyrexia (5% vs 16%), and cough (6%

vs 18%) were lower in not co-infected subjects compared to co-infected subjects. No other PTs with differences ≥5% were reported.

7.5.5 Drug-Drug Interactions

Please see Section 7.3.4 for discussion of renal adverse events observed with concurrent use of tenofovir (TDF) with ATV/RTV. Please refer to Section 7.4.2 for a discussion of renal laboratory findings.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

Overall rates of malignancies were similar in both treatment groups at Week 48 and Week 96. There were small numbers of various types of malignancies, such as Kaposi's sarcoma (ATV/RTV – 4, LPV/RTV – 3), diffuse large B cell lymphoma (ATV/RTV –1, LPV/RTV – zero), B cell lymphoma (ATV/RTV – zero, LPV/RTV – 1), and cervical cancer (ATV/RTV – zero, LPV/RTV – 1). Neoplasms (benign, malignant, or unspecified) diagnosed in the two treatment arms are shown in Table 32.

Table 32: Neoplasms (benign, malignant, unspecified) in Study 138 – Weeks 48 and 96

Preferred Term	ATV/RTV (n=441)		LPV/RTV (n=437)	
	Week 48	Week 96	Week 48	Week 96
Total # of subjects with AE, n (%)	13 (2.9)	20 (4.5)	10 (2.3)	16 (3.7)
Kaposi's sarcoma*	4 (0.9)	4 (0.9)	3 (0.7)	3 (0.7)
Diffuse large B-cell lymphoma*	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Cervical carcinoma*	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Neoplasm malignant	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Basal cell carcinoma	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
B-cell lymphoma	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Renal cell carcinoma, stage unspecified	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Testicular neoplasm	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Vulvovaginal HPV infection	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Skin papilloma	4 (0.9)	4 (0.9)	3 (0.7)	5 (1.1)
Papilloma	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Melanocytic nevus	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)
Prostate adenoma	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)

Fibroadenoma, breast	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Fibroma	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Leiomyoma	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Benign male reproductive tract neoplasm	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Lipoma	0 (0.0)	2 (0.5)	0 (0.0)	2 (0.5)

*AIDS defining malignancies; HPV, human papilloma virus
Source: January 5, 2009 submission. FDA analysis adverse event datasets.

At Week 48 and Week 96, no clinically significant difference between the two groups for AIDS-defining malignancies, such as Kaposi's sarcoma, diffuse large B cell lymphoma, or invasive cervical cancer was observed.

No AIDS-associated malignancies (such as Non-Hodgkin's disease, anal cancer, lung cancer, or testicular germ cell tumors) were reported through 96 weeks.

7.6.2 Human Reproduction and Pregnancy Data

Please refer to the original review for additional details. There are no adequate and well-controlled studies with ATV in pregnant women for the treatment of HIV-1 infection.

There were 18 enrolled subjects with on-study positive pregnancy tests, 15 of which were confirmed. Three subjects (AI424138-150-808 [ATV/RTV], AI424138-33-488 [LPV/RTV], and AI424138-63-308 [ATV/RTV]) had false-positive pregnancy tests. All three subjects went on to complete the study. Three subjects (AI424138-11-236, AI42413-852, and AI414138-104-189) were enrolled but never randomized due to positive pregnancy tests at screening. The following subjects had confirmed pregnancies before the Week 48 database lock and were updated with new information obtained after the Week 48 database lock (June 11, 2007):

1) Subject AI424138-9-1045 (ATV/RTV) had confirmed urine pregnancy test on 08-Mar-2007, after 166 days of dosing, and was discontinued from the study on that day. The subject developed gestational diabetes (considered not likely related to study drug) at gestational week 30 and was treated with modified diet. It was reported that the subject gave birth to a normal, healthy infant on (b) (6).
2) Subject 93-875 (ATV/RTV) had confirmed positive serum pregnancy test on 29-May-2007. Study drug was discontinued on 24-May-2007 after 336 days of dosing; she discontinued from the study on 24-May-2007. The subject was lost to follow up and no additional information is known.
3) Subject AI424138-95-700 (ATV/RTV) had a confirmed urine pregnancy test on 01-Apr-2007 after 276 days of dosing. Study drug was discontinued on 9-Apr-2007, and she discontinued from the study on 11-Apr-2007. It was reported that the subject gave birth to a normal, healthy infant on (b) (6)
4) Subject AI424138-16-155 (LPV/RTV) had a confirmed urine pregnancy test on 26-Mar-2007, after 335 days of dosing, and her medication was stopped on that day. She was

discontinued from the study on 29-Mar-2007. It was reported that subject gave birth to a normal, healthy infant on (b) (6).

5) Subject AI424138-19-129 (LPV/RTV) had a confirmed urine pregnancy test on 7-May-2007 after 356 days of dosing, and was discontinued from the study on that day. It was reported that subject gave birth to a normal, healthy infant on (b) (6).
6) Subject AI424138-50-994 (LPV/RTV) had a confirmed urine pregnancy test on 20-Sep-2006 after 86 days of dosing, and discontinued from the study on that date. On 19-Apr-2007 the site reported that the subject had had a spontaneous abortion, date unknown. The subject refused to provide additional information.
7) Subject AI424138-65-596 (LPV/RTV) had a positive urine pregnancy test on 19-Dec-2006 after 194 days of dosing and was discontinued from the study on that day. The pregnancy was at approximately 6 weeks gestational age. On (b) (6) subject experienced an incomplete spontaneous abortion (considered not related to study drug) that required hospitalization for medical curettage. The event was resolved upon discharge from the hospital (b) (6)

The following subjects had confirmed pregnancies after Week 48:

8) Subject AI424138-51-555 (ATV/RTV) had a confirmed serum pregnancy test on 07-Feb-2008 after 614 days of dosing. The pregnancy was at approximately 6 weeks gestational age. Study drug was discontinued on 05-Feb-2008. Subject discontinued from the study on 07-Feb-2008. The pregnancy was still ongoing at the time of this report.
9) Subject AI424138-63-226 (ATV/RTV) had a confirmed serum pregnancy test on 11-Feb-2008. The pregnancy was at approximately 4 weeks gestational age. Study drug was discontinued on 11-Feb-2008 after 655 days of dosing. Subject discontinued from the study on 24-May-2007. At approximately gestational week 10 on (b) (6) the subject experienced a spontaneous abortion (considered not related to study drug) that required hospitalization for medical curettage. The event was resolved upon discharge from the hospital.
10) Subject AI424138-110-791 (ATV/RTV) had a confirmed urine pregnancy test on 23-Apr-2008 after 666 days of dosing. The pregnancy was at approximately 5 weeks gestational age. On 28-Apr-2008 at approximately gestational week 6, the subject underwent an induced abortion (considered not related to study drug) via dilation and curretage due to a blighted ovum. Study drug was stopped one day later on 29-Apr-2008 when site was made aware of pregnancy (and termination) at subject's Week 96 visit; subject completed the study.
11) Subject AI424138-101-400 (ATV/RTV) was brought in for early termination visit on 30-Nov-2007, but study drug was not discontinued until 02-Dec-2007. It was reported that subject gave birth to a normal, healthy infant on (b) (6).
12) Subject AI424138-91-987 (ATV/RTV) had a confirmed urine pregnancy test on 30-Jun-2008, 60 days after study completion on 08-May-2008 (pregnancy test was negative on this date at final on-study visit). The pregnancy was still ongoing at the time of this report.
13) Subject AI424138-16-690 (LPV/RTV) had a confirmed urine pregnancy test on 29-Oct-2007. Study drug was discontinued on 29-Oct-2007 after 504 days of dosing. Subject

discontinued from the study on 30-Oct-2007. The subject was lost to follow up and no additional information is known.

14) Subject AI424138-90-725 (LPV/RTV) had a confirmed serum pregnancy test on 04-Oct-2007. The pregnancy was at approximately 6 weeks gestational age. Study drug was discontinued on 05-Oct-2007 after 467 days of dosing. Subject discontinued from the study on 09-Oct-2007. At approximately gestational week 11 on 14-Nov-2007, the subject experienced a spontaneous abortion (considered by investigators to be not likely related to study drug).
15) Subject AI424138-91-858 (LPV/RTV) had a confirmed serum pregnancy test on 21-Jan-2008 after 572 days of dosing. The pregnancy was at approximately 6 weeks gestational age. Study drug was discontinued on 20-Jan-2008. The subject discontinued from the study on 21-Jan-2008. The pregnancy was still ongoing at the time of this report.

7.6.3 Pediatrics and Effect on Growth

Not applicable. Study 138 enrolled HIV-infected adults ≥18 years old.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no known withdrawal or abuse potential with ATV. Human experience of acute overdose with ATV is limited and already described in the label. No new information regarding overdose was provided in this supplement.

8 Postmarketing Experience

Data from the Applicant's postmarketing database, as well as the FDA's Adverse Events Reporting System (AERS), were also reviewed to assess safety. No new safety findings were identified from postmarketing data evaluated during this review.

The Applicant coded AEs for postmarketing safety surveillance using MedDRA and summarized these findings in periodic safety update reports (PSURs). From 20-Jun-2003 through 19-Jun-2008, ten PSURs were submitted (Table 33). A total of 2357 (1994 initial, 363 follow-up) AE reports were received and/or validated, which included ATV as a suspect or interacting drug. Of these 2357 reports, 1527 reports were spontaneously reported from worldwide sources, 111 were derived from the published scientific literature, and 719 were received from clinical trials. Additionally, 1674 of 2357 reports qualified for classification as serious: 880 spontaneous reports, 77 literature reports, and 717 clinical trial reports. In the 10 PSURs, there were approximately 1370 males and 665 females who reported AE/adverse drug reactions (ADRs). Of note, 21 reports described overdose, 91 reports involved drug exposure during pregnancy, 64 reports described suspected drug interactions, 4 reports described suicide, and 6 reports described

incorrect medication administration. There were no reports that concerned potential drug abuse. A fatal outcome was reported in 100 of 2357 reports.

Reviewer Comment

No new safety findings were identified from postmarketing data evaluated during this review.

9 Appendices

9.1 Literature Review/References

Literature reviewed for this sNDA is cited in relevant sections of this document.

9.2 Labeling Recommendations (new text in bold)

The proposed package insert (PI or label) has been reviewed by all disciplines involved in the NDA review of ATV/RTV. The major recommendations for revisions to the clinical sections of the proposed label are listed below.

Warnings and Precautions (Section (b) (4) – Rash)

In controlled clinical trials, rash (all grades, regardless of causality) occurred in approximately 20% of patients treated with REYATAZ. (b) (4) Treatment-emergent adverse reactions of moderate or severe rash (occurring at a rate of ≥2%) are presented for the individual clinical studies [see *Adverse Reactions (6.1)*]. Dosing with REYATAZ was often continued without interruption in patients who developed rash. The discontinuation rate for rash in clinical trials was <1%. 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).*]

Section 6.1 – Clinical Trials Experience

Treatment-Emergent Adverse Reactions in Treatment-Naive Patients

The safety profile of REYATAZ in treatment-naive adults is based on 1625 HIV-1 infected patients in clinical trials. 536 patients received REYATAZ 300 mg with ritonavir 100 mg and 1089 patients received REYATAZ 400 mg or higher (without ritonavir).

The most common adverse reactions are nausea, jaundice/scleral icterus, and rash.

Selected clinical adverse reactions of moderate or severe intensity reported in ≥2% of treatment-naive patients receiving combination therapy including REYATAZ 300 mg with ritonavir 100 mg and REYATAZ 400 mg (without ritonavir) are presented in Tables 4 and 5, respectively.

(b) (4)

Selected Treatment-Emergent Adverse Reactions[a] of Moderate or Severe Intensity Reported in ≥2% of Adult Treatment-Naive Patients,[b] Study AI424-138

	96 weeks[c] REYATAZ 300 mg with ritonavir 100 mg (once daily) and tenofovir with emtricitabine[d] (n=441)	96 weeks[c] lopinavir 400 mg with ritonavir 100 mg (twice daily) and tenofovir with emtricitabine[d] (n=437)
Digestive System		
Nausea	4%	8%
Jaundice/scleral icterus	5%	*
Diarrhea	2%	12%
Skin and Appendages		
Rash	3%	2%

* None reported in this treatment arm

[a] Includes events of possible, probable, certain, or unknown relationship to treatment regimen.
[b] Based on the regimen containing REYATAZ.
[c] Median time on therapy.
[d] As a fixed-dose combination: 300 mg tenofovir, 200 mg emtricitabine once daily.

Laboratory Abnormalities in Treatment-Naive Patients

The percentages of adult treatment-naive patients treated with combination therapy including REYATAZ (atazanavir sulfate) 300 mg with ritonavir 100 mg and REYATAZ 400 mg (without ritonavir) with Grade 3–4 laboratory abnormalities are presented in Tables 7 and 8, respectively.

Table 7: Grade 3–4 Laboratory Abnormalities Reported in ≥2% of Adult Treatment-Naive Patients,[a] Study AI424-138

Variable	Limit[c]	96 weeks[b] REYATAZ 300 mg with ritonavir 100 mg (once daily) and tenofovir with emtricitabine[d] (n=441)	96 weeks[b] lopinavir 400 mg with ritonavir 100 mg (twice daily) and tenofovir with emtricitabine[d] (n=437)
Chemistry	High		
SGOT/AST	≥5.1 x ULN	3%	1%
SGPT/ALT	≥5.1 x ULN	3%	2%
Total Bilirubin	≥2.6 x ULN	44%	<1%
Lipase	≥2.1 x ULN	2%	2%
Creatine Kinase	≥5.1 x ULN	8%	7%
Total Cholesterol	≥240 mg/dL	11%	25%
Hematology	Low		
Neutrophils	<750 cells/mm^3	5%	2%

[a] Based on the regimen containing REYATAZ.
[b] Median time on therapy.
[c] ULN = upper limit of normal.
[d] As a fixed-dose combination: 300 mg tenofovir, 200 mg emtricitabine once daily.

Lipids, Change from Baseline in Treatment-Naive Patients

For Study AI424-138, changes from baseline in LDL-cholesterol, HDL-cholesterol, total cholesterol, and triglycerides are shown in Table 10.

Table 10: Lipid Values, Mean Change from Baseline, Study AI424-138

	REYATAZ/ritonavir[a,b]					lopinavir/ritonavir[b,c]				
	Baseline	Week 48		Week 96		Baseline	Week 48		Week 96	
	mg/dL (n=428[e])	mg/dL (n=372[e])	Change[d] (n=372[e])	mg/dL (n=342[e])	Change[d] (n=342[e])	mg/dL (n=424[e])	mg/dL (n=335[e])	Change[d] (n=335[e])	mg/dL (n=291[e])	Change[d] (n=291[e])
LDL-Cholesterol[f]	92	105	+14%	105	+14%	93	111	+19%	110	+17%
HDL-Cholesterol[f]	37	46	+29%	44	+21%	36	48	+37%	46	+29%
Total Cholesterol[f]	149	169	+13%	169	+13%	150	187	+25%	186	+25%
Triglycerides[f]	126	145	+15%	140	+13%	129	194	+52%	184	+50%

a REYATAZ 300 mg with ritonavir 100 mg once daily with the fixed-dose combination: 300 mg tenofovir, 200 mg emtricitabine once daily

b Values obtained after initiation of serum lipid-reducing agents were not included in these analyses At baseline, serum lipid-reducing agents were used in 1% in the lopinavir/ritonavir treatment arm and 1% in the REYATAZ/ritonavir arm. Through Week 48, serum lipid-reducing agents were used in 8% in the lopinavir/ritonavir treatment arm and 2% in the REYATAZ/ritonavir arm Through Week 96, serum lipid-reducing agents were used in 10% in the lopinavir/ritonavir treatment arm and 3% in the REYATAZ/ritonavir arm

c Lopinavir 400 mg with ritonavir 100 mg twice daily with the fixed-dose combination 300 mg tenofovir, 200 mg emtricitabine once daily

d The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 48 or Week 96 values and is not a simple difference of the baseline and Week 48 or Week 96 mean values, respectively

e Number of patients with LDL-cholesterol measured

f Fasting

6.3 Patients Co-infected with Hepatitis B and/or Hepatitis C Virus (new text in bold)

In study AI424-138, 60 patients treated with REYATAZ/ritonavir 300 mg/100 mg once daily, and 51 patients treated with lopinavir/ritonavir 400 mg/100 mg twice daily, each with fixed dose tenofovir-emtricitabine were seropositive for hepatitis B and/or C at study entry. (b) (4) ALT levels >5 times ULN developed in **10% (6/60)** of the REYATAZ/ritonavir-treated patients, and **8% (4/50)** of the lopinavir/ritonavir-treated patients. AST levels >5 times ULN developed in **10% (6/60)** of the REYATAZ/ritonavir-treated patients and none (0/50) of the lopinavir/ritonavir-treated patients.

FDA Comment

The proposed wording is acceptable.

Section 12.4 – Microbiology (new text in bold)

Clinical Studies of Treatment-Naive Patients Receiving REYATAZ 300 mg With Ritonavir 100 mg: In Phase III study AI424-138, an as-treated genotypic and phenotypic analysis was conducted on samples from patients who experienced virologic failure (HIV-1 RNA ≥400

copies/mL) or discontinued before achieving suppression on ATV/RTV (**n=39; 9%**) and LPV/RTV (**n=39; 9%**) through **96** weeks of treatment. In the ATV/RTV arm, one of the virologic failure isolates had a 56-fold decrease in ATV susceptibility emerge on therapy with the development of PI resistance-associated substitutions L10F, V32I, K43T, M46I, A71I, G73S, I85I/V, and L90M. **The NRTI resistance-associated substitution M184V also emerged on treatment in this isolate conferring emtricitabine resistance. Two ATV/RTV-virologic failure isolates had baseline phenotypic ATV resistance and IAS-defined major PI resistance-associated substitutions at baseline. The I50L substitution emerged on study in one of these failure isolates and was associated with a 17-fold decrease in ATV susceptibility from baseline and the other failure isolate with baseline ATV resistance and PI substitutions (M46M/I and I84I/V) had additional IAS-defined major PI substitutions (V32I, M46I, and I84V) emerge on ATV treatment associated with a 3-fold decrease in ATV susceptibility from baseline.** Five of the treatment failure isolates in the ATV/RTV arm developed phenotypic emtricitabine resistance **with the emergence of either the M184I (n=1) or the M184V (n=4) substitution on therapy** and none developed phenotypic tenofovir disoproxil resistance. In the LPV/RTV arm, one of the virologic failure patient isolates had a 69-fold decrease in LPV susceptibility emerge on therapy with the development of PI substitutions L10V, V11I, **I54V, G73S, and V82A** in addition to baseline PI substitutions L10L/I, V32I, I54I/V, A71I, G73G/S, V82V/A, L89V, and L90M. Six **LPV/RTV** virologic failure isolates developed **the M184V substitution** and phenotypic emtricitabine resistance and two developed phenotypic tenofovir disoproxil resistance.

14 CLINICAL STUDIES

14.1 Patients Without Prior Antiretroviral Therapy

Study AI424-138: a 96-week study comparing the antiviral efficacy and safety of atazanavir/ritonavir with lopinavir/ritonavir, each in combination with fixed-dose tenofovir-emtricitabine in HIV-1 infected treatment naive subjects. Study AI424-138 is a 96-week open-label, randomized, multicenter study, comparing REYATAZ (300 mg once daily) with ritonavir (100 mg once daily) to lopinavir with ritonavir (400/100 mg twice daily), each in combination with fixed-dose tenofovir with emtricitabine (300/200 mg once daily), in 878 antiretroviral treatment-naive treated patients. Patients had a mean age of 36 years (range: 19–72), 49% were Caucasian, 18% Black, 9% Asian, 23% Hispanic/Mestizo/mixed race, and 68% were male. The median baseline plasma CD4+ cell count was 204 cells/mm^3 (range: 2 to 810 cells/mm^3) and the mean baseline plasma HIV-1 RNA level was 4.94 $\log_{10}$ copies/mL (range: 2.60 to 5.88 $\log_{10}$ copies/mL). Treatment response and outcomes through Week 96 are presented in Table 21.

Table 21: Outcomes of Treatment Through Week 96 (Study AI424-138)

Outcome	REYATAZ 300 mg + ritonavir 100 mg (once daily) with tenofovir/emtricitabine (once daily)[a] (n=441) 96 Weeks	lopinavir 400 mg + ritonavir 100 mg (twice daily) with tenofovir/emtricitabine (once daily)[a] (n=437) 96 Weeks
Responder[b,c,d]	75%	68%
Virologic failure[e]	17%	19%
Rebound	8%	10%
Never suppressed through Week 96	9%	9%
Death	1%	(b) (4) %
Discontinued due to adverse event	3%	5%
Discontinued for other reasons[f]	4%	7%

[a] As a fixed-dose combination: 300 mg tenofovir, 200 mg emtricitabine once daily.
[b] Patients achieved HIV RNA <50 copies/mL at Week 96. Roche Amplicor®, v1.5 ultra-sensitive assay.
[c] Pre-specified ITT analysis at Week 48 using as-randomized cohort: ATV/RTV 78% and LPV/RTV 76% [difference estimate: 1.7% (95% confidence interval: -3.8%, 7.1%)].
[d] Pre-specified ITT analysis at Week 96 using as-randomized cohort: ATV/RTV 74% and LPV/RTV 68% [difference estimate: 6.1% (95% confidence interval: 0.3%, 12.0%)].
[e] Includes viral rebound and failure to achieve confirmed HIV RNA <50 copies/mL through Week 96.
[f] Includes lost to follow-up, patient's withdrawal, noncompliance, protocol violation, and other reasons.

Through 96 weeks of therapy the proportion of responders among patients with high viral loads (i.e., baseline HIV RNA ≥100,000 copies/mL) was comparable for the REYATAZ/ritonavir (165 of 223 patients, 74%) and lopinavir/ritonavir (148 of 222 patients, 67%) arms. At 96 weeks the median increase from baseline in CD4+ cell count was 261 cells/mm^3 for the REYATAZ/ritonavir arm and 273 cells/mm^3 for the lopinavir/ritonavir arm.

FDA Comment

The proposed wording is acceptable. Similar to the Week 48 data in the traditional approval, Week 96 efficacy outcomes are displayed in the label using as-treated analysis.

9.3 Advisory Committee Meeting

Not applicable.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21567	SUPPL-19	BRISTOL MYERS SQUIBB CO	REYATAZ (ATAZANAVIR SULFATE)

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/s/

KIRK M CHAN-TACK
11/03/2009

MARY E SINGER
11/04/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021567/S-019

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

NDA#:	21-567 (SE 019)
DRUG NAME:	Atazanavir with ritonavir (Reyataz™)
INDICATION:	Treatment of HIV Infection in treatment-naive patients
TYPE OF REVIEW:	Clinical
APPLICANT:	Bristol-Myers Squibb
DATES:	Jan. 5, 2009
REVIEW PRIORITY:	Standard
BIOMETRICS DIVISION:	DB4
STATISTICAL REVIEWER:	Thomas Hammerstrom, (HFD-725)
TEAM LEADER:	Greg Soon, PhD, (HFD-725)
MEDICAL DIVISION:	DAVP
CLINICAL TEAM:	Kirk Chan Tack, MD (HFD-530), Kim Struble, MD (HFD-530)
PROJECT MANAGER:	Paras Patel, (HFD-530)

STATISTICAL REVIEW AND EVALUATION

NDA#: 21-567

1. Executive Summary

The applicant submitted two randomized, controlled, open label, phase 4 clinical trials with treatment naive patients. Both were active controlled trials. One trial (trial 138) compared atazanavir boosted with ritonavir to boosted lopinavir; the other (trial 89) compared boosted atazanavir to unboosted atazanavir. On Dec. 21, 2007, in SN015 and SN017 for this NDA, the applicant submitted week 48 results for both trials and week 96 results for trial 89. These results have already been reviewed under SN015 and 017. In both cases, the boosted atazanavir regimen was, with high statistical confidence, no more than 10% worse than the comparator arm, thus meeting the DAVP criterion for clinical non-inferiority in treatment naive patients.

The current submission completes the results for trial 138 by presenting the week 96 data for that trial.

2. Introduction

2.1 Overview

The applicant submitted two randomized, controlled, open label, phase 4 clinical trials with treatment naive patients. Both were active controlled trials. One trial (trial 138) compared atazanavir boosted with ritonavir to boosted lopinavir; the other (trial 89) compared boosted atazanavir to unboosted atazanavir. On Dec. 21, 2007, in SN015 and SN017 for this NDA, the applicant submitted week 48 results for both trials and week 96 results for trial 89. These results have already been reviewed under SN015 and 017. In both cases, the boosted atazanavir regimen was, with high statistical confidence, no more than 10% worse than the comparator arm, thus meeting the DAVP criterion for clinical non-inferiority in treatment naive patients.

The current submission completes the results for trial 138 by presenting the week 96 data for that trial. The applicant has demonstrated in atazanvir/ritonavir at 300/100 mg qd is effective in treatment naive patients out to 96 weeks of therapy when combined with a background regimen of tenofovir (TDF) at 300 mg qd plus emtricitibine (FTC) at 200 mg qd. It is comparable to

LPV/r at 400/100 mg bid in these patients. The results at week 96 suggest superiority to LPV/r although they fall short of statistically significant superiority.

2.2 Data Sources

2.2.1 Objectives in Trials

The primary objective of trial 138 was to compare the efficacy of atazanavir+ritonavir(ATZ/r) at 300/100 mg qd to lopinavir+ritonavir (LPV/r) at 400/100 mg bid when each is combined with a background regimen of tenofovir (TDF) at 300 mg qd plus emtricitibine (FTC) at 200 mg qd, in the combined form of Truvada.

The patients were HIV-infected, treatment naive, with HIV RNA>=5,000 copies/ml at screening.

All results in section 2 will be those of the applicant. Results generated by the FDA reviewer will be contained in section 3.

2.2.2 Summary of Study Design

Trial 138 was a 96 week, open-label, randomized, two-arm, parallel, active controlled, multi-center trial. Subjects were randomly assigned in a 1:1 ratio to ATZ/r at 300/100 mg qd or LPV/r at 400/100 mg bid. All subjects also received TDF+FTC background regimen. Randomization was stratified by baseline HIV RNA < or >= 100 K c/ml.

Subjects could be discontinued early for confirmed increase of HIV RNA of .5 logs at week 12 or a confirmed HIV RNA >= 1,000 c/ml at week 48 or later. Subjects experiencing renal toxicity could replace the truvada background regimen with dual nucleosides without being counted as failures.

2.2.3 Patient Accounting and Baseline Characteristics

883 patients were randomized in Trial 138, 440 to ATZ/r and 443 to LPV/r. 97 discontinued treatment before week 48 and a further 28 discontinued treatment after week 48.

TABLE 2.2.3 A
PATIENT STATUS, RESIST TRIALS

	Trial 138		Trial 89	
	ATZ	LPV	A300/r	A400
Randomized	440	443	95	105
Treated	438	440	95	104
Withdrew by Week 48	39	58	11	10
Death	4	4	0	1
AE	10	14	8	1
LOE*	5	8	0	3
LTFU**	20	32	3	5
Withdrew Week 48-96	14	14	3	1
Death	1	1	0	0
AE	1	1	0	0
LOE*	7	1	0	1
LTFU**	5	11	3	0
Continuing at Wk 96	385	368	81	93

* LOE = lack of efficacy
** LFTU = lost to follow-up

In trial 138, the study population was 69% male with a median age of 35 years. They were 48% white, 18% black, and 9% were Asian. Subjects came from South America, 46%, North America, 8%, Europe, 24%, Asia, 20%, and Africa, 14%. The median CD4 count at baseline was 205 cells/mm^3; the median HIV RNA level was 4.98 logs. 13% were co-infected with hepatitis B or C. 5% of patients had prior CDC class C AIDS events. 12 subjects (5 on ATZ/r, 7 on LPV/r) had previously received ARV therapy for the prevention of mother-child transmission.

2.2.4 Summary of Methods of Assessment

2.2.4.1 Schedule of Measurements

Patients in trial 138 had HIV RNA and CD4 counts was measured at weeks 0, 4, 12, and then every 12 weeks to week 96. Plasma samples were assessed by Roche Amplicor 1.5 assay.

2.2.4.2 Criteria for Switching Regimen

Subjects in trial 138 were allowed to substitute two nucleosides for truvdaa in the background if renal toxicity was observed. Premature failures were declared for a confirmed increase in HIV viral load by .5 logs at week 12 or later or by a cofirmed level > 1,000 c/ml at week 48 or later.

2.2.4.3 Assessment of Treatment Effects

In trial 138, the primary endpoint at week 48 was percent of subjects with sustained viral load below 50 c/ml. Subjects were considered to have experience viral rebound to above 50 if lost to follow-up. A secondary viral endpoints was percent <400 c/mL. The current review compares results on these endpoints at week 96 with those found and reviewed earlier at week 48.

2.2.5 Summary of Statistical Analysis

In trial 138, confidence intervals for the difference between ATZ/r and lpv/r were computed using stratification by baseline HIV viral load and continent. Efficacy relative to imputed placebo was inferred if the 2-sided 95% lower bound for the difference was > -10%. The primary analysis used non-completers as failures.

A sensitivity analysis was conducted in which rebounders were treated as successes if they subsequently re-suppressed. Another sensitivity analysis imputed success rates for subjects lost to follow-up using a doubly-robust combining two logistic regressions, one for discontinuation and one for viral failure. Both regressions used continent, gender, baseline CD4 count,

baseline HIV RNA and week 12 HIV RNA. In this analysis, subjects observed to fail or observed as successes at the final week are left unchanged, only subjects lost while not yet failures are imputed. Since this analysis only imputes follow-on data for subjects missing their last several visits, use of the week 12 HIV RNA as a covariate is acceptable. One should note that this analysis does not do the unacceptable procedure of modelling final week response rates as a function of covariates, one of which is post-treatment.

2.2.6 Summary of Applicant's Results

The general analysis of this trial for accelerated and traditional approval has already been discussed in previous reviews. The important question here is the extent to which the FDA reviewer is able to replicate the applicant's analysis of the week 96 data. Therefore, the discussion of applicant's results will be presented below in section 3.1 along with the FDA analyses.

2.2.7. Summary of Applicant's Conclusions

The applicant concluded that the antiviral efficacy of atazanvir/ritonavir at 300/100 mg qd in treatment niave subjects was clinically and statistically non-inferior to that of either lopinavir/ritonavir or atazanvir alone at 400 mg qd when used with two other effective ARVs. The efficacy was preserved across different measures of efficacy and across subgroups. The applicant provided data out to 96 weeks but not provide analyses of this data. The FDA review will discuss this longer term data.

3. Statistical Evaluation

3.1 Evaluation of Efficacy

3.1.1 Results with Percent BLQ in Trial 138: ATZ/r vs LPV/r

The applicant provided two computer datasets that are relevant to the final classification of subjects at week 96 in trial 138. Theese datasets are AES, which contains information on all adverse events, regardless of whether they resulted in discontinuation, and TL5096, which contains a variable OUTCOME, that gives the classification of outcomes as proposed for labelling. Table 3.1.1 A gives the number and percentage successful at week 96, using an LOQ=50 by the FDA reviewer's computation and from the TL5096 dataset provided by the sponsor.

TABLE 3.1.1 A
SUCCESS RATES AT WEEK 96, LOQ=50

FDA_RESULT	OUTCOME_	LPV	ATV
Discordant Results			
SUCCESS	VIROLOGIC_FAILURE	1	0
REBOUND	RESPONDER	4	4
Concordant Results Ignoring AE's			
DEATH	DISC._BEFORE_ACHIEV._CONFIRM_SUPPRESSI.	4	4
DEATH	DISCONTINUED_WHILE_SUPPRESSED	1	2
DEATH	VIROLOGIC_FAILURE	1	0
AE_NEVER_SUPPRESSED	DISC._BEFORE_ACHIEV._CONFIRM_SUPPRESSI.	11	9
AE_WHILE_SUPPRESSED	DISCONTINUED_WHILE_SUPPRESSED	11	3
AE_AFTER_REBOUND	VIROLOGIC_FAILURE	0	1
Condcordant Results			
SUCCESS	RESPONDER	275	306
NEVER_SUPPRESSED	DISC._BEFORE_ACHIEV._CONFIRM_SUPPRESSI.	27	22
NEVER_SUPPRESSED	NEVER_TREATED	3	2
NEVER_SUPPRESSED	VIROLOGIC_FAILURE	13	20
REBOUND	DISCONTINUED_WHILE_SUPPRESSED	0	2
REBOUND	VIROLOGIC_FAILURE	61	52
LTFU_WHILE_SUPPRESSED	DISCONTINUED_WHILE_SUPPRESSED	28	16

There are 9 subjects on which there is disagreement. These are explicable by differences in the week 96 window. The one subject counted as success by FDA but not by the applicant actually rebounded at week 104. The eight subjects counted as successes by the applicant but not by the FDA actually rebounded

in weeks 96 to 102. The FDA computation required no rebound until the end of the week 96 window, defined as weeks 90 to 102. This is based on the typical long-term schedule of a visit every 12 weeks so that the visit window late in the trial is six weeks on either side of the target week.

When the failures are sub-divided by reason for failure, such as never suppressed, lost to follow-up while suppressed, or rebounded, the applicant's categories are uninformative. In addition, categories for failed due to discontinuations due to adverse events and specifically, death, should also be included. The applicant does not provide any variable which makes use of adverse event data. As one can see from the table, there were 12 deaths (split 6 and 5 between the two arms) and 35 subjects who discontined drug permanently after AE's, only one of them after a rebound. Table 3.1.1 B gives these adverse events.

TABLE 3.1.1 B
DISCONTINUATIONS DUE TO ADVERSE EVENTS
TRIAL 138, WEEK 96

OUTCOME_=DISC. BEFORE ACHIEV. CONFIRM. SUPPRESSI.

USUBJID	DISC_DAY	LASTDAY	AENAME
AI424138-77-146	0	14	HYPERSENSITIVITY_REACTION
AI424138-78-593	1	15	EXANTHEMA
AI424138-78-916	1	17	EXANTHEMA

OUTCOME_=DISCONTINUED_WHILE_SUPPRESSED

USUBJID	DISC_DAY	LASTDAY	AENAME
AI424138-105-973	333	335	LIPODYSTROPHY
AI424138-105-973	333	335	DARKENED_SKIN
AI424138-115-18	170	220	JAUNDICE
AI424138-147-626	421	502	VOMITING
AI424138-23-185	508	510	DIARRHEA
AI424138-23-250	294	296	DIARRHEA
AI424138-23-250	294	296	DIARRHEA
AI424138-23-616	168	170	DIARRHEA
AI424138-23-616	168	170	DIARRHEA
AI424138-50-872	588	622	RHABDOMYOLYSIS
AI424138-55-729	439	514	LIPOMA
AI424138-77-352	181	183	HYPERLIPIDEMIA
AI424138-86-928	590	592	HYPERLIPEMIA
AI424138-93-343	420	437	HYPERTROPHIC_CARDIOMYOPATHY

Table 3.1.1 C gives the FDA reviewers results on trial 138 for sustained suppression using LOQ of 400 and 50 at endpoints of 48 weeks and 96 weeks. The table gives the success rates for the LPV/r and ATZ/r arms separately as well as the point estimate and 95% confidence limits for ATZ/r - LPV/r and the p-value for testing superiority of ATZ/r.

TABLE 3.1.1 C
DIFFERENCES IN SUCCESS RATES, TRIAL 138,
WEEKS 48 AND 96, AS TREATED

	MEAN DIFF	95% BOUNDS LOWER	UPPER	ATV	LPV	P_VALUE
<400						
WK_48_AS_TREATED	4.0%	-0.9%	8.8%	381/443=86%	361/440=82%	0.1079
WK_96_AS_RANDOMIZED	6.2%	0.5%	11.8%	346/440=79%	321/443=72%	0.0323
WK_96_AS_TREATED	6.1%	0.4%	11.7%	348/443=79%	319/440=73%	0.0359
<50						
WK_48_AS_TREATED	1.1%	-4.4%	6.5%	348/443=79%	341/440=78%	0.7049
WK_96_AS_RANDOMIZED	6.3%	0.1%	12.6%	304/440=69%	278/443=63%	0.0465
WK_96_AS_TREATED						
Confirmed_sustained_suppression	6.3%	0.1%	12.6%	306/443=69%	276/440=63%	0.0462
SNAPSHOT1	6.1%	0.1%	12.1%	327/443=74%	298/440=68%	
SNAPSHOT2	6.8%	0.8%	12.7%	330/443=74%	298/440=68%	

There is one minor initial problem with trial 138: three of the subjects randomized to LPV/r actually received ATZ/r. Normally in such cases, one prefers an 'as randomized' analysis because such inadvertent switches run the risk of biasing prognostic factors. In non-inferiority analyses, there is a problem with inadvertent switches in the 'as randomized' analysis, namely that the 'as randomized' cohorts are actually mixtures of subjects on both drugs. This would tend to drive the arms toward equality even in the presence of a real difference.

Table 3.1.1.1 C includes a comparison of the FDA's results using the 'as treated' and 'as randomized'. One can see that the method and findings chosen are of no consequential difference and using the as treated results in the labelling is acceptable. In the analyses that follow, the FDA's results and the 'as treated' analysis will be used.

The last two lines of the table also include analyses using a snapshot view of the results at week 96, ignoring the previous history of the subject. These results merely require, for success, that the subject have HIV RNA<50 at week 96, even if there is no confirmation and even if there was a prior rebound. It has been argued that in long term trials that drugs may be temporarily discontinued due to toxicity, without starting a new regimen. This would result in a rebound but the subject might subquently re-suppress without ever being on a new regimen. The FDA reviewer has included both a SNAPSHOT1, which requires all observations in the weeks 90-102 window to be <50. If there are no such observations, both the last HIV RNA before week 90 and the first HIV RNA after week 102 must be <50. SNAPSHOT2 is preferred by the FDA clinical reviewers as being easier to compute but it is less logical. It requires that the last observation in the week 90-102 window by <50 and counts as a failure any subject with no HIV RNA in the window. This is illogical if the preceding and succeeding HIV measurements were both <50. Table 3.1.1 D compares the results of the history dependent endpoint with the snapshot endpoint (specifically, the one favored by the clinical reviewers).

TABLE 3.1.1 D
HISTORY DEPENDENT AND SNAPSHOT ENDPOINTS

	HISTORY	SNAPSHOT	LPV	ATV
Week 48				
	FAIL	FAIL	88	79
	SUCC	SUCC	338	346
	FAIL	SUCC	11	16
	SUCC	FAIL	3	2
Week 96				
	FAIL	FAIL	141	112
	SUCC	SUCC	275	305
	FAIL	SUCC	23	25
	SUCC	FAIL	0	1

Of the 48 subjects with rebounds by week 96 and thus counted as failures on the history dependent endpoint, 6 has temporary

drug interruptions although only 3 of these were followed by rebounds. 29 of these 48 subjects had rebounds of HIV RNA to between 51 and 400, 5 to between 401 and 999, 14 to > 1000. The remaining 6 discrepancies at week 96 correspond to subjects with an unconfirmed rebound at week 96 which was preceded and succeeded by values <50. The comparison of the endpoints at week 48 would be comparable. The most important observation remains that the difference between the arms does not change by as much as 1% with the choice of endpoint computation method.

Table 3.1.1 E gives the cross tabulation of the four results using both timepoints and both LOQ's. The table contains the counts, by arm, in each of six progressively more successful categories.

TABLE 3.1.1 E
CROSS-TABULATION OF <400, <50 AT WEEKS 48, 96

	LPV/R	ATZ/R
Failure all times, both LOQ	79	62
<400 at Wk 48 but not at Wk 96, Never <50	2	6
<400 at Wk 96, Never <50	22	29
<50 at Wk 48, >400 at Wk 96	38	29
<50 at Wk 48, >50, <400 at Wk 96	29	24
<50 at Wk 48 and 96	270	293
Total	440	443

In detail, there are a handful of anomalies hidden in the above tables. If one computes separately the standard suppression-rebound algorithm for LOQ=400 and LOQ=50, first using the original NDA data through week 48 for the week 48 endpoint and then using the extended week 96 data for the week 96 endpoint, the four resulting tables will look slightly incompatible, as can be seen below. This is because some subjects have anomalous trajectories of their HIV load. Some are confirmed <400 but not <50, then have confirmed rebound >400, and then have confirmed suprression <50. Some subjects do not achieve confirm suppression to below one or the other LOQ until after week 48 (although they have low viral loads just above the LOQ; low enough to warrant continuing the assigned regimen). Finally, some subjects have 1st suppression at week 48 but no confirmation until week 60 or 1st rebound at week 48, a rebound which is not

confirmed by the week 60 data. The latter subjects were counted as failures at week 48 using the week 48 data in the earlier review but were reclassified as successes at week 48 using the week 96 which includes the week 60 visit. Table 3.1.1 C counts the number of subjects with anomalous HIV histories as just described.

TABLE 3.1.1 C
ANOMALOUS TRAJECTORIES

Confirmed suppression, confirmed rebound <400, then 1st confirmed <50	3
1st Observed HIV<400 at wk 48, not confirmed until wk 60	2
Rebound >400 at wk 48, not confirmed at wk 60	1
Confirmed <400 by week 48, not confirmed <50 until after week 48	16

3.2 Evaluation of Safety

The FDA clinical reviewers did not raise any safety concerns requiring statistical analysis in the current submission.

4. Results in Special Populations

There was little evidence of interactions between treatment and any interesting covariates. ATZ/r, relative to either unboosted ATZ or LPV/r, appeared to be roughly equally effective for both sexes, both races studied , at all levels studied for age, baseline HIV RNA, baseline CD4 count, hepatitis co-infection, HIV duration or stage.

4.1 *Gender, Race, and Age*

Tables 4.1 A and B show success rates for both arms and 95% confidence intervals for the difference in success rates between ATZ/r and LPV/r for trial 138, stratified by randomization stratum, sex, race, and quartile of age. The table also gives the p-value for testing for homogeneity of treatment differences across strata. In this whole section, any stratum of any covariate that included <10% of the subjects was deleted from the analysis for that covariate. Thus, totals are not constant from one covariate to the next. Table 4.1 A shows success defined by sustained suppression to <400 copies/ml; 4.1 B shows success defined by sustained suppression to <50 copies/ml. As mentioned above, there are no apparent interactions.

TABLE 4.1 A

PERCENT<400, WK 96, BY GENDER, RACE, AGE, TRIAL 138

COVARIATE	MEAN DIFF	95% BOUNDS LOWER	UPPER	ATV	LPV	P_HOMOG
<400	6.1%	0.4%	11.7%	348/443=79.0%	319/440=73.0%	
<50	6.3%	0.1%	12.6%	306/443=69.0%	276/440=63.0%	
GENDER						
FEMALE	7.7%	-3.1%	18.5%	101/138=73.0%	91/139=65.0%	0.86885
MALE	5.2%	-1.3%	11.8%	247/305=81.0%	228/301=76.0%	
AGE_Q						
<29	13.3%	0.1%	26.5%	77/106=73.0%	54/91=59.0%	0.61664
29-35	8.5%	-2.2%	19.2%	101/124=81.0%	81/111=73.0%	
35-43	1.0%	-9.7%	11.7%	88/113=78.0%	93/121=77.0%	
>=43	4.2%	-6.4%	14.9%	82/100=82.0%	91/117=78.0%	
RACE						
ASIAN	3.5%	-12.1%	19.2%	37/43=86.0%	33/40=83.0%	0.96078
BLACK	3.9%	-10.3%	18.2%	60/85=71.0%	52/78=67.0%	
OTHER	7.3%	-4.1%	18.7%	87/108=81.0%	74/101=73.0%	
WHITE	6.8%	-1.3%	14.9%	164/207=79.0%	160/221=72.0%	

TABLE 4.1 B

PERCENT<50, WK 96, BY GENDER, RACE, AGE, TRIAL 138

COVARIATE	MEAN DIFF	95% BOUNDS LOWER	UPPER	ATV	LPV	P_HOMOG
<50	6.3%	0.1%	12.6%	306/443=69.0%	276/440=63.0%	
GENDER						
FEMALE	5.5%	-6.0%	17.0%	87/138=63.0%	80/139=58.0%	0.78942
MALE	6.7%	-0.7%	14.1%	219/305=72.0%	196/301=65.0%	
AGE_Q						
<29	9.5%	-4.3%	23.3%	66/106=62.0%	48/91=53.0%	0.32601
29-35	13.7%	1.9%	25.6%	93/124=75.0%	68/111=61.0%	
35-43	-2.0%	-13.6%	9.7%	79/113=70.0%	87/121=72.0%	
>=43	5.6%	-7.1%	18.3%	68/100=68.0%	73/117=62.0%	
RACE						
ASIAN	3.5%	-12.1%	19.2%	37/43=86.0%	33/40=83.0%	0.97652
BLACK	4.6%	-10.4%	19.5%	54/85=64.0%	46/78=59.0%	
OTHER	5.2%	-7.7%	18.0%	74/108=69.0%	64/101=63.0%	
WHITE	7.9%	-1.1%	17.0%	141/207=68.0%	133/221=60.0%	

4.2 *Other Baseline Covariates*

Other interactions are illustrated in tables 4.2 A-D and were discussed briefly above. Formal Mantel-Haenszel tests for homogeneity across levels of the various covariates showed no more statistically significant results than would be expected by chance and multiple tests.

TABLE 4.2 A

PERCENT<400, WK 96, BY BASELINE COVARIATES, TRIAL 138

	MEAN	95% BOUNDS				
COVARIATE	DIFF	LOWER	UPPER	ATV	LPV	P_HOMOG
<400	6.1%	0.4%	11.7%	348/443=79.0%	319/440=73.0%	
STRAT2						
<100K	3.3%	-4.8%	11.5%	168/220=76.0%	157/215=73.0%	0.32888
>=100K	8.7%	0.9%	16.5%	180/223=81.0%	162/225=72.0%	
LOGBASE_Q						
<4.6	3.5%	-7.8%	14.8%	88/119=74.0%	86/122=70.0%	0.85402
4.6-5.0	9.9%	-1.6%	21.4%	80/99=81.0%	78/110=71.0%	
5.0-5.4	6.0%	-4.8%	16.8%	97/118=82.0%	77/101=76.0%	
>=5.4	4.7%	-6.9%	16.2%	83/107=78.0%	78/107=73.0%	
RNABASE_Q						
<27_K	-4.3%	-17.5%	8.9%	59/86=69.0%	70/96=73.0%	0.25728
27-89_K	12.2%	1.5%	23.0%	98/120=82.0%	84/121=69.0%	
89-238_K	7.1%	-3.4%	17.6%	98/119=82.0%	85/113=75.0%	
>=238_K	6.1%	-5.0%	17.2%	93/118=79.0%	80/110=73.0%	
CD4BASE_Q						
<120	6.8%	-4.4%	18.0%	102/129=79.0%	73/101=72.0%	0.45976
120-210	1.8%	-9.4%	13.0%	80/105=76.0%	93/125=74.0%	
210-305	12.7%	2.2%	23.3%	92/109=84.0%	86/120=72.0%	
>=305	2.7%	-9.8%	15.3%	74/100=74.0%	67/94=71.0%	
CD4BASE_L						
<50	20.1%	3.8%	36.4%	55/68=81.0%	31/51=61.0%	0.14025
50-100	0.7%	-18.1%	19.5%	36/45=80.0%	23/29=79.0%	
100-200	-2.5%	-13.6%	8.5%	78/106=74.0%	102/134=76.0%	
>=200	7.8%	-0.1%	15.6%	179/224=80.0%	163/226=72.0%	

TABLE 4.2 A (continued)

PERCENT<400, WK 96, BY BASELINE COVARIATES, TRIAL 138

	MEAN DIFF	95% BOUNDS LOWER	UPPER	ATZ/R	LPV/R	PHOMOG
REGION						
AFRICA	3.8%	-11.1%	18.7%	51/67=76.0%	47/65=72.0%	0.56861
ASIA	2.1%	-14.2%	18.5%	33/39=85.0%	33/40=83.0%	
EUROPE	13.5%	-1.7%	28.7%	53/67=79.0%	42/64=66.0%	
N_AMERICA	-2.9%	-18.5%	12.6%	46/68=68.0%	48/68=71.0%	
S_AMERICA	8.3%	0.2%	16.4%	165/202=82.0%	149/203=73.0%	
COUNTRY						
ARGENTINA	-3.9%	-18.5%	10.6%	42/55=76.0%	57/71=80.0%	0.90662
BRAZIL	13.2%	-5.3%	31.7%	30/34=88.0%	24/32=75.0%	
CHILE	14.4%	-11.9%	40.8%	10/11=91.0%	13/17=76.0%	
DOM_REP	-1.3%	-29.0%	26.4%	17/22=77.0%	11/14=79.0%	
FRANCE	-1.5%	-30.1%	27.2%	13/18=72.0%	14/19=74.0%	
MEXICO	-2.5%	-22.1%	17.1%	25/35=71.0%	34/46=74.0%	
PANAMA	16.4%	-21.4%	54.1%	8/10=80.0%	7/11=64.0%	
PERU	15.4%	-3.0%	33.8%	41/51=80.0%	26/40=65.0%	
S_AFRICA	3.8%	-11.1%	18.7%	51/67=76.0%	47/65=72.0%	
SPAIN	15.8%	-16.3%	47.9%	10/13=77.0%	11/18=61.0%	
THAILAND	2.4%	-15.2%	20.1%	18/19=95.0%	12/13=92.0%	
US	-10.0%	-42.4%	22.4%	11/22=50.0%	9/15=60.0%	
AIDS_						
NO	6.6%	0.9%	12.4%	337/424=79.0%	303/416=73.0%	0.25792
YES	-8.8%	-37.9%	20.4%	11/19=58.0%	16/24=67.0%	
HBSAG						
NEGATIVE	5.9%	0.1%	11.7%	328/418=78.0%	304/419=73.0%	
POSITIVE	9.2%	-16.7%	35.0%	19/24=79.0%	14/20=70.0%	
HCAB						
NEGATIVE	6.2%	0.4%	12.0%	321/402=80.0%	299/406=74.0%	
POSITIVE	7.4%	-15.0%	29.8%	26/40=65.0%	19/33=58.0%	
HEPBC						
NEGATIVE	5.8%	-0.2%	11.8%	303/381=80.0%	286/388=74.0%	
POSITIVE	9.4%	-8.0%	26.8%	44/61=72.0%	32/51=63.0%	

TABLE 4.2 A (continued)

PERCENT<400, WK 96, BY BASELINE COVARIATES, TRIAL 138

	MEAN DIFF	95% BOUNDS LOWER	UPPER	ATZ/R	LPV/R	PHOMOG
BMI_Q						
<21	6.7%	-5.8%	19.2%	81/112=72.0%	65/99=66.0%	0.19412
21-23	10.0%	-2.7%	22.6%	77/97=79.0%	59/85=69.0%	
23-26	12.1%	2.4%	21.9%	104/124=84.0%	104/145=72.0%	
>=26	-3.8%	-14.3%	6.7%	86/110=78.0%	91/111=82.0%	
BPDIA_Q						
<68	1.3%	-10.2%	12.9%	89/121=74.0%	78/108=72.0%	0.56203
68-73	11.3%	0.4%	22.3%	97/119=82.0%	80/114=70.0%	
73-80	2.7%	-12.5%	17.9%	48/64=75.0%	47/65=72.0%	
>=80	7.5%	-1.9%	16.9%	114/139=82.0%	114/153=75.0%	
BPSYS_Q						
<106	10.9%	-0.7%	22.4%	95/123=77.0%	73/110=66.0%	0.71966
106-114	4.8%	-6.3%	15.9%	87/109=80.0%	81/108=75.0%	
114-123	7.3%	-3.5%	18.0%	90/110=82.0%	85/114=75.0%	
>=123	1.2%	-10.6%	13.0%	76/101=75.0%	80/108=74.0%	
HT_Q						
<160	14.4%	1.8%	26.9%	67/84=80.0%	68/104=65.0%	0.29324
160-168	2.8%	-8.6%	14.2%	91/122=75.0%	79/110=72.0%	
168-175	-1.1%	-12.2%	10.1%	83/110=75.0%	88/115=77.0%	
>=175	8.6%	-1.6%	18.8%	107/127=84.0%	84/111=76.0%	
WAMS_Q						
<76	8.6%	-1.1%	18.3%	129/171=75.0%	109/163=67.0%	0.14493
76-83	16.4%	3.9%	29.0%	70/86=81.0%	63/97=65.0%	
83-91	0.8%	-10.4%	12.1%	77/95=81.0%	77/96=80.0%	
>=91	-4.2%	-15.8%	7.3%	72/91=79.0%	70/84=83.0%	
WT_Q						
<58	12.1%	-0.3%	24.4%	81/106=76.0%	65/101=64.0%	0.70922
58-66	1.9%	-10.2%	14.1%	74/103=72.0%	79/113=70.0%	
66-75	6.7%	-4.2%	17.5%	94/117=80.0%	84/114=74.0%	
>=75	3.4%	-6.4%	13.1%	99/117=85.0%	91/112=81.0%	

TABLE 4.2 B

PERCENT<50, WK 96, BY BASELINE COVARIATE, TRIAL 138

COVARIATE	MEAN DIFF	95% BOUNDS LOWER	UPPER	ATV	LPV	P_HOMOG
<400	6.3%	0.1%	12,6%	306/443=69.0%	276/440=63.0%	
STRAT2						
<100K	3.5%	-5.3%	12.2%	154/220=70.0%	143/215=67.0%	0.41920
>=100K	9.1%	0.2%	17.9%	152/223=68.0%	133/225=59.0%	
LOGBASE_Q						
<4.6	3.4%	-8.3%	15.1%	84/119=71.0%	82/122=67.0%	0.76767
4.6-5.0	11.8%	-0.8%	24.5%	72/99=73.0%	67/110=61.0%	
5.0-5.4	6.7%	-5.6%	19.0%	85/118=72.0%	66/101=65.0%	
>=5.4	3.7%	-9.4%	16.9%	65/107=61.0%	61/107=57.0%	
RNABASE_Q						
<27_K	-3.6%	-17.3%	10.1%	56/86=65.0%	66/96=69.0%	0.28249
27-89_K	13.8%	2.3%	25.4%	91/120=76.0%	75/121=62.0%	
89-238_K	7.7%	-4.3%	19.7%	85/119=71.0%	72/113=64.0%	
>=238_K	5.4%	-7.3%	18.2%	74/118=63.0%	63/110=57.0%	
CD4BASE_Q						
<120	8.6%	-3.8%	21.0%	89/129=69.0%	61/101=60.0%	0.51606
120-210	1.6%	-10.9%	14.0%	68/105=65.0%	79/125=63.0%	
210-305	12.7%	0.9%	24.6%	82/109=75.0%	75/120=63.0%	
>=305	2.1%	-11.2%	15.4%	67/100=67.0%	61/94=65.0%	
CD4BASE_L						
<50	19.1%	1.8%	36.5%	49/68=72.0%	27/51=53.0%	0.26606
50-100	-0.1%	-21.7%	21.5%	31/45=69.0%	20/29=69.0%	
100-200	-1.2%	-13.5%	11.1%	66/106=62.0%	85/134=63.0%	
>=200	7.7%	-0.9%	16.3%	160/224=71.0%	144/226=64.0%	

TABLE 4.2 B (continued)
PERCENT<50, WK 96, BY BASELINE COVARIATE, TRIAL 138

REGION						
AFRICA	-2.1%	-18.0%	13.8%	45/67=67.0%	45/65=69.0%	0.51459
ASIA	2.1%	-14.2%	18.5%	33/39=85.0%	33/40=83.0%	
EUROPE	18.6%	2.2%	35.0%	47/67=70.0%	33/64=52.0%	
N_AMERICA	10.3%	-6.3%	26.9%	42/68=62.0%	35/68=51.0%	
S_AMERICA	4.8%	-4.4%	14.0%	139/202=69.0%	130/203=64.0%	
COUNTRY						
ARGENTINA	-3.6%	-20.1%	13.0%	36/55=65.0%	49/71=69.0%	0.98751
BRAZIL	14.2%	-8.4%	36.7%	25/34=74.0%	19/32=59.0%	
CHILE	11.2%	-20.2%	42.7%	9/11=82.0%	12/17=71.0%	
DOM_REP	-7.8%	-38.8%	23.3%	14/22=64.0%	10/14=71.0%	
FRANCE	8.8%	-22.3%	39.9%	12/18=67.0%	11/19=58.0%	
MEXICO	13.5%	-7.8%	34.9%	23/35=66.0%	24/46=52.0%	
PANAMA	16.4%	-21.4%	54.1%	8/10=80.0%	7/11=64.0%	
PERU	7.2%	-13.0%	27.4%	33/51=65.0%	23/40=58.0%	
S_AFRICA	-2.1%	-18.0%	13.8%	45/67=67.0%	45/65=69.0%	
SPAIN	13.7%	-20.3%	47.7%	9/13=69.0%	10/18=56.0%	
THAILAND	2.4%	-15.2%	20.1%	18/19=95.0%	12/13=92.0%	
US	-3.3%	-36.1%	29.4%	11/22=50.0%	8/15=53.0%	
AIDS_						
NO	6.6%	0.2%	13.0%	296/424=70.0%	263/416=63.0%	0.57185
YES	-1.5%	-31.6%	28.5%	10/19=53.0%	13/24=54.0%	
HBSAG						
NEGATIVE	6.4%	-0.1%	12.8%	287/418=69.0%	261/419=62.0%	
POSITIVE	5.0%	-21.5%	31.5%	18/24=75.0%	14/20=70.0%	
HCAB						
NEGATIVE	5.9%	-0.6%	12.3%	281/402=70.0%	260/406=64.0%	
POSITIVE	14.5%	-8.2%	37.3%	24/40=60.0%	15/33=45.0%	
HEPBC						
NEGATIVE	5.6%	-1.0%	12.3%	264/381=69.0%	247/388=64.0%	
POSITIVE	12.3%	-5.7%	30.3%	41/61=67.0%	28/51=55.0%	

TABLE 4.2 B (continued)
PERCENT<50, WK 96, BY BASELINE COVARIATE, TRIAL 138

BMI_Q						
<21	11.4%	-1.7%	24.5%	75/112=67.0%	55/99=56.0%	0.20729
21-23	13.5%	-0.4%	27.3%	69/97=71.0%	49/85=58.0%	
23-26	7.5%	-3.7%	18.7%	88/124=71.0%	92/145=63.0%	
>=26	-4.8%	-16.9%	7.3%	74/110=67.0%	80/111=72.0%	
BPDIA_Q						
<68	0.8%	-11.8%	13.3%	76/121=63.0%	67/108=62.0%	0.27720
68-73	15.9%	4.2%	27.7%	91/119=76.0%	69/114=61.0%	
73-80	7.2%	-9.0%	23.5%	45/64=70.0%	41/65=63.0%	
>=80	2.9%	-7.9%	13.8%	94/139=68.0%	99/153=65.0%	
BPSYS_Q						
<106	9.5%	-3.0%	22.0%	81/123=66.0%	62/110=56.0%	0.89585
106-114	7.7%	-4.5%	19.9%	80/109=73.0%	71/108=66.0%	
114-123	6.0%	-6.3%	18.3%	77/110=70.0%	73/114=64.0%	
>=123	2.5%	-10.3%	15.3%	68/101=67.0%	70/108=65.0%	
HT_Q						
<160	12.1%	-1.7%	25.9%	57/84=68.0%	58/104=56.0%	0.066110
160-168	-1.3%	-13.8%	11.2%	75/122=61.0%	69/110=63.0%	
168-175	-2.3%	-14.3%	9.8%	75/110=68.0%	81/115=70.0%	
>=175	16.7%	5.1%	28.3%	99/127=78.0%	68/111=61.0%	
WAMS_Q						
<76	8.9%	-1.4%	19.2%	117/171=68.0%	97/163=60.0%	0.14859
76-83	16.9%	2.9%	31.0%	58/86=67.0%	49/97=51.0%	
83-91	1.8%	-11.1%	14.7%	68/95=72.0%	67/96=70.0%	
>=91	-5.8%	-19.0%	7.5%	63/91=69.0%	63/84=75.0%	
WT_Q						
<58	8.6%	-4.6%	21.7%	71/106=67.0%	59/101=58.0%	0.98517
58-66	5.5%	-7.6%	18.6%	64/103=62.0%	64/113=57.0%	
66-75	5.2%	-6.9%	17.2%	82/117=70.0%	74/114=65.0%	
>=75	5.5%	-5.9%	17.0%	89/117=76.0%	79/112=71.0%	

5. Statistical Reviewer's Conclusions

The applicant has demonstrated in atazanvir/ritonavir at 300/100 mg qd is effective in treatment naive patients out to 96 weeks of therapy when combined with a background regimen of tenofovir (TDF) at 300 mg qd plus emtricitibine (FTC) at 200 mg qd. It is comparable to LPV/r at 400/100 mg bid in these patients. The results at week 96 suggest superiority to LPV/r although they fall short of statistically significant superiority.

Thomas Hammerstrom, Ph.D.
Mathematical Statistician

Concur: Dr. Soon
cc:
Archival NDA #21-567 (SN 019)
HFD-530
HFD-530/Dr. Birnkrant
HFD-530/Dr. Murray
HFD-530/Dr. Struble
HFD-530/Dr. Kirk Chan-Tack
HFD-725/Dr. Ram Tiwari
HFD-725/Dr. Hammerstrom
HFD-700/Dr. Nevius
HFD-725/Dr. Huque
HFD-725/Dr. Lin

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21567	SUPPL-19	BRISTOL MYERS SQUIBB CO	REYATAZ (ATAZANAVIR SULFATE)

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

/s/

THOMAS S HAMMERSTROM
10/14/2009

GUOXING SOON
11/16/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021567/S-019

MICROBIOLOGY REVIEW(S)

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
VIROLOGY REVIEW
NDA: 21-567 SE8 **SN**: 019 **DATE REVIEWED:** 08/03/2009
Virology Reviewer: Lisa K. Naeger, Ph.D.

Sponsor's Name and Address:
Bristol-Myers Squibb
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

Reviewer's Name: Lisa K. Naeger, Ph.D.

Initial Submission Dates:
Correspondence Date: 1/05/2009
CDER Receipt Date: 1/05/2009 (electronic)
Reviewer Receipt Date: 1/13/2009
Review Complete Date: 8/03/2009
PDUFA Date: 11/05/2009

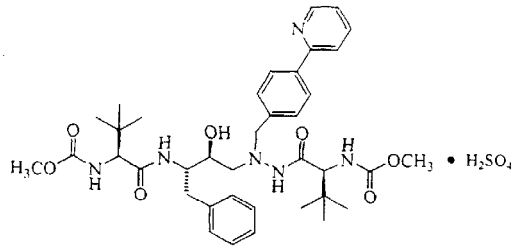
Related/Supporting Documents: IND 56,897 (BMS), NDA 21-567, NDA 21-567 B1 and B2, NDA 21-567 SE-002, (b) (4)

Product Name(s): Atazanavir (BMS-232632, ATV)
Proprietary: Reyataz™
Non-Proprietary/USAN: Atazanavir sulfate
Code Name/Number: BMS-232632

Chemical Name: Dimethyl (3S, 8S, 9S, 12S)-9-benzyl-3,12-di-tert-butyl-8-hydroxy-4,11-dioxo-6-[4-(2-pyridyl)benzyl]-2,5,6,10,13-pentaazaetradecanedioate sulfate (1:1)

Structural Formula:

Atazanavir (BMS-232632, ATV)



Molecular Formula: $C_{38}H_{52}N_6O_7 \cdot H_2SO_4$
Molecular Weight: 704.9

Dosage Form(s): 100/150/200 mg capsule
Route(s) of Administration: Oral
Pharmacological Category: Antiviral
Indication(s): Treatment of HIV infection in treatment-experienced individuals in combination with other antiretroviral agents

Dispensed: Rx X OTC_____

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
VIROLOGY REVIEW
NDA: 21-567 SE8 **SN**: 019 **DATE REVIEWED:** 08/03/2009
Virology Reviewer: Lisa K. Naeger, Ph.D.

Abbreviations: ARV, antiretroviral; ATV, atazanavir; ATV/r, atazanavir/ritonavir; BL, baseline; DC, discontinuation; EC, effective concentration; FC, fold change; FTC, emtricitabine; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; LPV/r, lopinavir/ritonavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PBMCs, peripheral blood mononuclear cells; PCR, polymerase chain reaction; PI, protease inhibitor; PR, protease; RNA, ribonucleic acid; RT, reverse transcriptase; RTI, reverse transcriptase inhibitor; TDF, tenofovir disoproxil fumarate; TLOVR, Time to Loss of Virologic Response; USPI, United States package insert; WT, wild-type

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DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
VIROLOGY REVIEW
NDA: 21-567 SE8 **SN**: 019 **DATE REVIEWED:** 08/03/2009
Virology Reviewer: Lisa K. Naeger, Ph.D.

EXECUTIVE SUMMARY

This submission is a supplemental NDA (sNDA) to NDA 21-567, NDA 21-567/SE-002 and NDA 21-567 SE5-017 for Atazanavir (Reyataz®), which received FDA approval on June 20, 2003, July 6, 2004 and October 21, 2008, respectively. This sNDA is being submitted to provide data to support using ATV/r in treatment-naïve HIV-1-infected patients for 96 weeks.

Study AI424138 was a 96-week study conducted to compare the proportion of subjects with HIV-1 RNA <50 copies/mL (copies/mL) at Week 96 between ATV/r QD + tenofovir (TDF) and emtricitabine (N=434) versus LPV/RTV 400/100 mg BID + TDF and emtricitabine (N=433) treatment regimens in treatment-naïve subjects. Genotypic and phenotypic resistance profiles were determined for subjects who met the criteria for virologic failure through Week 96 (HIV-1 RNA >400 copies/mL). For the FDA analysis, virologic failures included 83 subjects (40 ATV/r; 43 LPV/r) who had a virologic rebound without resuppression, were never suppressed through Week 96 and on study at Week 96, discontinued due to insufficient viral load response before Week 96 or discontinued before achieving suppression after Week 4. Of the 40 ATV/r and 43 LPV/r failures, 19 and 17 failed between Weeks 48 and 96, respectively. For the package insert, there were 39 virologic failures analyzed in both arms; 5 subjects were removed from the analysis because they had viral loads ≤400 copies/mL. Therefore, in an as-treated censored analysis, there were 9% of subjects who had virologic failure through 96 weeks in both the ATV/r and LPV/r arms. Baseline resistance was comparable between both arms.

Genotypes and phenotypes of the virologic failure subjects were analyzed for emergence of genotypic and phenotypic resistance. Five of the 39 isolates in the ATV/r arm were phenotypically ATV resistance (>2-fold change from reference) at failure. Two of these isolates were ATV resistant at baseline, while the other three had ATV resistance emerge on therapy.

Two ATV/r-Virologic Failure Isolates with Baseline ATV Resistance
The two baseline ATV-resistant isolates had IAS-defined major PI resistance-associated substitutions at baseline. The I50L substitution emerged on study in one of these subjects and was associated with a 17-fold decrease in ATV susceptibility from baseline. This subject isolate also had baseline RT resistance-associated substitutions M41L, D67G, M184V, T215Y and T219G which conferred baseline emtricitabine and TDF resistance. The other failure isolate with baseline ATV resistance had additional IAS-defined major PI substitutions (V32I, M46I and I84V) emerge on ATV treatment associated with a 3-fold decrease in ATV susceptibility from baseline. This isolate had baseline RT substitutions M41L, T215Y, K103K/R and M184V, which conferred baseline emtricitabine resistance, but not detectable TDF resistance.

Three ATV/r-Virologic Failure Isolates Had Reduced ATV Susceptibility Emerge on Therapy
One ATV/r-virologic failure subject isolate developed the major IAS PI resistance-associated substitutions V32I, M46I, and L90M on ATV/r treatment as well as L10L/F, I15I/V, K20K/R, E35D, K43K/T, A71I, G73S, and I85I/V. These substitutions conferred a

56-fold decrease in ATV susceptibility from reference and a 71-fold reduction from baseline. The RT resistance-associated substitution M184V emerged on treatment conferring emtricitabine resistance. The RT mixture substitutions K65K/R, K70K/E and L210L/W also emerged, but did not confer detectable TDF resistance. The other two subjects had no major IAS-defined major PI mutations at baseline and did not have any PI or RT mutations emerge on treatment. The ATV phenotype for these two isolates was 2.11- and 2.14-fold fold reduced susceptibility and probably reflects the variability of the assay rather than true reduced ATV susceptibility. (b) (4)

LPV/r-Virologic Failure Isolates

In the LPV/RTV arm, one virologic failure patient isolates had a 69-fold decrease in LPV susceptibility emerge on therapy with the development of PI resistance-associated substitutions L10V, V11I, I54V, G73S and V82A in addition to baseline PI substitutions L10I/L, V32I, I54I/V, A71I, G73S/G, V82A/V, L89V and L90M. Five of the LPV/r treatment failure isolates developed phenotypic emtricitabine resistance with the emergence of the M184V substitution, one had both emtricitabine and TDF resistance emerge on treatment and one additional virologic failure subject isolate had TDF resistance emerge on treatment.

Overall, the M184V substitution and phenotypic emtricitabine resistance emerged on treatment in 1 ATV/r and 6 LPV/r virologic failure subjects. Phenotypic resistance to TDF emerged in 2 LPV/r virologic failure isolates and was present at baseline in one ATV/r virologic failure isolate. One treatment failure isolate in the ATV/r arm had ATV resistance emerge on therapy. Only one subject isolate with baseline ATV resistance and 3 major PI substitutions at baseline had the emergence of the I50L substitution. Cross-resistance to other PIs emerged in some treatment failure subject isolates treated with ATV/r. However, some of the failure subject isolates were cross-resistant at baseline.

This supplemental NDA for ATV/r is approvable with respect to virology for the treatment of treatment-naïve HIV-1 infected patients. There are no virology specific Phase IV commitments that are being requested for this application.

1. Recommendations

1.1. *Recommendation and Conclusion on Approvability*

This supplemental NDA for ATV/r is approvable with respect to virology for the treatment of HIV-infected treatment-naïve patients.

1.2. *Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.*

There are no virology specific phase IV commitments recommended for this application.

2. Administrative

2.1 Reviewer's Signature(s)

Lisa K. Naeger
[Lisa K. Naeger, Ph.D.]
Sr. Microbiologist, HFD-530

2.2 Concurrence

HFD-530/Micro TL Signature _____ Date_____
Julian O'Rear, Ph.D.

3. OND MICROBIOLOGY REVIEW

3.1 Important Milestones in Product Development

After review of NDA-21567, Reyataz® (atazanavir sulfate) capsules received FDA approval on June 20, 2003 for the treatment of HIV-1 infection in combination with other antiretroviral agents. A supplemental NDA 21-567 was approved July 6, 2004 to support the use of the protease inhibitor, atazanavir (ATV), for the treatment of HIV infection in treatment-experienced adults, in combination with other antiretroviral agents, using an alternative "boosted" dosing regimen of Reyataz administered as 300 mg with 100 mg ritonavir (RTV) taken once daily (QD) with food. A pediatric supplement in support of using ATV/r in children ≥6 years was approved in March 2008. The recommended dosage of REYATAZ for pediatric patients (6 to less than 18 years of age) was based on body weight and should not exceed the recommended adult dosage. The data were 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. In October 2008, ATV/r was approved for use in treatment-naïve HIV-1 infected patients.

3.2 Methodology

Genotypic and Phenotypic Methods
Genotypic and phenotypic resistance profiles are tabulated for subjects who met the criteria for virologic failure through Week 96 as defined by the TLOVR algorithm for HIV-1 RNA >400 copies/mL. Virologic failure includes subjects who had a virologic rebound, were never suppressed through Week 96 and on study at Week 96, discontinued due to insufficient viral load response before Week 96 or discontinued before achieving suppression after Week 4. HIV-1 isolates are tested for phenotypic resistance to selected protease inhibitors (PIs), nucleoside reverse transcriptase inhibitors (NRTIs), and non-nucleoside reverse transcriptase inhibitors (NNRTIs) using the PhenoSense™ assay, and substitutions to the HIV-1 reverse transcriptase and protease genomes are determined using the GenoSure™ assay (Monogram Biosciences, Inc., CA). The protocol specifies that on-study resistance testing be conducted at the time of virologic failure as determined by the Investigator and BMS Medical Monitor, or confirmed HIV-1 RNA ≥400 copies/mL. Because of virologic limitations of the assays employed, testing may only be feasible if the subject has HIV-1 RNA >500 copies/mL.

PhenoSense™ Assay Cutoffs for ARVs

Name	Brand	Cutoff (Lower - Upper)
Abacavir	Ziagen	(4.5 - 6.5)
Didanosine	Videx	(1.3 - 2.2)
Emtricitabine	Emtriva	(3.5)
Lamivudine	Epivir	(3.5)
Stavudine	Zerit	(1.7)
Tenofovir	Viread	(1.4 - 4)
Zidovudine	Retrovir	(1.9)
Delavirdine	Rescriptor	(6.2)
Efavirenz	Sustiva	(3)

Nevirapine	Viramune	(4.5)
Atazanavir	Reyataz	(2.2)
	Reyataz/r	(5.2)
Darunavir	Prezista/r	(10 - 90)
Fosamprenavir	Lexiva	(2)
	Lexiva/r	4 - 11)
Indinavir	Crixivan	(2.1)
	Crixivan/r	(10)
Lopinavir	Kaletra	(9 - 55)
Nelfinavir	Viracept	(3.6)
Ritonavir	Norvir	(2.5)
Saquinavir	Invirase	(1.7)
	Invirase/r	(2.3 - 12)
Tipranavir	Aptivus/r	(2 - 8)

3.3 Prior FDA Microbiological Reviews

NDA-21567
Reviewer: Lisa K. Naeger, Ph.D.
Initial Submission Dates: December 20, 2002
Reviewer Receipt Date: January 6, 2003
Review Complete Date: June 18, 2003
Approval Date: June 20, 2003

NDA-21567 SE2: RTV boosted ATV supplement
Reviewer: Lisa K. Naeger, Ph.D.
Initial Submission Dates: October 30, 2003
Review Complete Date: May 4, 2004
Approval Date: July 6, 2004

(b) (4)

NDA-21567 SE5-015: pediatric supplement
Reviewer: Lisa K. Naeger, Ph.D.
Correspondence Date: September 27, 2007
Review Complete Date: February 13, 2008
PDUFA Date: March 26, 2008

NDA-21567 SE5-017: (ATV/r in treatment-naïve HIV-1 infected patients)
Reviewer: Lisa K. Naeger, Ph.D.
Correspondence Date: December 21, 2007
Review Complete Date: August 12, 2008
PDUFA Date: October 21, 2008

3.4 State of antimicrobials used for the indication (s) sought:

Since HAART regimens have been introduced, the number of AIDS cases has decreased dramatically; however, HAART does not eradicate HIV-1 from subjects and even though the number of serum HIV-1 RNA copies is reduced to undetectable levels, HIV-1 re-emerges quickly after discontinuation of HAART. Therefore, with the currently available regimens, it is likely that HIV-infected subjects will require antiretroviral therapy throughout their lives.

There are currently twenty-three FDA-approved anti-HIV-1 drugs including including NNRTIs (delavirdine, efavirenz, etravirine, nevirapine), NRTIs (abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine, zidovudine), PIs (atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir), the fusion inhibitor enfuvirtide, the CCR5 coreceptor antagonist maraviroc and the integrase inhibitor raltegravir. Maraviroc inhibits the interaction between the viral envelope glycoprotein gp120 and the human CCR5 receptor membrane protein and inhibits entry of the virus into the cell. Enfuvirtide is a gp41 fusion inhibitor preventing the joining of the viral and cellular membranes necessary for virus entry. NRTIs mimic nucleosides and target HIV-1 RT by competing with natural deoxynucleoside triphosphates for binding to RT and by incorporating into newly synthesized viral DNA resulting in chain-termination. NNRTIs inhibit HIV-1 RT by binding near the catalytic site of RT and acting as noncompetitive inhibitors. Raltegravir inhibits the viral encoded integrase which catalyzes the integration of linear viral DNA into host cell DNA forming the provirus. PIs work at the late stage of viral replication to prevent virus production from infected cells. They block the HIV-1 protease enzyme, which is necessary for the production of mature virions, resulting in defective particles which are unable to infect new cells.

Unfortunately, HIV-1 develops resistance to antiretroviral drugs over time usually from the accumulation of multiple mutations. HAART regimens are also associated with acute toxicities such as diarrhea, kidney stones, rash, CNS toxicities and hepatotoxicity. Long-term toxicities from antiretroviral therapies include mitochondrial toxicities associated with NRTIs (lactic acidosis, myopathy, neuropathy, pancreatitis), and disorders of lipid metabolism (dyslipidemia) and glucose metabolism (lipodystophy, hypercholesterolemia, hypertriglyceridemia) associated with PIs. These tolerability issues make compliance to therapy more challenging. Compliance is an important determinant of successful virologic suppression for subjects on HAART. Regimens that are well-tolerated and easy to administer with a few pills once daily are likely to aid in subject compliance and improve clinical outcomes. There is a need for new anti-HIV-1 drugs that are well-tolerated and easy to use with new modes of action and low likelihood of viral resistance development. Additionally, drugs that are effective against viruses resistant to all currently approved drugs are needed for the heavily treatment-experienced population.

3.5 Clinical Studies

CLINICAL STUDY AI424138

A 96-Week Study Comparing the Antiviral Efficacy and Safety of Atazanavir/ritonavir (ATV/r) with Lopinavir/ritonavir (LPV/r), Each in Combination with Fixed Dose Tenofovir (TDF)-Emtricitabine in HIV-1 Infected Treatment Naive Subjects

This study was conducted to compare the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 96 between the ATV/r QD + tenofovir (TDF) and emtricitabine versus LPV/r 400/100 mg BID + TDF and emtricitabine treatment regimens. Eight hundred and eighty-three randomized subjects were analyzed for efficacy and 878 treated subjects were analyzed for safety. Genotypic and phenotypic resistance profiles were determined for subjects who met the criteria for virologic failure through Week 96 (HIV-1 RNA >400 copies/mL).

3.6 Clinical Virology

STUDY AI424138 CLINICAL VIROLOGY

Baseline Genotypes

Overall, the baseline resistance was comparable between both arms of Study AI424138. In the ATV/r, 4 baseline isolates had >2-fold change to ATV/r susceptibility and 1 had >10-fold change in LPV/r susceptibility. In the LPV/r, 5 baseline isolates had >2-fold change to ATV/r susceptibility and none had >10-fold change in LPV/r susceptibility. There were 17 subjects (9 in ATV/r arm and 8 in LPV/r arm) with isolates that contained IAS-defined major PI resistance-associated substitutions at baseline (IAS-USA 2008 Major PI resistance mutations include amino acid substitutions D30N, V32I, L33F/V, M46L/I, I47V/A, G48V, I50V/L, V82X, I84V, N88S, L90M). Of those with major baseline PI substitutions, 4/9 (44%) in the ATV/r arm were virologic failures and 2/8 (25%) were virologic failures in the LPV/r arm.

Eight hundred and eighty-three randomized subjects were analyzed for efficacy with 868 evaluable subjects for resistance testing. Resistance data was available up to Week 96. Baseline genotypes were determined for 831 subjects (434 in ATV/r arm and 433 in LPV/r arm) and baseline phenotypes were determined for 141 subjects (70 in ATV/r arm and 71 in LPV/r arm) (Table 1).

Table 1. Summary of Resistance Data in Study AI424138 (As–treated)

	ATV/r	LPV/r
Number of Subjects in Resistance 96 Week Dataset	434	433
N (As-treated)	384	370
Baseline genotypes	434	433
Baseline phenotypes	70	71
Responders	344 (79%)	327 (75%)
Virologic Failures	39 (9%)	39 (9%)

Genotypic and phenotypic resistance profiles were determined for subjects who met the criteria for virologic failure through Week 96 (HIV-1 RNA >400 copies/mL). For the FDA analysis, virologic failures included 40 subjects in the ATV/r arm and 43 subjects in the LPV/ arm) who had a virologic rebound without resuppression, were not suppressed at Week 96, discontinued due to insufficient viral load response before Week 96 or discontinued before achieving suppression after Week 4. Five subjects (0003-00246, 0065-00596, 0111-00736, 0115-00009, 0115-00014) were removed from the analysis because they had viral loads ≤400 copies/mL; therefore, there were 39 virologic failures analyzed in both arms. In an as-treated censored analysis, there were 9% subjects with virologic failure through 96 weeks in both the ATV/r and LPV/r arms (Table 1). Of the ATV/r-virologic failures, 5 had no post-baseline genotype or phenotype.

Analysis of Treatment Failures

Table 2. Resistance Summary of Virologic Failures in Study AI424138

	ATV/r	LPV/r
Virologic Failures	39 (9%)	39 (9%)
Baseline genotypes	39	39
Baseline phenotypes	37	31
Baseline IAS-Defined Major PI Substitutions	4	2
ATV-Resistance at Baseline	2	3
ATV-Resistance Emergence at Failure	5	1
I50L Emergence at Failure	1	0
LPV Resistance at Baseline	1	0
LPV Resistance Emergence at Failure	0	0
Emtricitabine Resistance at Baseline	2	1
Phenotypic Emtricitabine Resistance Emergence at Failure	1	6
TDF Resistance at Baseline	1	0
TDF Resistance Emergence at Failure	0	2

ATV-R = ATV fold reduction in susceptibility ≥2; LPV-R = LPV fold reduction in susceptibility>10; TDF-R = TDF fold reduction in susceptibility >1.4; Emtricitabine fold reduction in susceptibility >3.5

Genotypes and phenotypes of the virologic failure subjects were analyzed for emergence of genotypic and phenotypic resistance (Table 2, 3 and 4). Five of the 39 isolates in the ATV/r arm were phenotypically ATV resistance (>2-fold change from reference) at failure (Table 2 and 3). Two of these isolates were ATV resistant at baseline (0099 00021 and 0099 00026) while the other three had ATV resistance emerge on therapy. The two baseline ATV-resistant isolates had IAS-defined major PI resistance-associated substitutions at baseline. The I50L substitution emerged on study in one of these subjects (Subject 0099 00021) and was associated with a 17-fold decrease in ATV susceptibility from baseline (baseline ATV fold change = 19). Subject 0099 00021 also had baseline RT resistance-associated substitutions M41L, D67G, M184V, T215Y and T219G which conferred baseline emtricitabine and TDF resistance. The other subject (0099 00026) had additional IAS-defined major PI substitutions (V32I, M46I and I84V) emerge on ATV treatment associated with a 3-fold decrease in ATV susceptibility from baseline. Subject 0099 00026 had baseline RT substitutions M41L,

T215Y, K103K/R and M184V, which conferred baseline emtricitabine resistance, but not detectable TDF resistance. Subject 0099 00049 developed the major IAS PI substitutions V32I, M46I, and L90M as well as L10L/F, I15I/V, K20K/R, E35D, K43K/T, G73S, and I85I/V. These substitutions conferred a 56-fold decrease in ATV susceptibility from reference and a 71-fold reduction from baseline. The RT substitution M184V also emerged on treatment conferring emtricitabine resistance. The RT mixture substitutions K65K/R, K70K/E and L210L/W also emerged, but surprisingly did not confer detectable TDF resistance.

Subjects 0019 00128 and 0064 00220 had no major IAS-defined major PI resistance-associated substitutions at baseline and did not have any PI or RT resistance-associated substitutions emerge on treatment. The ATV phenotype for these two isolates was 2.11- and 2.14-fold reduced susceptibility and probably reflects the variability of the assay rather than true reduced ATV susceptibility. (b) (4)

Table 3. ATV-Resistant Virologic Failures with Phenotypic Evidence

PID	Baseline Genotype	PI Substitutions Emerging	RT Substitutions	Baseline Phenotype (FC)	Phenotype at Failure (FC)
0019 00128*	T12S I15V L19I M36I R41K D60E L63D H69K I72T L89M I93L			1.86	2.11
0064 00220*	L10V T12K E35D M36M/I R41K L63V A71V V77I I93L			1.24	2.14
0099 00021	L10I,K14K/R,I15V, E35D,M36I,N37D, **G48M**, **F53L,I54V**, L63P,A71V,V77I, **V82A L90M**, I93L	L10I/V K14 R K20R **I50L** I62V T74S	M41L (BL) D67G (BL) K70K/T M184V (BL) T215Y (BL) K219G(BL)	19	ATV-R (318) FTC-R (BL) TDF-R (BL)
0099 00026	L10F,**M46M/I**,Q58E, I62I/M/V,L63P,I64I/V ,H69H/R, V77V/I, **I84I/V**,I85I/V,L89M, **L90M**,I93L	W6W/G K20K/R **V32I** E34E/G E35E/D M36I **M46I** I72I/M **I84V** I85V	M41L (BL) M184V (BL) T215Y (BL) K103K/R	10	ATV-R (30) FTC-R (BL)
0099 00049	T12A/S,I13I/V,M36I, N37D,I62V,L63P, A71A/T,I72V, I93L	L10L/F I15I/V K20K/R **V32I** E35D K43K/T **M46I** R57R/G A71I/T G73S I85I/V **L90M**	E44E/G A62V **K65K/R** S68S/N K70K/E I94I/L D177D/G **M184V** H208H/L **L210L/W** **K219K/R**		ATV–R (56) FTC-R

(b) (4)

FTC-R = phenotypic emtricitabine resistance; TDF-R = phenotypic tenofovir disoproxil fumarate resistance; ATV-R = phenotypic ATV resistance; BL = baseline; FC = fold change

In the LPV/RTV arm, one virologic failure patient isolates had a 69-fold decrease in LPV susceptibility emerge on therapy with the development of PI substitutions L10V, V11I, I54V, G73S, and V82A in addition to baseline PI substitutions V32I, I54I/V, V82A/V, L90M, L10I/L, A71I, G73S/G and L89V (Table 4). Five of the LPV/r treatment failure isolates developed emtricitabine resistance with the emergence of the M184V substitution, one had both emtricitabine and TDF resistance emerge on treatment and one additional virologic failure subject isolate had TDF resistance emerge on treatment.

Overall, the M184V substitution and emtricitabine resistance emerged on treatment in 1 ATV/r and 6 LPV/r virologic failure subjects. Phenotypic resistance to TDF emerged in 2 LPV/r virologic failure isolates and was present at baseline in one ATV/r virologic failure isolate (Table 2).

Table 4. LPV Virologic Failures with Phenotypic and/or Genotypic Evidence of Resistance

PID	TRT	Baseline PI Genotype	PI Substitutions Emerging	RT Substitutions Emerging	Phenotype (FC)
0018 00591				M184V	FTC-R
0018 00629	LPV/r	I15V E35D K43R H69K A71T V77I I93L		I5I/M M184V E248E/K	FTC-R
0013 00351	LPV/r	T12S,I15V,L19I/M,K20R E35D,M36I,N37D,R41K, R57R/K,L63L/A/P/V, H69K,T74S,V82V/I, L89M,I93L	L10L/P		ATV-R (BL) (3)
0020 00860	LPV/r	T12S,I15V,L19I,M36I/L, R41K,D60E,Q61E, I62I/V,L63P,H69K, V77V/I, L89M,I93L		L210L/W	
0029 00788		L10L/I I15V L19I K20R V32I E35D M36I I54I/V L63P A71I G73G/S V82A/V I85V L89V L90M I93L (6.1)	L10V V11I I54V G73S V82A	K70N M184V T215Y	69-fold FTC-R TDF-R
0050 00171	LPV/r	L10V A71V V77I I93L	G86G/D	M184V P225P/S	FTC-R
0050 00664	LPV/r	V82I		M184V	FTC-R
0062 00240	LPV/r		I13V,E35E/D,M36I,I62V, L63H/Q,I64V,H69Y	A98S Q102K	TDF-R
0095 00665	LPV/r	I15V,R41R/K, I64V,H69H/Q,I72I/M		M184M/V (BL) M184V	FTC-R (BL)
0099 00050	LPV/r	E35F M36I A71V V77I P79P/S			ATV (BL) (2.3)
0111 00638				M184V	FTC-R

FTC-R = phenotypic emtricitabine resistance; TDF-R = phenotypic tenofovir disoproxil fumarate resistance; ATV-R = phenotypic ATV resistance; BL = baseline; FC = fold change

Cross-Resistance

Cross-resistance to other PIs emerged in some treatment failure subject isolates treated with ATV/r. In addition, some of the failure subject isolates were cross-resistant at baseline. Three of the ATV/r-resistant virologic failure subject isolates were cross resistant to other PIs, two of which were cross-resistant at baseline (Table 5). Two ATV/r failure isolates were cross-resistant to LPV; one at baseline.

Table 5. Cross-Resistance to PIs of Virologic Failure Isolates

PID	TRT Failure	Baseline Cross-Resistance	Cross Resistance at Failure
0099 00021	ATV/r	IDV, LPV, NFV, RTV, SQV	
0099 00026	ATV/r	APV, IDV, NFV, RTV, SQV	DRV
0099 00049	ATV/r		APV, IDV, NFV, RTV, SQV

3.7 CONCLUSION

This supplemental NDA for ATV/r is approvable with respect to microbiology for the treatment of treatment-naïve HIV-1 infected patients. Results from Study AI424138 show a comparable number of treatment failures in treatment-naïve patients treated with ATV/r and LPV/r. One treatment failure isolate in the ATV/r arm had ATV resistance emerge on therapy. Only one subject isolate with baseline ATV resistance and 3 major PI substitutions at baseline had the emergence of the I50L substitution. The M184V substitution and emtricitabline resistance emerged on treatment in 1 ATV/r and 6 LPV/r virologic failure subjects. Phenotypic resistance to TDF emerged in 2 LPV/r virologic failure isolates and was present at baseline in one ATV/r virologic failure isolate.

There are no virology specific Phase IV commitments that are being requested for this application.

The following indication is acceptable:

(b) (4)

For treatment-naive and treatment-experienced patients, the recommended dosage is REYATAZ 300 mg with ritonavir 100 mg once daily (all as a single dose with food).

4 *SPONSOR* PROPOSED USPI

(b) (4)

5. FDA PROPOSED USPI

(b) (4)

6. APPENDICES

APPENDIX A. STUDY 138 ATV/R VIROLOGIC FAILURE LISTING FOR AS-TREATED ANALYSIS (N=39) (≥400 copies/mL)

Bolded (failure after Week 48)

Subject ID	Outcome at Week 96
*0003 00246	DISCONTINUED BEFORE ACHIEVING CONFIRMED SUPPRESSION
0013 00350	DISCONTINUED BEFORE ACHIEVING CONFIRMED SUPPRESSION
0015 00091	**VIROLOGIC FAILURE**
0015 00586	VIROLOGIC FAILURE
0016 00358	VIROLOGIC FAILURE
0016 00359	**VIROLOGIC FAILURE**
0017 00110	DISCONTINUED BEFORE ACHIEVING CONFIRMED SUPPRESSION
0017 00565	**VIROLOGIC FAILURE**
0018 00765	DISCONTINUED BEFORE ACHIEVING CONFIRMED SUPPRESSION
0019 00128	**VIROLOGIC FAILURE**
0019 00142	VIROLOGIC FAILURE
0019 00651	**VIROLOGIC FAILURE**
0020 00194	VIROLOGIC FAILURE
0023 00742	**VIROLOGIC FAILURE**
0032 00234	VIROLOGIC FAILURE
0033 00152	**VIROLOGIC FAILURE**
0034 00259	VIROLOGIC FAILURE
0037 00361	VIROLOGIC FAILURE
0038 00887	DISCONTINUED BEFORE ACHIEVING CONFIRMED SUPPRESSION
0051 00819	VIROLOGIC FAILURE
0063 00305	**DISCONTINUED BEFORE ACHIEVING CONFIRMED SUPPRESSION**
0063 00308	VIROLOGIC FAILURE
0063 00414	**VIROLOGIC FAILURE**
0064 00220	**VIROLOGIC FAILURE**
0064 00615	VIROLOGIC FAILURE
0092 00096	DISCONTINUED BEFORE ACHIEVING CONFIRMED SUPPRESSION
0092 00453	**VIROLOGIC FAILURE**
0093 00340	**VIROLOGIC FAILURE**
0093 00426	**VIROLOGIC FAILURE**
0093 00875	DISCONTINUED BEFORE ACHIEVING CONFIRMED SUPPRESSION
0095 00701	**VIROLOGIC FAILURE**
0099 00021	VIROLOGIC FAILURE
0099 00026	**VIROLOGIC FAILURE**
0099 00049	**VIROLOGIC FAILURE**
0101 01053	**VIROLOGIC FAILURE**
0103 00746	DISCONTINUED BEFORE ACHIEVING CONFIRMED SUPPRESSION
0112 00930	**VIROLOGIC FAILURE**
0119 00469	DISCONTINUED BEFORE ACHIEVING CONFIRMED SUPPRESSION
0121 00051	VIROLOGIC FAILURE
0145 00395	**VIROLOGIC FAILURE**

*removed with viral load <400

APPPENDIX B. STUDY 138 LPV/R VIROLOGIC FAILURE LISTING FOR AS-TREATED ANALYSIS (N=39) (≥400 copies/ml)

Bolded (failure after Week 48)

Subject ID	Outcome at Week 96
0007 00023	**VIROLOGIC FAILURE**
0013 00351	VIROLOGIC FAILURE
0014 00266	**VIROLOGIC FAILURE**
0017 00535	VIROLOGIC FAILURE
0017 00687	DISCONTINUED BEFORE ACHIEVING CONFIRMED SUPPRESSION
0018 00591	**VIROLOGIC FAILURE**
0018 00629	**DISCONTINUED BEFORE ACHIEVING CONFIRMED SUPPRESSION**
0018 00798	DISCONTINUED BEFORE ACHIEVING CONFIRMED SUPPRESSION
0019 00548	DISCONTINUED BEFORE ACHIEVING CONFIRMED SUPPRESSION
0020 00860	VIROLOGIC FAILURE
0026 01057	VIROLOGIC FAILURE
0029 00788	**VIROLOGIC FAILURE**
0032 00879	DISCONTINUED BEFORE ACHIEVING CONFIRMED SUPPRESSION
0037 00208	**VIROLOGIC FAILURE**
0050 00171	VIROLOGIC FAILURE
0050 00664	VIROLOGIC FAILURE
0050 00668	**VIROLOGIC FAILURE**
0050 00994	DISCONTINUED BEFORE ACHIEVING CONFIRMED SUPPRESSION
0050 01016	VIROLOGIC FAILURE
0050 01022	DISCONTINUED BEFORE ACHIEVING CONFIRMED SUPPRESSION
0055 00039	**VIROLOGIC FAILURE**
0061 00404	**VIROLOGIC FAILURE**
0062 00240	VIROLOGIC FAILURE
0063 00306	**VIROLOGIC FAILURE**
*0065 00596	DISCONTINUED BEFORE ACHIEVING CONFIRMED SUPPRESSION
0071 00517	VIROLOGIC FAILURE
0072 00955	VIROLOGIC FAILURE
0093 00368	**VIROLOGIC FAILURE**
0095 00665	VIROLOGIC FAILURE
0097 00477	DISCONTINUED BEFORE ACHIEVING CONFIRMED SUPPRESSION
0099 00050	**VIROLOGIC FAILURE**
0099 00393	**VIROLOGIC FAILURE**
0101 00387	**VIROLOGIC FAILURE**
0104 00190	DISCONTINUED BEFORE ACHIEVING CONFIRMED SUPPRESSION
0110 00794	VIROLOGIC FAILURE
0111 00638	**VIROLOGIC FAILURE**
*0111 00736	DISCONTINUED BEFORE ACHIEVING CONFIRMED SUPPRESSION
0112 00201	VIROLOGIC FAILURE
*0115 00009	DISCONTINUED BEFORE ACHIEVING CONFIRMED SUPPRESSION
*0115 00014	DISCONTINUED BEFORE ACHIEVING CONFIRMED SUPPRESSION
0118 01015	**VIROLOGIC FAILURE**
0153 00730	**VIROLOGIC FAILURE**
0158 01051	DISCONTINUED BEFORE ACHIEVING CONFIRMED SUPPRESSION

*removed with viral load <400

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21567	GI-1	BRISTOL MYERS SQUIBB CO	REYATAZ (ATAZANAVIR SULFATE)
NDA-21567	SUPPL-19	BRISTOL MYERS SQUIBB CO	REYATAZ (ATAZANAVIR SULFATE)

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/s/

LISA K NAEGER
11/04/2009

JULIAN J O'REAR
11/04/2009

MICROBIOLOGY FILING CHECKLIST FOR NDA or Supplement

NDA Number: 21,567 **Applicant: BMS** **Stamp Date: Jan. 5, 2009**

Drug Name: Atazanavir **NDA Type: sNDA**

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comments
1	Is the virology information (nonclinical and clinical) provided and described in different sections of the NDA organized in a manner to allow substantive review to begin?	X		
2	Is the virology information (nonclinical and clinical) indexed, paginated and/or linked in a manner to allow substantive review to begin?	X		
3	Is the virology information (nonclinical and clinical) legible so that substantive review can begin?	X		
4	On its face, has the applicant submitted cell culture data in necessary quantity, using necessary clinical and non-clinical strains/isolates, and using necessary numbers of approved current divisional standard of approvability of the submitted draft labeling?			n/a
5	Has the applicant submitted any required animal model studies necessary for approvability of the product based on the submitted draft labeling?			n/a
6	Has the applicant submitted all special/critical studies/data requested by the Division during pre-submission discussions?			n/a
7	Has the applicant submitted the clinical virology datasets in the appropriate format as described in the relevant guidance documents and are the datasets complete?	X		
8	Has the applicant used standardized or nonstandardized methods for virologic outcome measures? If nonstandardized methods were used, has the applicant included complete details of the method, the name of the laboratory where actual testing was done and performance characteristics of the assay in the laboratory where the actual testing was done?	X		Standardized methods were used
9	Has the applicant submitted draft labeling consistent with current regulation, divisional and Center policy, and the design of the development package?	X		
10	Has the applicant submitted annotated microbiology draft labeling consistent with current divisional policy, and the design of the development package?	X		
11	Have all the study reports, published articles, and other references been included and cross-referenced in the	X		

MICROBIOLOGY FILING CHECKLIST FOR NDA or Supplement

	Content Parameter	Yes	No	Comments
	annotated draft labeling or summary section of the submission?			
12	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X	

IS THE MICROBIOLOGY SECTION OF THE APPLICATION FILEABLE? ___Yes___

If the NDA is not fileable from the microbiology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Microbiologist Date

Microbiology Team Leader Date

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

/s/

Lisa Naeger
2/20/2009 12:10:44 PM
MICROBIOLOGIST

Julian O Rear
2/20/2009 12:20:02 PM
MICROBIOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021567/S-019

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER LABELING REVIEW
(PHYSICIAN LABELING RULE)

Division of Antiviral Products

Application Numbers: NDA 21-567/S-019

Name of Drug: Reyataz® (atazanavir sulfate) 100 mg, 150 mg, 200 mg and 300 mg capsules

Applicant: Bristol-Myers Squibb Company

Submission Date: January 5, 2009

Receipt Date: January 5, 2009

Material Reviewed:

Type of Labeling Reviewed: WORD

Last approved labeling: 21-567 S-017 (September 30, 2008)

Proposed labeling: (S-017)

Background and Summary

Bristol-Myers Squibb Company submitted a Prior Approval Efficacy Supplement to revise the package insert (PI) to provide for 96 week clinical safety and efficacy data on the use of atazanavir and ritonavir in treatment-naïve adult patients. The Division of Antiviral Products (DAVP) reviewed the label and made the labeling edits to BMS. On October 27, 2009, a teleconference was held between the Division and BMS to discuss the differences in calculations for Table 21. BMS agreed to make the changes suggested by the Division and submitted the final official submission of label on November 2, 2009.

Recommendations

The major changes to the label for supplement 019 include revisions to three tables in **Clinical Trial Experience in Adults** under **ADVERSE REACTIONS** and **resistance** under **Microbiology** section and Table 21 under **CLICAL STUDIES.**

The label was reviewed and the following changes were made:

1. The indications and usage statement was revised to include the information from the 96 weeks duration in antiretroviral-naïve patients and 48 weeks duration in treatment-experienced adult and pediatric patients of at least 6 years of age.

This indication is based on analyses of plasma HIV-1 RNA levels and CD4+ cell counts from controlled studies of 96 weeks duration in antiretroviral-naive and 48 weeks duration in antiretroviral-treatment-experienced adult and pediatric patients at least 6 years of age.

2. Three tables in section 6.1 **Clinical Trial Experience in Adults** were updated with the 96 week data.

Table 4: Selected Treatment-Emergent Adverse Reactions[a] of Moderate or Severe Intensity Reported in ≥2% of Adult Treatment-Naive Patients,[b] Study AI424-138

	96 weeks[c] REYATAZ 300 mg with ritonavir 100 mg (once daily) and tenofovir with emtricitabine[d] (n=441)	96 weeks[c] lopinavir 400 mg with ritonavir 100 mg (twice daily) and tenofovir with emtricitabine[d] (n=437)
Digestive System		
Nausea	4%	8%
Jaundice/scleral icterus	5%	*
Diarrhea	2%	12%
Skin and Appendages		
Rash	3%	2%

* None reported in this treatment arm.

[a] Includes events of possible, probable, certain, or unknown relationship to treatment regimen.

[b] Based on the regimen containing REYATAZ.

[c] Median time on therapy.

[d] As a fixed-dose combination: 300 mg tenofovir, 200 mg emtricitabine once daily.

Table 7: Grade 3–4 Laboratory Abnormalities Reported in ≥2% of Adult Treatment-Naive Patients,[a] Study AI424-138

Variable	Limit[c]	96 weeks[b] REYATAZ 300 mg with ritonavir 100 mg (once daily) and tenofovir with emtricitabine[d] (n=441)	96 weeks[b] lopinavir 400 mg with ritonavir 100 mg (twice daily) and tenofovir with emtricitabine[d] (n=437)
Chemistry	High		
SGOT/AST	≥5.1 x ULN	3%	1%
SGPT/ALT	≥5.1 x ULN	3%	2%
Total Bilirubin	≥2.6 x ULN	44%	<1%
Lipase	≥2.1 x ULN	2%	2%
Creatine Kinase	≥5.1 x ULN	8%	7%
Total Cholesterol	≥240 mg/dL	11%	25%
Hematology	Low		
Neutrophils	<750 cells/mm^3	5%	2%

a Based on the regimen containing REYATAZ.

b Median time on therapy.

c ULN = upper limit of normal.

d As a fixed-dose combination: 300 mg tenofovir, 200 mg emtricitabine once daily.

Table 10: Lipid Values, Mean Change from Baseline, Study AI424-138

	REYATAZ/ritonavir[a,b]					lopinavir/ritonavir[b,c]				
	Baseline	Week 48		Week 96		Baseline	Week 48		Week 96	
	mg/dL (n=428[e])	mg/dL (n=372[e])	Change[d] (n=372[e])	mg/dL (n=342[e])	Change[d] (n=342[e])	mg/dL (n=424[e])	mg/dL (n=335[e])	Change[d] (n=335[e])	mg/dL (n=291[e])	Change[d] (n=291[e])
LDL-Cholesterol[f]	92	105	+14%	105	+14%	93	111	+19%	110	+17%
HDL-Cholesterol[f]	37	46	+29%	44	+21%	36	48	+37%	46	+29%
Total Cholesterol[f]	149	169	+13%	169	+13%	150	187	+25%	186	+25%
Triglycerides[f]	126	145	+15%	140	+13%	129	194	+52%	184	+50%

a REYATAZ 300 mg with ritonavir 100 mg once daily with the fixed-dose combination: 300 mg tenofovir, 200 mg emtricitabine once daily

b Values obtained after initiation of serum lipid-reducing agents were not included in these analyses At baseline, serum lipid-reducing agents were used in 1% in the lopinavir/ritonavir treatment arm and 1% in the REYATAZ/ritonavir arm. Through Week 48, serum lipid-reducing agents were used in 8% in the lopinavir/ritonavir treatment arm and 2% in the REYATAZ/ritonavir arm Through Week 96, serum lipid-reducing agents were used in 10% in the lopinavir/ritonavir treatment arm and 3% in the REYATAZ/ritonavir arm

c Lopinavir 400 mg with ritonavir 100 mg twice daily with the fixed-dose combination 300 mg tenofovir, 200 mg emtricitabine once daily

d The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 48 or Week 96 values and is not a simple difference of the baseline and Week 48 or Week 96 mean values, respectively

e Number of patients with LDL-cholesterol measured

f Fasting

3. BMS updated the resistance section under Microbiology with the resistance information from the 96 week data.

Old text from September 30, 2008 version:

Clinical Studies of Treatment-Naive Patients Receiving REYATAZ 400 mg Without Ritonavir: ATV-resistant clinical isolates from treatment-naive patients who experienced virologic failure on REYATAZ 400 mg treatment without ritonavir often developed an I50L substitution (after an average of 50 weeks of ATV therapy), often in combination with an A71V substitution, but also developed one or more other PI substitutions (eg, V32I, L33F, G73S, V82A, I85V, or N88S) with or without the I50L substitution. In treatment-naive patients, viral isolates that developed the I50L substitution, without other major PI substitutions, showed phenotypic resistance to ATV but retained in cell culture susceptibility to other PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir); however, there are no clinical data available to demonstrate the effect of the I50L substitution on the efficacy of subsequently administered PIs.

Revised text from the current version:

Clinical Studies of Treatment-Naive Patients Receiving REYATAZ 300 mg With Ritonavir 100 mg: In Phase III study AI424-138, an as-treated genotypic and phenotypic analysis was conducted on samples from patients who experienced virologic failure (HIV-1 RNA ≥400 copies/mL) or discontinued before achieving suppression on ATV/RTV (n=39; 9%) and LPV/RTV (b) (4) 9%) through 96 weeks of treatment. In the ATV/RTV arm, one of the virologic failure isolates had a 56-fold decrease in ATV susceptibility emerge on therapy with the development of PI resistance-associated substitutions L10F, V32I, K43T, M46I, A71I, G73S, I85I/V, and L90M. The NRTI resistance-associated substitution M184V also emerged on treatment in this isolate conferring emtricitabine resistance. Two ATV/RTV-virologic failure isolates had baseline phenotypic ATV resistance and IAS-defined major PI resistance-associated substitutions at baseline. The I50L substitution emerged on study in one of these failure isolates and was associated with a 17-fold decrease in ATV susceptibility from baseline and the other failure isolate with baseline ATV resistance and PI substitutions (M46M/I and I84I/V) had additional IAS-defined major PI substitutions (V32I, M46I, and I84V) emerge on ATV treatment associated with a 3-fold decrease in ATV susceptibility from baseline. Five of the treatment failure isolates in the ATV/RTV arm developed phenotypic emtricitabine resistance with the emergence of either the M184I (n=1) or the M184V (n=4) substitution on therapy and none developed phenotypic tenofovir disoproxil resistance. In the LPV/RTV arm, one of the virologic failure patient isolates had a 69-fold decrease in LPV susceptibility emerge on therapy with the development of PI substitutions L10V, V11I, I54V, G73S, and V82A in addition to baseline PI substitutions L10L/I, V32I, I54I/V, A71I, G73G/S, V82V/A, L89V, and L90M. Six LPV/RTV virologic failure isolates developed the M184V substitution and phenotypic emtricitabine resistance and two developed phenotypic tenofovir disoproxil resistance.

4. Table 21 and text below table 21 were revised to update with 96 week data under

CLINICAL STUDIES. Footnote d was also added in the table.

Table 21: Outcomes of Treatment Through Week 96 (Study AI424-138)

Outcome	REYATAZ 300 mg + ritonavir 100 mg (once daily) with tenofovir/emtricitabine (once daily)[a] (n=441) 96 Weeks	lopinavir 400 mg + ritonavir 100 mg (twice daily) with tenofovir/emtricitabine (once daily)[a] (n=437) 96 Weeks
Responder[b,c,d]	(b) (4)75%	68%
Virologic failure[e]	(b) (4)17%	(b) (4)19%
Rebound	(b) (4)8%	10%
Never suppressed through Week 96	(b) (4)9%	(b) (4)9%
Death	1%	(b) (4)1%
Discontinued due to adverse event	3%	5%
Discontinued for other reasons[f]	(b) (4)4%	(b) (4)7%

[a] As a fixed-dose combination: 300 mg tenofovir, 200 mg emtricitabine once daily.

[b] Patients achieved HIV RNA <50 copies/mL at Week 96. Roche Amplicor®, v1.5 ultra-sensitive assay.

[c] Pre-specified ITT analysis at Week 48 using as-randomized cohort: ATV/RTV 78% and LPV/RTV 76% [difference estimate: 1.7 %(95% confidence interval: ¯3.8%, 7.1%)].

[d] Pre-specified ITT analysis at Week 96 using as-randomized cohort: ATV/RTV 74% and LPV/RTV 68% [difference estimate: 6.1%(95% confidence interval: 0.3%, 12.0%)].

[e] Includes viral rebound and failure to achieve confirmed HIV RNA <50 copies/mL through Week 96.

[f] Includes lost to follow-up, patient's withdrawal, noncompliance, protocol violation, and other reasons.

Through 96 weeks of therapy the proportion of responders among patients with high viral loads (ie, baseline HIV RNA ≥100,000 copies/mL) was comparable for the REYATAZ/ritonavir ((b) (4)165 of 223 patients (b) (4)74%) and lopinavir/ritonavir ((b) (4)148 of 222 patients (b) (4)67%) arms. At 96 weeks the median increase from baseline in CD4+ cell count was 261 cells/mm^3 for the REYATAZ/ritonavir arm and 273 cells/mm^3 for the lopinavir/ritonavir arm.

Sherly Abraham, R. Ph.
Regulatory Project Manager

Supervisory Comment/Concurrence:

Karen Winestock
Chief, Project Management Staff
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Drafted: SA/November 3, 2009
Revised: Karen Winestock
Initialed: Karen Winestock
Finalized: KW/November 4, 2009

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21567	SUPPL-19	BRISTOL MYERS SQUIBB CO	REYATAZ (ATAZANAVIR SULFATE)

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/s/

SHERLY ABRAHAM
11/05/2009

KAREN D WINESTOCK
11/05/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021567/S-019

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21-567 SUPPL # 019 HFD # 530

Trade Name Reyataz

Generic Name Atazanavir Sulfate

Applicant Name Bristol Myers Squibb Co

Approval Date, If Known November 5, 2009

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-567 original-1

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study AI 424138
96 Week Study
Title: A 96 Week Study Comparing the Antiviral Efficacy and Safety of Atazanavir/ritonavir with Lopinavir/ritonavir, Each in Combination with Fixed Dose Tenofovir-Emtricitabine in HIV-1 Infected Treatment Naïve Subjects

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☒ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

AI424138

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

NDA 21-567 N-000
NDA 21-567/S-017

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in

interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Sherly Abraham
Title: Regulatory Project Manager
Date: November 4, 2009

Name of Office/Division Director signing form: Jeffrey Murray, M.D.
Title: Deputy Division Director

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21567	SUPPL-19	BRISTOL MYERS SQUIBB CO	REYATAZ (ATAZANAVIR SULFATE)

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/s/

SHERLY ABRAHAM
11/05/2009

JEFFREY S MURRAY
11/05/2009

From: Abraham, Sherly
Sent: Monday, November 02, 2009 11:20 AM
To: 'Percival, Lisa'
Subject: RE: Reyataz

Hi Lisa,

Please find the following clarification on behalf of the review team:

For death, we recommend using the following cut-off:
Any subject who died while on-treatment or within 30 days of discontinuing study drug was considered an "on-treatment" death.

I hope this helps. Please let me know if you have additional questions.

Thanks,
Sherly

Sherly Abraham, RPh
Regulatory Project Manager
10903 New Hampshire Ave.,Bldg 22,Room(6369)
Silver Spring, MD 20903
(301) 796-3198
Sherly.Abraham@fda.hhs.gov

From: Percival, Lisa [mailto:Lisa.Percival@bms.com]
Sent: Friday, October 30, 2009 2:50 PM
To: Abraham, Sherly
Subject: RE: Reyataz

Hi Sherly,
Thank you. I've received your email and attachment. I sincerely apologize for all the questions, but one thing is still unclear and we want to be sure to have the right numbers when we respond. The fax instructs us to use "NNCPRNL to determine the final status if NNCPRNL is DEATH OR ADVERSE EVENT." Can you please clarify if the reviewer wants us to use NNCPRNL if a patient actually died or only if the NNCPRNL reason is actually listed as "DEATH"? We have one patient, 42-613, who discontinued the study with NNCPRNL=WITHDREW CONSENT, then the patient subsequently died. If FDA wants this patient counted as an outcome of "Death" in table 21, then we will program to use "Death" for all patients who died rather than the NNCPRNL. Please confirm if FDA intended for all patients' outcomes to be counted as "Death" if the patient died or if we should use NNCPRNL to determine outcome for patients who died - even if that outcome is something other than "Death".

Once I hear back, I will be able to provide you an estimate on timing for sending the revised proposed label.
Thank you and kind regards,

Lisa

From: Abraham, Sherly [mailto:Sherly.Abraham@fda.hhs.gov]
Sent: Friday, October 30, 2009 2:09 PM
To: Percival, Lisa
Subject: RE: Reyataz

Hi Lisa,

Please find the attached fax with our comments. Please let me know when you will be submitting the label to the sNDA. Please send me an acknowledgment email confirming the receipt of the information.

Thanks,
Sherly

Sherly Abraham, RPh
Regulatory Project Manager
10903 New Hampshire Ave.,Bldg 22,Room(6369)
Silver Spring, MD 20903
(301) 796-3198
Sherly.Abraham@fda.hhs.gov

From: Percival, Lisa [mailto:Lisa.Percival@bms.com]
Sent: Monday, October 26, 2009 2:19 PM
To: Winestock, Karen; Abraham, Sherly
Subject: Reyataz

Hi Karen,
I received a message that you called and will be sending a fax today. However, I am not sure you have the updated fax number that I sent to Sherly, which is 203-677-7435. I apologize for any inconvenience, but if you've already sent the fax, would you mind please to re-send as I no longer have access to the other fax number.
I am also always available via email.
Thanks and regards,
Lisa

This message (including any attachments) may contain confidential, proprietary, privileged and/or private information. The information is intended to be for the use of the individual or entity designated above. If you are not the intended recipient of this message, please notify the sender immediately, and delete the

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21567	SUPPL-19	BRISTOL MYERS SQUIBB CO	REYATAZ (ATAZANAVIR SULFATE)

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/s/

SHERLY ABRAHAM
11/04/2009

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: October 30, 2009

To: Lisa Percival **Associate Director**	**From: Sherly Abraham, R.Ph**
Company: Bristol-Myers Squibb	Division of Antiviral Products
Fax number: 203-677-3818	**Fax number:** (301) 796-9883
Phone number: 203-677-6803	**Phone number:** (301) 796-3198

Subject: Outcome data

Total no. of pages including cover: 3

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

RECORD OF ELECTTRONIC MAIL CORRESPONDENCE

Date: **October 30, 2009**

To: **Lisa Percival, Associate Director**

From: **Sherly Abraham, R.Ph., Regulatory Project Manager**

Through: **Thomas Hammerstrom, Ph.D., Statistics Reviewer**
Greg Soon, Ph.D., Statistical Team Leader
Mary Singer, M.D., Acting Medical Team Leader
Kirk Chan-Tack, M.D., Medical Officer

NDA: **NDA 21-567/S-019 Reyataz**

Subject: **Outcome Table**

Please refer to your October 28, 2009, electronic mail correspondence that informed the Division that BMS cannot confirm the FDA successes using the 'snapshot rule' from the October 27, 2009, teleconference, and need to resolve the discrepancies with FDA before you submit the revised proposed USPI. The following comments are conveyed to you on behalf of the review team:

We agree with all of your comments. On reflection, all patients except patient 93-372 should be considered successes. For missing week 96 data, we prefer interpolation rather than treating any missing as failure, even when it is bracketed by successes. Please use NNCPRNL to determine final status if NNCPRNL is DEATH OR ADVERSE EVENT. Otherwise use OUTCOME_.

We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

Sherly Abraham, R.Ph.
Regulatory Project Manager
Division of Antiviral Products

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21567	SUPPL-19	BRISTOL MYERS SQUIBB CO	REYATAZ (ATAZANAVIR SULFATE)

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/s/

SHERLY ABRAHAM
10/30/2009

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: October 27, 2009

To: Lisa Percival **Associate Director**	**From: Karen Winestock, CPMS**
Company: Bristol-Myers Squibb	Division of Antiviral Products
Fax number: 203-677-3818	**Fax number:** (301) 796-9883
Phone number: 203-677-6803	**Phone number:** (301) 796-3198

Subject: Outcome data

Total no. of pages including cover: 18

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

RECORD OF ELECTTRONIC MAIL CORRESPONDENCE

Date: **October 27, 2009**

To: **Lisa Percival, Associate Director**

From: **Karen Winestock, Chief, Regulatory Project Management Staff**

Through: **Thomas Hammerstrom, Ph.D., Statistics Reviewer**
Greg Soon, Ph.D., Statistical Team Leader
Mary Singer, M.D., Acting Medical Team Leader
Kirk Chan-Tack, M.D., Medical Officer

NDA: **NDA 21-567/S-019 Reyataz**

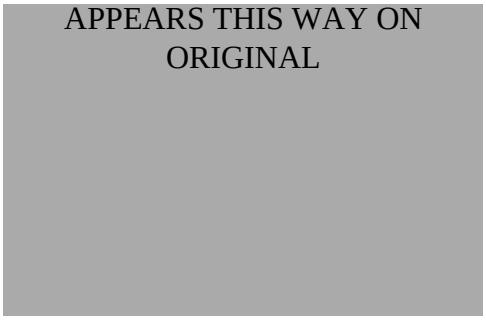
Subject: **Outcome Table**

As discussed during the October 27, 2009 telephone conference, FDA is providing the 'Outcome" Table.

We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

Karen Winestock,
Chief, Regulatory Project Management Staff
Division of Antiviral Products

15 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page



DAVP ✍ 10903 New Hampshire Ave. ✍ Silver Spring, MD 20993-0002 ✍ (301) 796-08348 ✍ Fax: (301) 796-9883

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21567	SUPPL-19	BRISTOL MYERS SQUIBB CO	REYATAZ (ATAZANAVIR SULFATE)

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/s/

KAREN D WINESTOCK
10/27/2009

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: October 26, 2009

To: Lisa Percival **Associate Director**	**From:** Sherly Abraham, R. Ph. Regulatory Project Manager
Company: Bristol-Myers Squibb	Division of Antiviral Products
Fax number: 203-677-3818	**Fax number:** (301) 796-9883
Phone number: 203-677-6803	**Phone number:** (301) 796-3198

Subject: Table 21 Labeling Edits

Total no. of pages including cover: 3

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF FACSIMILE CORRESPONDENCE

Date: **October 26, 2009**

To: **Lisa Percival, Associate Director**

From: **Sherly Abraham, R.Ph., Regulatory Project Manager**

Through: **Jeffrey Murray, M.D., MPH, Deputy Director**
Fraser Smith, Ph.D., Statistics Acting Team Leader
Thomas Hammerstrom, Ph.D., Statistics Reviewer
Mary Singer, M.D., Acting Medical Team Leader
Kirk Chan-Tack, M.D., Medical Officer

NDA: **NDA 21-567/S-019 Reyataz**

Subject: **Table 21 Labeling Edits**

The Division of Antiviral Products (DAVP) has reviewed your reply to FDA's efficacy comments in electronic facsimile dated September 18, 2009, and official submission dated September 29, 2009. The following comments are being conveyed to you on behalf of the review team:

1) We recommend that you display Week 96 data only in Table 21. FDA analyses of Week 96 data are provided below. FDA analyses are based on the following snapshot rule, which requires that the last observation in the week 90-102 window to be <50; and counts as a failure any subject with no HIV RNA in the window. Based on FDA analyses using the snapshot rule defined above, we recommend the following revisions for Table 21 (Week 96 data):

	ATV (n=443)		LPV (n=440)	
FDA_RESULT	N	%	N	%
SUCCESS	330	75%	298	68%
VIROLOGIC FAILURE	78	18%	86	20%
REBOUND	38	9%	44	10%
NEVER_SUPPRESSED	40	9%	42	10%
DEATH	6	1%	6	1%
Discontinued due to AE	13	3%	22	5%
Loss to Follow-Up	16	4%	28	6%

2)We recommend the following modification to your proposed text following Table 21 (Changes are highlighted):

3) We have also provided a list of USUBJID for subjects who discontinued due to adverse events, if you wish to discuss these issues further.

```
NREASON3=DEAT
FAIL=1 (OBSERVED)
FAIL=0 (CENSORED)
    USUBJID          DAY    LASTDAY    FAILDAY    FAIL    AENAME
AEACTL
AI424138-10-287       22        16          1        1     MULTI-ORGAN FAILURE
NONE
AI424138-110-794     122       124         84        1     KAPOSI'S SARCOMA
DRUG DISCONT.
AI424138-15-111       42        40          1        1     RENAL FAILURE
DRUG DISCONT.
AI424138-3-246        99       102          1        1     CARDIAC ARREST
DRUG DISCONT.
```

AI424138-32-580	12	10	1	1	CYTOMEGALOVIRUS INFECTION
DRUG DISCONT.					
AI424138-38-889	218	207	169	0	LUMBAR PAIN
NONE					
AI424138-40-911	325	320	252	0	THROMBOSIS MESENTERIC ARTERY
NONE					
AI424138-42-613	42	42	1	1	INTERSTITIAL PNEUMONIA
DRUG INTERRUPTED					
AI424138-42-706	27	28	0	1	DIARRHOEA
NONE					
AI424138-62-390	284	286	1	1	CARDIAC ARREST
DRUG DISCONT.					
AI424138-64-248	13	9	1	1	CEREBRAL TOXOPLASMOSIS
DRUG DISCONT.					
AI424138-67-960	333	335	257	0	ACCIDENT AUTOMOBILE
NONE					

NREASON3=AE_NEVER_SUPPRESSED

USUBJID	DAY	LASTDAY	FAILDAY	FAIL	AENAME
AEACTL					
AI424138-112-156	23	26	1	1	KAPOSI'S SARCOMA
DRUG DISCONT.					
AI424138-112-202	99	79	0	1	ICTERUS
DRUG DISCONT.					
AI424138-115-14	168	115	1	1	DIARRHEA
DRUG DISCONT.					
AI424138-115-9	191	103	1	1	PROTEINURIA AGGRAVATED
DRUG DISCONT.					
AI424138-151-158	30	9	1	1	THROMBOCYTOPENIA
DRUG DISCONT.					
AI424138-17-110	403	171	1	1	PULMONARY TUBERCULOSIS
DRUG DISCONT.					
AI424138-18-765	337	360	1	1	ABDOMINAL PAIN
DRUG DISCONT.					
AI424138-22-676	124	91	1	1	FURUNCLE
DRUG DISCONT.					
AI424138-26-1057	239	188	1	1	MAJOR DEPRESSION
DRUG DISCONT.					
AI424138-3-968	40	41	1	1	GERD
DRUG DISCONT.					
AI424138-35-286	41	30	0	1	FANCONI SYNDROME
DRUG DISCONT.					
AI424138-36-452	171	18	1	1	EXTRAPULMONARY TUBERCULOSIS
DRUG DISCONT.					
AI424138-37-442	224	19	1	1	GENERALIZED RASH
DRUG DISCONT.					
AI424138-39-998	29	25	1	1	RASH
DRUG DISCONT.					
AI424138-43-573	63	63	1	1	DIARRHEA
DRUG DISCONT.					
AI424138-77-146	20	14	0	1	HYPERSENSITIVITY REACTION
DRUG DISCONT.					
AI424138-78-593	29	15	1	1	EXANTHEMA
DRUG DISCONT.					
AI424138-78-916	25	17	1	1	EXANTHEMA
DRUG DISCONT.					
AI424138-83-180	233	88	1	1	DIARRHEA
DRUG DISCONT.					
AI424138-86-981	53	37	1	1	NAUSEA
DRUG DISCONT.					

NREASON3=AE_WHILE_SUPPRESSED

USUBJID	DAY	LASTDAY	FAILDAY	FAIL	AENAME	AEACTL
AI424138-105-973	333	335	333	0	LIPODYSTROPHY	DRUG DISCONT.
AI424138-115-18	245	220	170	0	JAUNDICE	DRUG DISCONT.
AI424138-147-626	501	502	421	0	VOMITING	DRUG DISCONT.
AI424138-23-185	339	510	508	0	DIARRHEA	DRUG DISCONT.
AI424138-23-250	294	296	294	0	DIARRHEA	DRUG DISCONT.
AI424138-23-616	168	170	168	0	DIARRHEA	DRUG DISCONT.
AI424138-23-78	501	503	428	0	ABDOMINAL BLOATING	DRUG DISCONT.
AI424138-50-872	624	622	588	0	RHABDOMYOLYSIS	DRUG DISCONT.
AI424138-55-729	439	514	511	0	LIPOMA	DRUG DISCONT.
AI424138-77-352	29	183	181	0	HYPERLIPIDEMIA	DRUG DISCONT.
AI424138-86-928	619	592	590	0	HYPERLIPEMIA	DRUG DISCONT.
AI424138-91-1011	280	282	255	0	PULMONARY TUBERCULOSIS	DRUG DISCONT.
AI424138-93-343	433	437	420	0	HYPERTROPHIC CARDIOMYOPATHY	DRUG DISCONT.
AI424138-96-997	256	171	169	0	DIARRHEA	DRUG DISCONT.

NREASON3=AE_AFTER_REBOUND

USUBJID	DAY	LASTDAY	FAILDAY	FAIL	AENAME	AEACTL
AI424138-147-600	633	594	417	1	MYCOBACTERIUM AVIUM COMPLEX	IN DRUG DISCONT.

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Sherly Abraham, R.Ph.,
Regulatory Project Manager
Division of Antiviral Products

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21567	SUPPL-19	BRISTOL MYERS SQUIBB CO	REYATAZ (ATAZANAVIR SULFATE)

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/s/

KAREN D WINESTOCK
10/26/2009

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: October 13, 2009

To: Lisa Percival **Associate Director**	**From:** Sherly Abraham, R. Ph. Regulatory Project Manager
Company: Bristol-Myers Squibb	Division of Antiviral Products
Fax number: 203-677-3818	**Fax number:** (301) 796-9883
Phone number: 203-677-6803	**Phone number:** (301) 796-3198

Subject: Virology Labeling Edits

Total no. of pages including cover: 3

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF FACSIMILE CORRESPONDENCE

Date: **October 13, 2009**

To: **Lisa Percival, Associate Director**

From: **Sherly Abraham, R.Ph., Regulatory Project Manager**

Through: **Jules O'Rear, Ph.D., Clinical Virology Team Leader**
Lisa Naeger, Ph.D., Clinical Virology Reviewer
Scott Proestel, M.D., Medical Team Leader
Kirk Chan-Tack, M.D., Medical Officer

NDA: **NDA 21-567/S-019 Reyataz**

Subject: **Virology Labeling Edits**

The Division of Antiviral Products (DAVP) has reviewed your September 28, 2009, submission. The following comments are being conveyed to you on behalf of the review team:

Please make the following change to your package insert in Section 12.4 Microbiology under Resistance:

"The I50L substitution emerged on study in one of these failure isolates and was associated with a 17-fold decrease in ATV susceptibility from baseline and the other failure isolate with baseline ATV resistance and PI substitutions (M46M/I and I84I/V) had additional IAS-defined major PI substitutions (V32I, M46I, and I84V) emerge on ATV treatment associated with a 3-fold decrease in ATV susceptibility from baseline."

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_____

Sherly Abraham, R.Ph.,
Regulatory Project Manager
Division of Antiviral Products

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21567	SUPPL-19	BRISTOL MYERS SQUIBB CO	REYATAZ (ATAZANAVIR SULFATE)

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/s/

SHERLY ABRAHAM
10/13/2009

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: August 7, 2009

To: **Lisa Percival** **Associate Director**	Jaewon Hong **From:** Regulatory Project Manager
Company: Bristol-Myers Squibb	Division of Antiviral Drug Products
Fax number: **203-677-3818**	**Fax number:** 301-796-9883
Phone number: **203-677-6803**	**Phone number:** 301-796-2013

Subject: Labeling and Stats comments

Total no. of pages including cover:

Comments:

Document to be mailed: ❑ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

Date: August 7, 2009

Sponsor: Bristol- Myers Squibb

NDA: 21-567/ S-019

Drug: Reyataz® (atazanavir sulfate)

To: Lisa Percival

From: Jaewon Hong, Pharm.D., Regulatory Project Manager

Through: Kirk Chan-Tack, M.D., Medical Reviewer
Jules O'Rear, Ph.D., Clinical Virology Team Leader

Subject: Labeling comments for Section 12.4 and Statistics comments for N21-567/ S-019

The following comment is being conveyed to you on behalf of the clinical review team. Please refer to your NDA 21-567 (S-019) submitted January 5, 2009.

Labeling comments
(Recommended changes are underlined)

Section 12.4 Microbiology
Paragraph 5 after Table 18 (changes shown in red)

Clinical Studies of Treatment-Naive Patients Receiving REYATAZ 300 mg With Ritonavir 100 mg: In Phase III study AI424-138, an as-treated genotypic and phenotypic analysis was conducted on samples from patients who experienced virologic failure (b) (4) or discontinued before achieving suppression on ATV/RTV (b) (4) and LPV/RTV (b) (4) through 96 weeks of treatment. In the ATV/RTV arm, one of the virologic failure isolates had a 56-fold decrease in ATV susceptibility emerge on therapy with the development of PI resistance-associated substitutions L10F, V32I, K43T, M46I, A71I, G73S, I85I/V and L90M. (b) (4) Two ATV/r-virologic failure isolates had baseline ATV resistance and IAS-defined major PI resistance-associated substitutions at baseline. The I50L substitution emerged on study in one of these failure isolates and was associated with a 17-fold decrease in ATV susceptibility from baseline (b) (4)

In the LPV/RTV arm, one of the virologic failure patient isolates had a 69-fold decrease in LPV susceptibility emerge on therapy with the development of PI substitutions L10V, (b) (4)

Statistics

1. Please reconcile the following results from the SAS data set with the Usubjid and a zero-one variable for suppression <50 at week 96 for all subjects.
    a. Your analyses suggest that the proportion of subjects who achieved HIV-RNA <50 at Week 96 are 75% for ATV/RTV compared to 69% for LPV/RTV (Table 21).
    b. FDA analyses show that the proportion of subjects who achieved HIV-RNA <50 at Week 96 are 70% for ATV/RTV compared to 63% for LPV/RTV.

    Please revise your label accordingly or please provide detailed rationale to explain your results.

2. Please explain why there are 2 datasets (TL5096 and TLOVR50) with success-failure indicators. According to FDA analyses, neither of these datasets give results that correlate with your proposed labeling.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

_____
Jaewon Hong, Pharm.D.
Regulatory Project Manager
Division of Antiviral Products
Division of Antimicrobial Products

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21567	SUPPL-19	BRISTOL MYERS SQUIBB CO	REYATAZ (ATAZANAVIR SULFATE)

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/s/

JAEWON HONG
09/03/2009

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: August 7, 2009

To: **Lisa Percival** **Associate Director**	Jaewon Hong **From:** Regulatory Project Manager
Company: Bristol-Myers Squibb	Division of Antiviral Drug Products
Fax number: **203-677-3818**	**Fax number:** 301-796-9883
Phone number: **203-677-6803**	**Phone number:** 301-796-2013

Subject: Labeling and Stats comments

Total no. of pages including cover:

Comments:

Document to be mailed: ❑ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

Date: August 7, 2009

Sponsor: Bristol- Myers Squibb

NDA: 21-567/ S-019

Drug: Reyataz® (atazanavir sulfate)

To: Lisa Percival

From: Jaewon Hong, Pharm.D., Regulatory Project Manager

Through: Kirk Chan-Tack, M.D., Medical Reviewer
Jules O'Rear, Ph.D., Clinical Virology Team Leader

Subject: Labeling comments for Section 12.4 and Statistics comments for N21-567/ S-019

The following comment is being conveyed to you on behalf of the clinical review team. Please refer to your NDA 21-567 (S-019) submitted January 5, 2009.

Labeling comments
(Recommended changes are underlined)

Section 12.4 Microbiology
Paragraph 5 after Table 18 (changes shown in red)

Clinical Studies of Treatment-Naive Patients Receiving REYATAZ 300 mg With Ritonavir 100 mg: In Phase III study AI424-138, an as-treated genotypic and phenotypic analysis was conducted on samples from patients who experienced virologic failure (b) (4) or discontinued before achieving suppression on ATV/RTV (b) (4) and LPV/RTV (b) (4) through 96 weeks of treatment. In the ATV/RTV arm, one of the virologic failure isolates had a 56-fold decrease in ATV susceptibility emerge on therapy with the development of PI resistance-associated substitutions L10F, V32I, K43T, M46I, A71I, G73S, I85I/V and L90M. (b) (4) Two ATV/r-virologic failure isolates had baseline ATV resistance and IAS-defined major PI resistance-associated substitutions at baseline. The I50L substitution emerged on study in one of these failure isolates and was associated with a 17-fold decrease in ATV susceptibility from baseline (b) (4)

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Statistics

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2. Please explain why there are 2 datasets (TL5096 and TLOVR50) with success-failure indicators. According to FDA analyses, neither of these datasets give results that correlate with your proposed labeling.

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_____
Jaewon Hong, Pharm.D.
Regulatory Project Manager
Division of Antiviral Products
Division of Antimicrobial Products

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/s/

JAEWON HONG
08/07/2009

JULIAN J O'REAR
08/07/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-567/S-019 **PRIOR APPROVAL SUPPLEMENT**

Bristol-Myers Squibb Company
Attention: Lisa Percival, Associate Director
5 Research Parkway
Signature 91 Bldg.-3SIG-515
Wallingford, CT 06492

Dear Mrs. Percival:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	REYATAZ® (atazanavir) capsules
NDA Number:	21-567
Supplement number:	019
Date of supplement:	January 5, 2009
Date of receipt:	January 5, 2009

This supplemental application proposes the following change:

Revisions to the U.S. Package Insert to provide for 96 week clinical safety and efficacy data on the use of atazanavir and ritonavir in treatment-naïve adult patients.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 6, 2009 in accordance with 21 CFR 314.101(a)

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any question, call Paras M. Patel. R.Ph., Regulatory Project Manager, at (301) 796-0783.

Sincerely,

{See appended electronic signature page}

Karen Winestock
Chief Project Management Staff
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Karen Winestock

1/13/2009 05:36:55 PM