CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206352Orig1s000
021567Orig1s035

MICROBIOLOGY / VIROLOGY REVIEW(S)

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
VIROLOGY REVIEW
NDA: 206352 **SDN**: 000 **DATE REVIEWED:** 03/06/2014
Virology Reviewer: Eric F. Donaldson, Ph.D.

Reviewer's Name: Eric F. Donaldson, Ph.D.

Sponsor: Bristol-Myers Squibb Company
5 Research Parkway
Mailstop 2CW-506
Wallingford, CT 06492
Tel: 860-508-9480
Fax: 203-677-7435
Lisa Percival, Director of Global Regulatory Sciences
Email: Lisa.Percival@bms.com

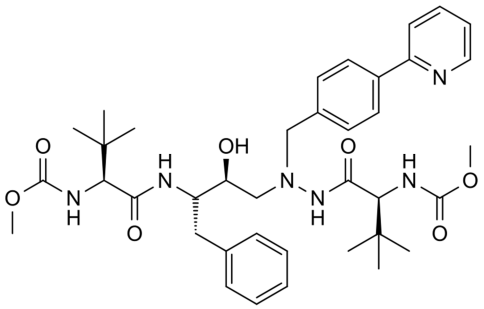
Initial Submission Dates:
Correspondence Date: 12/02/13
CDER Receipt Date: 12/02/13
Assigned Date: 12/05/13
NDA Review Complete Date: 05/09/14
PDUFA Date: 06/02/14

Submission #	Date Received by CDER	Date Assigned
N206352 SDN 000	12/02/2013	12/02/2013
N206352 SDN 004	02/19/2014	02/21/2013
N206352 SDN 006	02/26/2014	02/28/2013

Product Names: Atazanavir (Reyataz®)

Chemical Name: methyl N-[(1S)-1-{[(2S,3S)-3-hydroxy-4-[(2S)-2-[(methoxycarbonyl)amino]-3,3-dimethyl-N'-{[4-(pyridin-2-yl)phenyl]methyl}butanehydrazido]-1-phenylbutan-2-yl]carbamoyl}-2,2-dimethylpropyl]carbamate

Structure, physical or biological composition:



Atazanavir

Molecular Formula: $C_{38}H_{52}N_6O_7$

Molecular Weight: 704.856

Drug Category: HIV-1 antiviral

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
VIROLOGY REVIEW
NDA: 206352 **SDN**: 000 **DATE REVIEWED:** 03/06/2014
Virology Reviewer: Eric F. Donaldson, Ph.D.

Indication: For the treatment of HIV-1 in combination with other antiretroviral drugs

Dosage Form/Route of administration: (b) (4) *Powder:* Must be taken with ritonavir and food and should not be used in children who weigh less than 10 kg or who weigh 25 kg or more

Supporting documents: NDA022282, ANDA (b) (4), ANDA200196, ANDA091673, ANDA091611, ANDA078785, and sNDA21567

Abbreviations: α-1AGP, alpha-1 acidic glycoprotein; APV, amprenavir; ARV, antiretroviral; ATV, atazanavir; CC, cytotoxic concentration; CI, combination index; d4T, stavudine; DC, discontinuation; ddI, didanosine; DNA, deoxyribonucleic acid; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; IC, inhibitory concentration; IDV, indinavir; LOQ, Limit of Quantification; LPLV, last patient last visit; LPV, lopinavir; moi, multiplicity of infection; mAb, monoclonal antibody; NFV, nelfinavir; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PBMCs, peripheral blood mononuclear cells; PCR, polymerase chain reaction; PI, protease inhibitor; pol, polymerase; PPT, polypropylene tubes; PR, protease; RNA, ribonucleic acid; RT, reverse transcriptase; RTI, reverse transcriptase inhibitor; RTV, ritonavir; TLOVR, Time to Loss of Virologic Response; TP, triphosphate; SQV, saquinavir; WT, wild-type

Table of Contents

Executive Summary

Atazanavir is a protease inhibitor indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection that was originally approved by the FDA in 2003 (NDA-21567, approved on June 20, 2003). It is currently approved in capsular form for pediatric patients 6 years of age to less than 18 years of age with dosage based on body weight not to exceed the adult dose. Data from two Phase 3b clinical trials were submitted to support this supplemental NDA with AI424397 (PRINCE I) and AI424451 (PRINCE II) being conducted in pediatric subjects from ≥3 months to <6 years in age to evaluate an ATV powder formulation dosed by weight with ritonavir.

The Clinical Virology assessments for this supplemental NDA focused on resistance analysis of subjects who met the criteria of virologic failure defined as either an incomplete virologic response or viral rebound. In study AI424397 (PRINCE I), there were a total of 9 subjects (out of 56 who received treatment) for which paired resistance data comprised of genotypic data derived from baseline and time near failure samples could be compared to determine if treatment-emergent, resistance-associated substitutions arose. For study AI424451 (PRINCE II), paired resistance data were available for 13 subjects out of 78 subjects who had been treated (some were still receiving treatment at the time of submission). Clinical Virology performed an independent assessment of the resistance findings and compared results with those reported by the sponsor.

In general, the resistance analysis results reported by the sponsor were consistent with independent analysis of the resistance data performed by Clinical Virology. No treatment-emergent ATV-associated substitutions (defined in the FDA label) were detected among the nine treatment failures in Study AI424397 (PRINCE I), but four other known PI resistance-associated substitutions arose in one subject each (L19I/R, M36M/I, H69K/R, and I72I/V). The sponsor reported that none of the subjects acquired phenotypic resistance to ATV, ATV/RTV, or any NNRTI or NRTI. In Study AI424451 (PRINCE II), ATV-associated resistance substitutions arose in one subject (AI424451-14-69), including M46M/V, V82V/I, I84I/V, and L90L/M; however, the sponsor reported that these substitutions did not result in phenotypic resistance to ATV or ATV/RTV (ATV phenotypic fold change: 1.74) as assessed by the Monogram Phenosense GT test. Additional substitutions associated with resistance to other PIs also arose in one subject each, including V11V/I, G16G/E, D30D/G, E35E/D, K45K/R, L63P/S, and I72I/T. Q61D and Q61/E/G emerged in two subjects who failed treatment with ATV/RTV. Three subjects developed M184V in the reverse transcriptase protein of their virus, and all 3 exhibited phenotypic resistance to emtricitabine (FTC) and lamivudine (3TC). In general, the resistance data sets for PRINCE I and PRINCE II were too small to draw any significant conclusions, and the resistance patterns were consistent with those observed in previous cohorts exposed to ATV and ATV/RTV.

This supplemental NDA seeking an indication for pediatric subjects ≥3 months to (b) (4) with an ATV powder formulation in combination with liquid RTV is approvable from the Clinical Virology perspective.

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
VIROLOGY REVIEW
NDA: 206352 **SDN**: 000 **DATE REVIEWED:** 03/06/2014
Virology Reviewer: Eric F. Donaldson, Ph.D.

1 Recommendations

1.1 Recommendation and Conclusion on Approvability

This supplemental NDA is approvable from the Clinical Virology perspective.

1.2 Recommendation on Phase 4 Commitments

None.

2 Summary of Virology Assessments

2.1 Nonclinical Virology

The nonclinical virology profile for atazanavir (ATV) was originally reviewed by Dr. Lisa Naeger (NDA21567 SDN 000). No additional nonclinical virology data were analyzed or submitted to support this supplemental NDA.

2.2 Clinical Virology

Atazanavir is a protease inhibitor indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection that was originally approved by the FDA in 2003 (NDA-21567 was approved on June 20, 2003). It is currently approved in capsular form for pediatric patients 6 years of age to less than 18 years of age with dosage based on body weight not to exceed the adult dose. Data from two Phase 3b clinical trials were submitted to support this supplemental NDA with AI424397 (PRINCE I) and AI424451 (PRINCE II) being conducted in pediatric subjects from 3 months to <6 years in age to evaluate an ATV powder formulation dosed by weight with ritonavir. Per protocol dosing and weight bands were: 150 mg for 5 - <10 kg, 200 mg for 10 - <15 kg, and 250 mg for 15 - <25 kg along with 80 mg/mL of liquid RTV.

The Clinical Virology assessments for this supplemental NDA focused on resistance analysis of subjects who met the criteria of virologic failure defined as either an incomplete virologic response or viral rebound. In study AI424397 (PRINCE I), there were a total of 9 subjects (out of 56 who received treatment) for whom paired resistance data comprised of genotypic data derived from baseline and time near failure samples could be compared to determine if treatment-emergent, resistance-associated substitutions arose. For study AI424451 (PRINCE II), paired resistance data were available for 13 subjects out of 78 subjects who had been treated (some were still receiving treatment at the time of submission). Clinical Virology performed an independent assessment of the resistance findings and compared results with those reported by the sponsor.

In general, the resistance analysis results reported by the sponsor were consistent with independent analysis of the resistance data performed by Clinical Virology. No treatment-emergent ATV-associated substitutions (defined in the FDA label) were detected among the nine treatment failures in Study AI424397 (PRINCE I), but four other known PI resistance-associated substitutions arose in one subject each (L19I/R, M36M/I, H69K/R, and I72I/V). The sponsor reported that none of the subjects acquired phenotypic resistance to ATV, ATV/RTV, or any NNRTI or NRTI. In Study AI424451 (PRINCE II), ATV-associated resistance substitutions arose in one subject (AI424451-14-69), including M46M/V, V82V/I, I84I/V, and L90L/M; however, the sponsor reported that these substitutions did not result in phenotypic

resistance to ATV or ATV/RTV (ATV phenotypic fold change: 1.74) as assessed by the Monogram Phenosense GT test. Additional substitutions associated with resistance to other PIs also arose in one subject each, including V11V/I, G16G/E, D30D/G, E35E/D, K45K/R, L63P/S, and I72I/T. Q61D and Q61/E/G emerged in two subjects who failed treatment with ATV/RTV. Three subjects developed M184V in the reverse transcriptase protein of their virus, and all 3 exhibited phenotypic resistance to emtricitabine (FTC) and lamivudine (3TC). In general, the resistance data sets for PRINCE I and PRINCE II were too small to draw any significant conclusions, and the resistance patterns were consistent with those observed in previous cohorts exposed to ATV and ATV/RTV.

3 Administrative Signatures

3.1 Reviewer's Signature

_____
Eric F. Donaldson, Ph.D.
Virology Reviewer, Division of Antiviral Products

3.2 Concurrence

_____
Julian J. O'Rear, Ph.D.
Virology Team Leader, Division of Antiviral Products

OND Virology Review

1 Introduction and Background

Atazanavir sulfate (BMS-232632; Reyataz®; ATV) is an azapeptide protease inhibitor of human immunodeficiency virus type-1 (HIV-1). ATV, in combination with other antiretroviral drugs, has been marketed for the treatment of HIV-1 infection in adult and pediatric patients ≥6 years of age. The efficacy and safety of ATV-containing regimens has been demonstrated in a diverse population of HIV-infected adults across a wide spectrum of $CD4^+$ cell counts, baseline HIV-1 RNA levels, and prior treatment regimens, between genders, and across different races.

The development of ATV in pediatric patients was based on data from Study AI424020 (also designated as Pediatric AIDS Clinical Trials Group 1020-A) that exhibited comparable safety of the combination of ATV/ritonavir (RTV) to that in the adult studies. These data were previously submitted and reviewed to support the current approved capsule dosing recommendations of ATV in pediatric patients in the United States (US) and other countries. In 2010, Bristol-Myers Squibb Company provided revised capsule dosing recommendations, supported by both modeling and simulation analyses and clinical data, in order to address some of the limitations of the dosing recommendations that were approved in the US and some other countries.

Atazanavir powder for oral use (POU) was developed for use in pediatric patients who are unable to swallow a solid oral dosage form. The relative bioavailability (Study AI424010) of an early prototype of the ATV POU was low, and modifications to the formulation were necessary. A subsequent relative bioavailability study (AI424025) of the ATV POU that was initially used in pediatric clinical trials was conducted. This ATV POU contained (b) (4) aspartame that exceeded the acceptable daily intake in

some pediatric subjects. The ATV POU was modified again with (b) (4) aspartame (b) (4)), and a taste assessment in adult volunteers (AI424466) was conducted comparing the sweetness and palatability of 2 ATV POU formulations with reduced aspartame ((b) (4) to the ATV POU with (b) (4) aspartame in support of a switch to the formulation with (b) (4) aspartame in the pediatric clinical trials.

Two ongoing Phase 3b pediatric studies, AI424397 and AI424451, are being conducted to confirm that the proposed doses of ATV powder formulation with RTV in optimized regimens given in infants and children ≥3 months to <11 years are safe and well tolerated and produce systemic exposures comparable to those demonstrated to be efficacious in adults. The sponsor reported that based on the results of the pooled data analyses from the 2 pediatric studies, ATV POU boosted with RTV and an optimized nucleoside reverse transcriptase background therapy given in subjects ≥3 months to <11 years was effective through 48 weeks, and was generally safe and well tolerated. No new safety findings were identified in the pediatric population taking ATV POU that had not been reported in other ATV pediatric and adult studies.

At the proposed doses of ATV POU and RTV liquid of 200/80 mg once daily (QD) for pediatric patients who weigh 10 to <15 kg and 250/80 mg QD for those who weigh 15 to <25 kg, ATV exposures were similar to those predicted by a population pharmacokinetic model, and provide exposures to ATV similar to those demonstrated to be safe and efficacious in HIV-infected adults. Overall, the sponsor proposes that these newly available dosing recommendations and pediatric powder formulation will address the unmet medical needs of infants and children unable to swallow a solid oral dosage form of ATV.

1.1 Important Milestones in Product Development

- NDA-21567 was approved on June 20, 2003 for the treatment of HIV-1 infection in adults in combination with other antiretroviral agents formulated in 100, 150 and 200 mg capsules.

1.2 Methodology

This review focused primarily upon resistance analysis to determine if substitutions known to be associated with ATV failure arose more frequently in the pediatric population in general or in pediatric subjects who were closer to the upper limit of the weight bands used to define the dose to be administered.

For resistance analyses, baseline samples from naïve subjects were screened by genotype using the Monogram Genosure® MG assay, while samples from ARV-experienced subjects were screened by genotype and phenotypic analyses using the Monogram Phenosense™ GT assay where subjects had to show a <2.2 fold change in susceptibility for ATV (cutoff value for ATV/RTV was <5.2). Identification of resistance-associated substitutions was performed by comparing amino acid sequences derived from subject samples that were taken at baseline and a timepoint close to virologic failure. The sponsor provided tables for all subjects who reported these data, and the summaries assembled by the sponsor were compared to summaries derived by Clinical Virology using Excel and Jump

1.3 Prior FDA Virology Reviews

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
VIROLOGY REVIEW
NDA: 206352 **SDN**: 000 **DATE REVIEWED:** 03/06/2014
Virology Reviewer: Eric F. Donaldson, Ph.D.

The original NDA21567 was reviewed (NDA21567 SDN 000) and approved from the Clinical Virology perspective by Lisa K. Naeger, Ph.D. on 6/18/2003 and by the division on 6/20/2003.

1.4 Major Virology Issues that Arose during Product Development

None.

1.5 State of Antivirals Used for the Indication Sought

This would be the first HIV-1 protease inhibitor approved for use in patients between the ages of ≥3 months to (b) (4).

2 Nonclinical Virology Overview

Atazanavir (ATV, BMS-232632) is an azapeptide HIV-1 protease inhibitor that exhibits anti-HIV activity with an EC_{50} value of 2 to 5 nM against a variety of HIV-1 isolates grown in PBMCs, macrophages, CEM-SS, and MT-2 cells in cell culture. ATV specifically and selectively blocks the cleavage of the viral Gag and Gag-Pol precursor proteins in HIV-infected cells preventing viral particle maturation. Cytotoxicity with ATV is observed at concentrations >5,000-fold higher than that required for anti-HIV activity.

HIV-1 resistant to ATV was selected in cell culture using three different HIV-1 strains. These ATV-resistant HIV-1 isolates showed a 93- to 183-fold decrease in susceptibility to atazanavir compared to parental wild-type virus. Genotypic analyses indicated that I50L, A71V, N88S/D and I84V substitutions appeared to be key changes with possible roles in ATV resistance. Direct evidence for a role of the I50L substitution in ATV resistance was obtained by constructing recombinant viruses with the protease gene from clinical isolates. ATV resistance corresponded to the presence of the I50L and A71V substitutions in the protease coding sequence. Results showed that the I50L substitution, sometimes combined with A71V and other changes, appears to be a signature substitution for ATV and mediates increased susceptibility to other PIs by an unknown mechanism. Clinical isolates resistant to one or two currently approved PIs (the majority nelfinavir-resistant with D30N substitutions) were generally susceptible to ATV. Assessment of clinical isolates resistant to one or more PIs in patients never exposed to ATV showed that susceptibility to ATV decreased as the level of cross-resistance to other PIs increased.

3 Relevant Findings from Other Disciplines

3.1 Summary of Efficacy in Phase 3b Trials AI424397 (PRINCEI) and AI424451 (PRINCEII)

Study AI424397 (PRINCE I) is an ongoing Phase 3b prospective single-arm, open-label, multicenter study to evaluate the safety, efficacy, and pharmacokinetics (PK) of ATV powder boosted with RTV with an optimized NRTI background therapy in HIV-infected, ARV-naïve and -experienced pediatric subjects ≥3 months to <6 years and weighing ≥5 - <25 kg. The primary purpose of this study was to confirm that the proposed dose of ATV powder formulation with RTV in optimized NRTI background regimens given in ARV-naïve and -experienced infants and children 3 months to (b) (4) are safe and well

tolerated and produce systemic exposures comparable to those demonstrated to be safe and efficacious in adults.

Study AI424451(PRINCE II) is an ongoing Phase 3b prospective single-arm, open-label, multicenter study investigating the safety, efficacy, and PK of ATV powder boosted with RTV with an optimized NRTI background therapy in HIV-infected, ARV-naïve and -experienced pediatric subjects ≥3 months to <11 years and weighing ≥5 - <35 kg.

The primary objective of both pediatric studies was to describe the safety of ATV powder formulation boosted with RTV-based highly active ARV therapy regimens in pediatric subjects dosed through 48 weeks. All efficacy endpoints were secondary, and focused on the ATV powder formulation. Values after the start of ATV capsule were excluded. Efficacy endpoints were also summarized by prior ARV use (ARV naive, ARV experienced).

In Study AI424397 (PRINCE I), 56 subjects were treated, and 46 subjects (82%) completed the Stage 1 treatment period. A modified ITT analysis at Week 48 on the ATV powder cohort (i.e., subjects who did not switch to ATV capsule at or before Week 48), 74% of subjects had HIV-1 RNA <400 copies/mL (95% CI: 60.3, 85.0) and 61% of subjects had HIV-1 RNA <50 copies/mL (95% CI: 46.9, 74.1). At Week 48, virologic response rates increased with higher baseline weight band. At Week 48, in ARV-experienced and -naïve subjects, the incidence of subjects with HIV-1 RNA <400 copies/mL (75% and 74%, respectively) and <50 copies/mL (60% and 62%, respectively) was consistent.

In Study AI424451 (PRINCE II), the first subject first visit occurred on 08-Jul-2011, and interim results were provided through the data cutoff date of 07-Jun-2013 (with a LPLV date for this data cutoff of 18-Apr-2013). The study is still enrolling to meet its target of 95 subjects treated. By the data cutoff date, only 41 subjects of 78 treated subjects (53%) had completed the 48-week Stage 1 treatment period, and the interpretation of this interim data was limited by the small number of subjects who had the opportunity to complete Week 48 in each individual weight band. All 23 subjects treated in the 5 - <10 kg weight band received 150 mg of ATV powder boosted with 80 mg RTV liquid. No subjects had enrolled in the new 5 - <10 kg cohort that would receive 200 mg of ATV boosted with 80 mg RTV. Only 1 subject had been treated in the 25 - <35 kg weight band, and this subject discontinued before Week 48 due to a lack of efficacy.

Overall, based on a modified ITT analysis at Week 48 of the eligible Week 48 ATV powder cohort, 68% of subjects had HIV-1 RNA <400 copies/mL and 52% of subjects had HIV-1 RNA <50 copies/mL. At Week 48, in ARV-experienced and -naïve subjects, the response rates of subjects with HIV-1 RNA <400 copies/mL (64% and 72%, respectively) and <50 copies/mL (56% and 48%, respectively) were similar.

4 Clinical Virology

4.1 Overview of Resistance Analysis from the Pivotal Phase 3 Trials

Genotypic and phenotypic evaluation of clinical isolates from ATV-treated subjects designated as virologic failures with decreased ATV susceptibility demonstrated that ATV displayed different resistance patterns depending on the subject population. When unboosted ATV was used in subjects with no previous antiretroviral experience, clinical isolates developed a unique I50L substitution frequently accompanied by an A71V change. The I50L substitution resulted in ATV resistance, impaired

viral growth, and increased susceptibility to other PIs. In contrast, isolates from treatment-experienced subjects treated with RTV boosted ATV and ATV/SQV generally did not develop the I50L substitution but acquired several additional amino acid changes, including I84V, L90M, M46I and N88S/D. These additional substitutions in the protease also conferred cross-resistance to the other approved PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir). A significantly higher percentage of the clinical isolates from ATV treatment arms with PI substitutions I84V, L90M, A71V, M46I and N88S/D at baseline were virologic failures compared to isolates from other treatment arms. These analyses indicated that these substitutions in the HIV-1 protease are detrimental to ATV antiviral activity and may affect the virologic response to ATV treatment clinically.

4.2 Overview of Phase 3b Trial AI424397 (PRINCE I)

Study AI424397 is an ongoing Phase 3b prospective single-arm, open-label, multicenter study to evaluate the safety, efficacy, and pharmacokinetics (PK) of ATV powder boosted with RTV with an optimized NRTI background therapy in HIV-infected, ARV-naïve and -experienced pediatric subjects ≥3 months to <6 years and weighing ≥5 - <25 kg (Figure 1). The primary purpose of this study was to confirm that the proposed dose of ATV powder formulation with RTV in optimized NRTI background regimens given in ARV-naïve and -experienced infants and children 3 months to (b) (4) are safe and well tolerated and produce systemic exposures comparable to those demonstrated to be safe and efficacious in adults. Subjects were dosed by weight (Figure 1).

For Study AI424397 (PRINCE I), the following virology-related enrollment criteria were used:

1. Sensitivity at screening to ATV and at least 2 NRTIs
2. Experienced subjects who had received ATV or ATV/RTV at any time prior to study enrollment or who had a prior history of 2 or more PI failures were not allowed in the study
3. Baseline samples from naïve subjects were screened by genotype, while samples from ARV-experienced subjects were screened by genotype and phenotypic analyses (fold change in susceptibility <2.2 fold).
4. Per protocol, genotypic resistance at screening to ATV was defined by the presence of the following substitutions in the PR gene:
    - Any major substitutions: I50L, I84V, N88S
    - ≥2 of the following minor or cross resistant substitutions: M46I/L, G48V, I54L/V/M/T/A, V82A/T/FI, L90M, V32I
    - ≥3 of the following minor substitutions: L10I/F/V/C, L24I, L33I/F/V, F53L/Y, A71V/I/T/L, G73C/S/T/A

Efficacy was defined as: Proportions of subjects with HIV-1 RNA <50 copies/mL and <400 copies/mL evaluated at each scheduled visit through Week 48. Assess change from baseline in HIV-1 RNA levels, $CD4^+$ cell counts, and $CD4^+$ percentages.

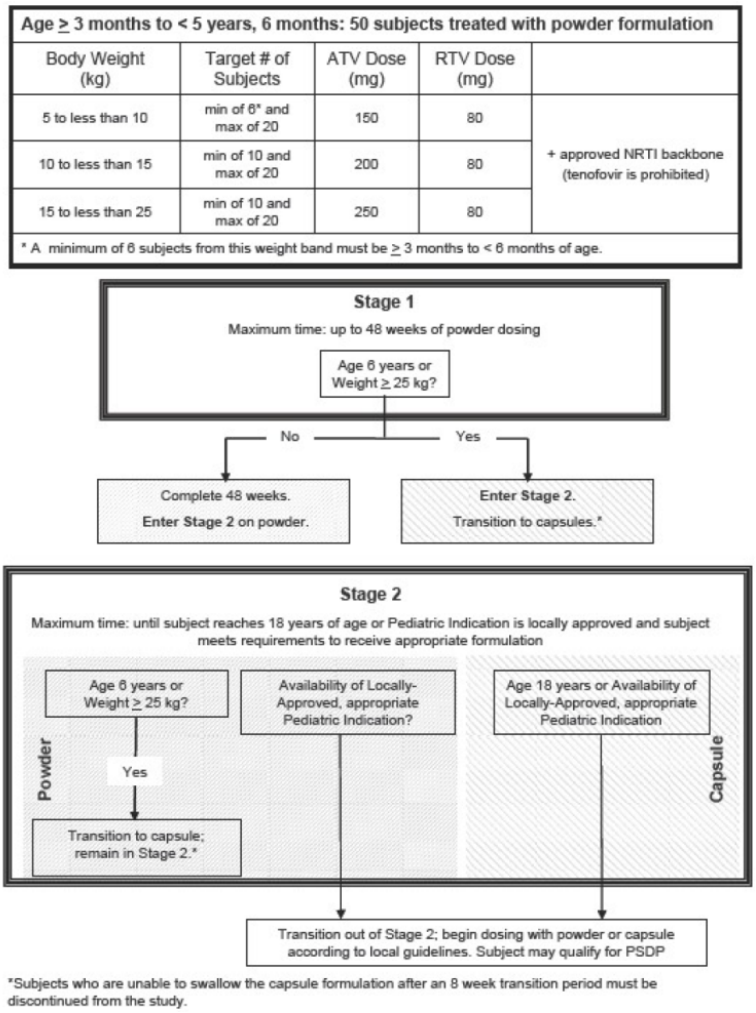


Figure 1. AI424397 (PRINCE I) study schema (Figure 3.1, page 31, AI424397 Complete Study Report).

In Study AI424397 (PRINCE I), 56 subjects were treated, and 46 subjects (82%) completed the Stage 1 treatment period. A modified ITT analysis at Week 48 on the ATV powder cohort (i.e., subjects who did not switch to ATV capsule at or before Week 48), 74% of subjects had HIV-1 RNA <400 copies/mL (95% CI: 60.3, 85.0) and 61% of subjects had HIV-1 RNA <50 copies/mL (95% CI: 46.9, 74.1). At Week 48, virologic response rates increased with higher baseline weight band. At Week 48, in ARV-experienced and -naïve subjects, the incidence of subjects with HIV-1 RNA <400 copies/mL (75% and 74%, respectively) and <50 copies/mL (60% and 62%, respectively) was consistent.

4.3 Overview of Phase 3 Trial PRINCE II

Study AI424451 is an ongoing Phase 3b prospective single-arm, open-label, multicenter study investigating the safety, efficacy, and PK of ATV powder boosted with RTV with an optimized NRTI background therapy in HIV-infected, ARV-naïve and -experienced pediatric subjects ≥3 months to <11 years and weighing ≥5 - < 35 kg (Figure 2). Subjects were dosed by weight.

Age ≥ 3 months to < 11 years: Minimum 56 subjects treated with ATV powder formulation for 48 weeks				
Body Weight (kg)	Target # of Subjects	ATV Dose (mg)	RTV Dose (mg)	
5 to less than 10	Minimum of 5	150	80	+ approved NRTI backbone (tenofovir is prohibited)
	Minimum of 6	200	80	
10 to less than 15	Minimum of 10	200	80	
15 to less than 25	Minimum of 10	250	80	
25 to less than 35	Minimum of 6	300	100	
The study will commit to enroll a minimum of 30 ARV experienced patients .				

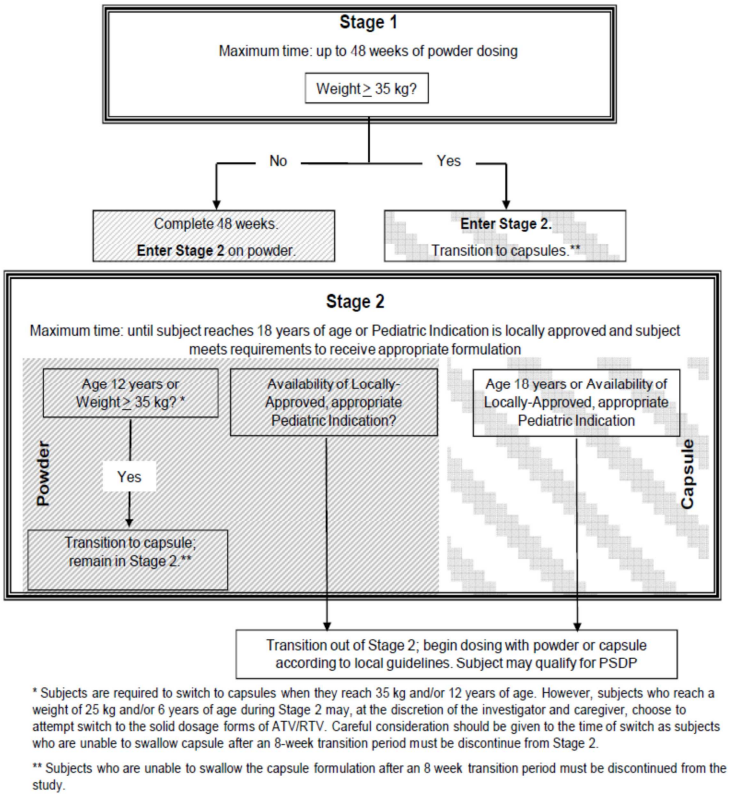


Figure 2. Study AI424451 (PRINCE II) study schema (Figure 3.1, page 32, AI424451 CSR).

For Study AI424451 (PRINCE II), the following virology-related enrollment criteria were used:

- Sensitivity at screening to ATV and at least 2 NRTIs
- Experienced subjects who had received ATV or ATV/RTV at any time prior to study enrollment or who had a prior history of 2 or more PI failures were not allowed in the study
- Baseline samples from naïve subjects were screened by genotype: Monogram Genosure® MG assay, while samples from ARV-experienced subjects were screened by genotype and phenotypic analyses: Monogram Phenosense™ GT assay: subjects had to show a <2.2 fold change in susceptibility for ATV (cutoff value for ATV/RTV was <5.2 fold). This test measures the impact of genotype on activity of ATV.
- Per protocol, subjects with the following substitutions at screening were excluded from enrollment:
    - Any major substitutions: I50L, I84V, N88S

- 2 of the following minor or cross resistant substitutions: M46I/L, G48V, I54L/V/M/T/A, V82A/T/FI, L90M, V32I.

Efficacy was defined as: Proportions of subjects with HIV-1 RNA <50 copies/mL and <400 copies/mL evaluated at each scheduled visit through Week 48. Assess change from baseline in HIV-1 RNA levels, $CD4^+$ cell counts, and $CD4^+$ percentages.

In Study AI424451 (PRINCE II), interim results were provided through the data cutoff date of 07-Jun-2013. The study is still enrolling to meet its target of 95 subjects treated. By the data cutoff date, only 41 subjects of 78 treated subjects (53%) had completed the 48-week Stage 1 treatment period, and the interpretation of the interim data was limited by the small amount of subjects who had the opportunity to complete Week 48 in each individual weight band. All 23 subjects treated in the 5 - <10 kg weight band received 150 mg of ATV powder boosted with 80 mg RTV liquid. No subjects had enrolled in the new 5 - <10 kg cohort that would receive 200 mg of ATV boosted with 80 mg RTV. Only 1 subject had been treated in the 25 - <35 kg weight band, and this subject discontinued before Week 48 due to a lack of efficacy.

Overall, based on a modified ITT analysis at Week 48 of the eligible Week 48 ATV powder cohort, 68% of subjects had HIV-1 RNA <400 copies/mL and 52% of subjects had HIV-1 RNA <50 copies/mL. At Week 48, in ARV-experienced and -naive subjects, the response rates of subjects with HIV-1 RNA <400 copies/mL (64% and 72%, respectively) and <50 copies/mL (56% and 48%, respectively) were similar.

4.4 Treatment-Emergent Resistance Analysis

For both Phase 3b trials submitted in NDA206352, the following definitions were used:

1. Virologic failure was defined as an incomplete virologic response or viral rebound
   a. Incomplete virologic response was defined as:
      i. Less than a 1 $\log_{10}$ drop from baseline in plasma HIV RNA level by Week 16 confirmed by a second plasma HIV RNA level redrawn within 2 and 4 weeks from original sample; or
      ii. A plasma HIV RNA level >200 copies/mL after Week 24, confirmed by a second plasma HIV RNA level redrawn within 2 and 4 weeks from original sample; or
      iii. Repeated plasma HIV RNA level ≥50 copies/mL (above the lower limit of quantification using the Amplicor v1.5 PCR assay, or Abbott RealTime HIV-1 assay after the Roche Amplicor assay was discontinued, for measuring HIV RNA) after Week 48.
2. Virologic failure was defined as an incomplete virologic response or viral rebound
   a. Viral rebound was defined as:
      i. A plasma HIV RNA level ≥400 copies/mL (using the Amplicor v1.5 PCR assay, or Abbott RealTime HIV-1 assay after the Roche Amplicor assay was discontinued, for measuring HIV RNA) confirmed by a second plasma HIV RNA level of ≥400 copies/mL redrawn within 2 and 4 weeks from original sample) at any time in a subject who had previously achieved a plasma HIV RNA level <50 copies/mL.
      ii. A plasma HIV RNA level ≥50 copies/mL and <1,000 copies/mL (using the Amplicor v1.5 PCR assay, or Abbott RealTime HIV-1 assay after the Roche Amplicor assay was discontinued, for measuring HIV RNA) followed by a return to virologic suppression was considered a viral blip and not a viral rebound.

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
VIROLOGY REVIEW
NDA: 206352 **SDN**: 000 **DATE REVIEWED:** 03/06/2014
Virology Reviewer: Eric F. Donaldson, Ph.D.

Criteria for resistance testing for Study AI424397 (PRINCE I) were:

1. Subjects meeting the criteria for virologic failure at any time during the study.
2. Discontinuation from study medications for any reason except withdrawal of consent.
3. Paired resistance data was available for 9 baseline and on-study samples
4. Genotypic substitutions at baseline were summarized for virologic failures using the most current version of the International AIDS Society-USA (IAS-USA) list and Stanford HIV Drug Resistance Database.
5. This resistance summary included:
    a. Genotypable isolates
    b. PI substitutions from genotypable isolates
    c. Selected RT substitutions from genotypable isolates
    d. Protease inhibitor substitutions were categorized as major, minor and polymorphisms
    e. Selected RT substitutions include all NNRTI and NRTI substitutions listed in IAS-USA and those not listed in IAS-USA that have at least 1 substitution score ≥5 according to values assigned by HIVdb.

In general, the results reported by the sponsor were consistent with independent analysis. No treatment-emergent ATV-associated substitutions were detected among the nine treatment failures with paired sequence data in Study AI424397 (PRINCE I), but four other known PI resistance-associated substitutions arose in one subject each, including L19I/R, M36M/I, H69K/R, and I72I/V (Table 1). The sponsor reported that none of the subjects acquired phenotypic resistance to ATV, ATV/RTV, or any NNRTI or NRTI.

Table 1. Resistance analysis of subjects who failed treatment in AI424397 (PRINCE I) (DAVP analysis).

USUBJID	WEIGHT (BL)	VISIT	ARVEXP	PI L19	PI M36	PI H69	PI I72	RT E6	RT Y56	RT K65	RT T69	RT Q102	RT K103	RT I142	RT S156	RT E169	RT M184	RT G190	RT D192	RT I195	RT H208	RT V241	RT V245	RT S251	RT T286	RT A288	RT E298
AI424397-15-50	5 - <10 kg	PRE-TREAT	ARV EXPER	I	I	R						K	K/N												V		
AI424397-15-50	5 - <10 kg	WEEK 12	ARV EXPER	I	I	R		E/K				K		I/V				G/A	D/N				V/L		A/V		
AI424397-1-40	10 - <15 kg	PRE-TREAT	ARV EXPER	T	I	K						K			S/L		V						Q		A		
AI424397-1-40	10 - <15 kg	WEEK 40	ARV EXPER	T	I	K						K/R					V						Q		A	A/T	
AI424397-14-17	10 - <15 kg	PRE-TREAT	ARV EXPER	T	I	K						K					V						Q				
AI424397-14-17	10 - <15 kg	WEEK 16	ARV EXPER	T	I	K			Y/C	K/R		K					V						Q				
AI424397-28-65	15 - <25 kg	PRE-TREAT	ARV EXPER					D/N				K	K/R				V							S/C			
AI424397-28-65	15 - <25 kg	WEEK 16	ARV EXPER				I/V	D/N			T/N	K	K/R				V							S/C			
AI424397-28-65	15 - <25 kg	WEEK 24	ARV EXPER					D/N				K	K/E/G/R		S/L		V				H/Y			S/C			
AI424397-12-80	5 - <10 kg	PRE-TREAT	ARV NAIVE	I		R	T					K															
AI424397-12-80	5 - <10 kg	WEEK 12 ST2	ARV NAIVE	I		R	T					K															
AI424397-12-80	5 - <10 kg	WEEK 32	ARV NAIVE	I		K/R	T					K															
AI424397-14-87	5 - <10 kg	PRE-TREAT	ARV NAIVE	I	I	K						K											Q				
AI424397-14-87	5 - <10 kg	WEEK 40	ARV NAIVE	I	I	K						K	K/N			E/A	V					V/I	Q	S/I			
AI424397-28-63	5 - <10 kg	PRE-TREAT	ARV NAIVE	I								K	R										E				
AI424397-28-63	5 - <10 kg	WEEK 12 ST2	ARV NAIVE	I/R								K	R										E				
AI424397-29-7	10 - <15 kg	PRE-TREAT	ARV NAIVE									K															
AI424397-29-7	10 - <15 kg	WEEK 16	ARV NAIVE		M/I							K															
AI424397-29-7	10 - <15 kg	F/U WEEK 2	ARV NAIVE									K								I/T							
AI424397-36-76	15 - <25 kg	PRE-TREAT	ARV NAIVE											T									E				
AI424397-36-76	15 - <25 kg	WEEK 40	ARV NAIVE											T									E				E/D

Blue, known PI resistance-associated substitutions; red, known resistance-associated substitutions of NRTIs/NNRTIs; yellow, concurrence between sponsor and virology

Criteria for resistance testing for Study AI424451 (PRINCE II) were:

1. Subjects meeting the criteria for virologic failure at any time during the study and had a confirmed HIV RNA ≥400 copies/mL
2. Discontinuation from study medications for any reason except withdrawal of consent and the last plasma HIV-1 RNA >400 copies/mL.
3. Paired resistance data for 13 baseline and on study samples

In general, the results reported by sponsor were consistent with independent analysis performed by DAVP. ATV-associated resistance substitutions arose in one subject (AI424451-14-69), including M46M/V, V82V/I, I84I/V, and L90L/M (Table 2); however, the sponsor reported that these substitutions did not result in phenotypic resistance to ATV or ATV/RTV (ATV phenotypic fold change: 1.74) as assessed by the Monogram Phenosense GT test.

Table 2. Resistance analysis of subject who failed in AI424451 (PRINCE II) (DAVP analysis).

USUBJID	WEIGHTCC (BL)	ARVEXP	VISIT	PI_V11	PI_G16	PI_D30	PI_E35	PI_K45	PI_M46	PI_Q61	PI_L63	PI_I72	PI_V82	PI_I84	PI_L90	RT_P236	RT_K32	RT_V35	RT_I37	RT_K43	RT_K82	RT_E89	RT_K101	RT_Q102	RT_K103	RT_D113	RT_I135	RT_I142	RT_C162	RT_K173	RT_I178	RT_V179	RT_M184	RT_Q197	RT_T200	RT_Q207	RT_F214	RT_P225	RT_V241	RT_P243	RT_E44	RT_V246	RT_V254	RT_I270	RT_A272	RT_I274	RT_R277	RT_L283	RT_P294	RT_L301
AI424451-14-31	5 - < 10 kg	ARV EXPER	PRETREAT															K					K/					S	A				E	A	G	L					Q		P						
AI424451-14-31	5 - < 10 kg	ARV EXPER	WEEK 32															K					K/R					S	A		I/V	V/I	E	A	E/G	L					Q		P			R/K			
AI424451-5-32	5 - < 10 kg	ARV EXPER	PRETREAT								P	I/M						I					K	R		T		N/S			D				E	L			V	M		P		R/K			
AI424451-5-32	5 - < 10 kg	ARV EXPER	WEEK 32								P/S	I/M						I					K	R		T		S			D				E	F/L			I/V	I/V/M		P		R/K			
AI424451-14-69	10 - < 15 kg	ARV EXPER	PRETREAT															T			R		K					S	A		I			A	E						Q		S						
AI424451-14-69	10 - < 15 kg	ARV EXPER	WEEK 24										V/A/I/T					T			R	K/E	K					S	A/I/T/V		I	V		A	E						Q		S						
AI424451-14-69	10 - < 15 kg	ARV EXPER	WEEK 12						M/V				V/I	I/V	L/M			T			R	E/G	K					S	I/L/V		I	V		A	E		P/L	V/L			Q		S						
AI424451-33-4	10 - < 15 kg	ARV EXPER	PRETREAT							E	P												K			R							A							M/T				K				
AI424451-33-4	10 - < 15 kg	ARV EXPER	F/U WEEK 6		G/E					E	P	I/T				P/S							K			R							A							M				K				
AI424451-10-102	15 - < 25 kg	ARV EXPER	PRETREAT		E						N	V						I					K	N		M	V	S	A/T			V	E/K	E						Q		P		K				
AI424451-10-102	15 - < 25 kg	ARV EXPER	WEEK 32		E		E/D				N	V					K/E	I/T					K	K/N		M	I/V	S	K/T			M/V		E	E			P/T			Q		P		K				
AI424451-1-98	15 - < 25 kg	ARV EXPER	PRETREAT				D			D/N								T					K			C		F		I/M		K/R									P						
AI424451-1-98	15 - < 25 kg	ARV EXPER	WEEK 12			D/G	D			D/E								T					K			C		F		I/M		K/R									P						
AI424451-1-98	15 - < 25 kg	ARV EXPER	F/U WEEK 2				D			D								T					K			C		F		M		R									P						
AI424451-6-112	15 - < 25 kg	ARV EXPER	PRETREAT				N											T		R			K			M/T	T	S	A	L	V			K	L					Q		P						
AI424451-6-112	15 - < 25 kg	ARV EXPER	WEEK 24				N											T		R			K			M	T	S	A	L	V			K	L					Q		P						
AI424451-6-113	15 - < 25 kg	ARV EXPER	PRETREAT								P							T					K	N				S	A				A	D						Q								
AI424451-6-113	15 - < 25 kg	ARV EXPER	WEEK 16								P							T					K	N				S	A				A	D						Q								
AI424451-14-44	5 - < 10 kg	ARV NAIVE	PRETREAT															T					K					S	T				A	E			I			K		S						
AI424451-14-44	5 - < 10 kg	ARV NAIVE	WEEK 24															T		K/R			K					S	T				A	E			I			K/Q		S						
AI424451-14-44	5 - < 10 kg	ARV NAIVE	WEEK 48					K/R										T					K		D/E		I/M	S	T				A	E			I			K	I/M	S	I/S		L/R			
AI424451-14-65	5 - < 10 kg	ARV NAIVE	PRETREAT								A							T					K					A	E				A	E						Q		P						
AI424451-14-65	5 - < 10 kg	ARV NAIVE	WEEK 48	V/I							A							T					K					A	E			V	A	E						Q		P				P/S		
AI424451-30-8	10 - < 15 kg	ARV NAIVE	PRETREAT							E	P	T						V/I					K					S		I/L/M			T/A	E						E				K		Q		
AI424451-30-8	10 - < 15 kg	ARV NAIVE	WEEK 40							E/G	P	T						V/I	I/L				K					S		I/M		V	A	E						E	V/I			K		Q		
AI424451-6-90	10 - < 15 kg	ARV NAIVE	PRETREAT							N								T					K			V		S	T			V	P	A	E							P						
AI424451-6-90	10 - < 15 kg	ARV NAIVE	WEEK 32							N								T					K			V		S	T			V	P/S	A	E							P						
AI424451-44-45	15 - < 25 kg	ARV NAIVE	PRETREAT				D	K/R			P												K	N		T	M	S					A		L						S						
AI424451-44-45	15 - < 25 kg	ARV NAIVE	F/U WEEK 2				D				P												K	N		T	M	S					A		L			I/V			P/S						
AI424451-44-45	15 - < 25 kg	ARV NAIVE	WEEK 32				D				P							V/I					K	N		T	M	S					A		L						S						
AI424451-5-1	25 - < 35 kg	ARV NAIVE	PRETREAT									V	I					I					K	N				S					A		L			V	K				K				
AI424451-5-1	25 - < 35 kg	ARV NAIVE	WEEK 24									V	I					I			K/R		K	N				S					A		L			V	K				K				V

Blue, known PI resistance-associated substitutions; red, known resistance-associated substitutions to various RT inhibitors; yellow, concurrence between sponsor and virology

Additional substitutions associated with resistance to other PIs also arose one subject each, including V11V/I, G16G/E, D30D/G, E35E/D, K45K/R, L63P/S, and I72I/T. Q61D and Q61/E/G emerged in two subjects who failed treatment with ATV/RTV. Three subjects developed M184V in the reverse transcriptase protein of their virus, and all 3 exhibited phenotypic resistance to emtricitabine (FTC) and lamivudine (3TC) plus partial sensitivity to ddI (Table 2).

4.5 Baseline Resistance Analysis

Given that the number of subjects in both studies was small, there were only a few treatment failures from each study, and only substitutions of interest were reported by the sponsor, a comprehensive baseline resistance analysis was not performed by DAVP. The sponsor did not identify any baseline substitutions that correlated with treatment failure, and in fact, screened subjects prior to enrollment to eliminate subjects with known resistance-associated substitutions that lead to ATV failure.

In Study AI424397 (PRINCE I), 32 of 56 subjects were treatment naïve and 5 of these subjects had no resistance-associated substitutions for PIs, NNRTIs, or NRTIs (defined by IAS-USA and Stanford HIV Drug Resistance Database) at baseline. The remaining 27 treatment-naïve subjects had HIV-1 isolates with combinations of resistance-associated substitutions for PIs (n=27) and NNRTIs and/or NRTIs (n=27) (IAS-USA and Stanford HIV Drug Resistance Database) at baseline; none of these isolates exhibited phenotypic resistance to ATV or ATV/RTV as assessed by the Monogram Phenosense GT test or contained the combination of substitutions defined in the exclusion criteria. In Study AI424451 (PRINCE II), 39 of 78 subjects were treatment naïve and all 29 treatment-naïve subjects had HIV-1 isolates with combinations of resistance-associated substitutions for PIs (n=29) and NNRTIs and/or NRTIs (n=29) (IAS-USA and Stanford HIV Drug Resistance Database) at baseline; none of these

isolates exhibited phenotypic resistance to ATV or ATV/RTV as assessed by the Monogram Phenosense GT test or contained the combination of substitutions defined in the exclusion criteria.

5 Conclusion

This supplemental NDA is approvable from the Clinical Virology perspective.

In general, the resistance analysis results reported by the sponsor were consistent with independent analysis of the resistance data performed by Clinical Virology. No treatment-emergent ATV-associated substitutions were detected among the nine treatment failures in Study AI424397 (PRINCE I), but four other known PI resistance-associated substitutions arose in one subject each (L19I/R, M36M/I, H69K/R, and I72I/V). The sponsor reported that none of the subjects acquired phenotypic resistance to ATV, ATV/RTV, or any NRTI or NNRTI. In Study AI424451 (PRINCE II), ATV-associated resistance substitutions arose in one subject (AI424451-14-69), including M46M/V, V82V/I, I84I/V, and L90L/M; however, the sponsor reported that these substitutions did not result in phenotypic resistance to ATV or ATV/RTV (ATV phenotypic fold change: 1.74) as assessed by the Monogram Phenosense GT test. Additional substitutions associated with resistance to other PIs also arose one subject each, including V11V/I, G16G/E, D30D/G, E35E/D, K45K/R, L63P/S, and I72I/T. Q61D and Q61/E/G emerged in two subjects who failed treatment with ATV/RTV. Three subjects developed M184V in the reverse transcriptase protein of their virus, and all 3 exhibited phenotypic resistance to emtricitabine (FTC) and lamivudine (3TC) plus partial sensitivity to ddI. In general, the resistance data sets for PRINCE I and PRINCE II were too small to draw any significant conclusions, and the resistance patterns were consistent with those observed in previous cohorts exposed to ATV and ATV/RTV. There were no novel resistance findings associated with these two pediatric clinical trials.

6 Package Insert

6.1 Proposed Package Insert (with Reviewer-recommended changes)

Only sections relevant to Clinical Virology are shown, with recommended changes highlighted in red:

1 INDICATIONS AND USAGE

REYATAZ® (atazanavir (b) (4)) is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection for patients 3 months and older and weighing at least 10 kg.

LIMITATIONS OF USE:

REYATAZ is not recommended for use in pediatric patients below the age of 3 months due to the risk of kernicterus.

- (b) (4)
- Use of REYATAZ/ritonavir in treatment-experienced patients should be guided by the number of baseline primary protease inhibitor resistance substitutions [*see Microbiology (12.4)*].

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 (b) (4) *Microbiology* (12.4).]

12.1 Mechanism of Action

Atazanavir is an ~~azapeptide~~ (b) (4) HIV-1 antiviral drug [see (b) (4) *Microbiology* (12.4)]

12.4 Microbiology

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 21.

Table 21: 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]

Table 21: 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 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.

Clinical Studies of Pediatric Subjects in PRINCE I and PRINCE II: No treatment-emergent ATV-associated substitutions were detected among treatment failures in PRINCE I, but four known resistance-associated substitutions to other PIs arose in one subject each (L19I/R, M36M/I, H69K/R, and I72I/V). None of these viruses acquired phenotypic resistance to ATV, ATV/RTV, or any NNRTI or NRTI. In PRINCE II, ATV-associated resistance substitutions arose in the virus of one subject, including M46M/V, V82V/I, I84I/V, and L90L/M; however, these substitutions did not result in phenotypic resistance to ATV (ATV phenotypic fold change: 1.74, using a commercial investigational assay with an ATV cutoff of 2.2 fold change). Additional substitutions associated with resistance to other PIs also arose in the viruses of one subject each, including V11V/I, G16G/E, D30D/G, E35E/D, K45K/R, L63P/S, and I72I/T. Q61D and Q61/E/G emerged in the viruses of two subjects who failed treatment with ATV/RTV. Viruses from three subjects developed M184V in the reverse transcriptase, and all three exhibited phenotypic resistance to emtricitabine and lamivudine.

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 was a 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, NNRTIs, and (b) (4) NRTIs. The mean time of prior exposure to antiretrovirals was 139 weeks for PIs, 85 weeks for NNRTIs, and 283 weeks for NRTIs (b) (4) 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 27. 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 (b) (4) quantification. [See (b) (4) *Microbiology*, Tables 22 and 23 (12.4).]

6.2 Final Approved Package Insert

The final approved Package Insert was not complete at the time this review was due.

7 Recommendations

None.

8 References

None.

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

/s/

ERIC F DONALDSON
05/09/2014

JULIAN J O REAR
05/09/2014

VIROLOGY FILING CHECKLIST FOR NDA or Supplement

NDA Number: 206352 **Applicant:** Bristol-Myers Squibb **Stamp Date:** 012/02/2013

Drug Name: Atazanavir **NDA Type:** Pediatric **PDUFA Goal Date:** 06/02/2014

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?			Not Applicable
5	Has the applicant submitted any required animal model studies necessary for approvability of the product based on the submitted draft labeling?			Not Applicable
6	Has the applicant submitted all special/critical studies/data requested by the Division during pre-submission discussions?			Not Applicable
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 for virologic outcome measures 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		

VIROLOGY 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__

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

There are currently no issues from the Clinical Virology perspective.

Eric F. Donaldson, Ph.D. Date
Clinical Virology Reviewer

Jules O'Rear, Ph.D. Date
Clinical Virology Team Leader

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

/s/

ERIC F DONALDSON
01/10/2014

JULIAN J O REAR
01/10/2014

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 19 December 2013

TO: NDA 206352

FROM: Bryan S. Riley, Ph.D.
Team Leader (Acting)
OPS/New Drug Microbiology Staff

THROUGH: Stephen E. Langille, Ph.D.
Master Review Microbiologist
OPS/New Drug Microbiology Staff

cc: Sammie Beam, RPh
Regulatory Project Manager
OND/Division of Antiviral Products

SUBJECT: Product Quality Microbiology assessment of Microbial Limits for Reyataz (atazanavir sulfate) (b) (4) Powder for Oral Use [Submission Date: 02 December 2013]

The Microbial Limits specification for Reyataz (b) (4) Powder for Oral Use is acceptable from a Product Quality Microbiology perspective. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.

Reyataz is a powder which is mixed with food or beverage for oral administration. Once mixed with vehicle for administration, the drug product may be held at room temperature for up to one hour.

The drug product is tested for Microbial Limits at release using a method consistent with USP Chapter <61> (Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests) and <62> (Microbiological Examination of Non-sterile Products: Tests for Specified Microorganisms). The Microbial Limits acceptance criteria are consistent with USP Chapter <1111> (Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use).

M E M O R A N D U M

Table 1 – Microbial Limits Specifications

Test	Acceptance Criteria
Total Aerobic Microbial Count (USP <61>)	NMT (b) (4) CFU/g
Total Yeast and Mold Count (USP <61>)	NMT (b) (4) CFU/g
E. coli (USP <62>)	Absent in (b) (4) g

The Microbial Limits test methods were verified to be appropriate for use with the drug product following procedures consistent with those in USP Chapter <61> and <62>.

The drug product will not be tested for Microbial Limits as part of the post-approval stability protocol. However, the drug product has very low water content (NMT (b) (4)%) and is therefore not likely to support microbial proliferation. The long term stability studies also demonstrated no increase in microbial content over time.

ADEQUATE

Reviewer Comments – The microbiological quality of the drug product is controlled via a suitable testing protocol.

END

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

/s/

BRYAN S RILEY
12/23/2013

STEPHEN E LANGILLE
12/23/2013