

Official Title of Study: A PROSPECTIVE SINGLE ARM OPEN-LABEL, INTERNATIONAL,
MULTICENTER STUDY TO EVALUATE THE SAFETY, EFFICACY AND
PHARMACOKINETICS OF ATAZANAVIR (ATV) POWDER BOOSTED
WITH RITONAVIR (RTV) WITH AN OPTIMIZED NRTI BACKGROUND
THERAPY, IN HIV INFECTED, ANTIRETROVIRAL, NAIVE AND
EXPERIENCED PEDIATRIC SUBJECTS FROM 3 MONTHS TO LESS
THAN 11 YEARS. (PEDIATRIC ATAZANAVIR INTERNATIONAL
CLINICAL EVALUATION: THE PRINCE II STUDY)

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STATISTICAL ANALYSIS PLAN

A PROSPECTIVE SINGLE ARM OPEN-LABEL, INTERNATIONAL, MULTICENTER STUDY TO EVALUATE THE SAFETY, EFFICACY AND PHARMACOKINETICS OF ATAZANAVIR (ATV) POWDER BOOSTED WITH RITONAVIR (RTV) WITH AN OPTIMIZED NRTI BACKGROUND THERAPY, IN HIV INFECTED, ANTIRETROVIRAL, NAIVE AND EXPERIENCED PEDIATRIC SUBJECTS FROM 3 MONTHS TO LESS THAN 11 YEARS. (PEDIATRIC ATAZANAVIR INTERNATIONAL CLINICAL EVALUATION: THE PRINCE II STUDY)

PROTOCOL AI424451

VERSION 2.0

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- [REDACTED]

Research Hypothesis:

Regimens consisting of ATV powder boosted with RTV with an optimized dual-NRTI backbone are safe and well tolerated in pediatric subjects ≥ 3 months to < 11 years who are ≥ 5 kg to < 35 kg.

Schedule of Analyses:

The primary analysis will be conducted when Week 24 data of all treated subjects are available (in Stage 1) to confirm the safety of ATV powder with RTV in pediatric patients. The final analysis will be conducted after the last subject in Stage 2 completes the study. Other analyses may be conducted if needed for submission to health authorities and at the request of the DMC.

2 STUDY DESCRIPTION

2.1 Study Design

This study is a Phase 3b prospective, international, multicenter, non-randomized study of a cohort of HIV infected pediatric subjects ≥ 3 months to < 11 years of age and weight ≥ 5 kg to < 35 kg, treated with ATV powder and RTV optimized regimens.

The study consists of two stages:

Stage 1

Subjects must be ≥ 3 months to < 11 years of age at the time of first treatment. In-clinic study visits in Stage 1 will be at Day 1, Week 2, Week 4, then every 4 weeks through Week 16, then every 8 weeks through a minimum of 24 weeks or a maximum of 48 weeks.

Dosing of ATV in Stage 1 is performed only with the powder formulation, dosed according to weight, as outlined in Protocol Table 3.1.1-1. When dosing with ATV powder, RTV oral solution is dosed at 80 mg for body weight less than 25 kg, and RTV oral solution or RTV capsules or tablets 100 mg for body weight 25 kg to less than 35 kg.

Subjects who reach the weight of ≥ 35 kg during Stage 1 must immediately enter Stage 2 and be switched to the capsule formulation of ATV and the corresponding capsule/tablet formulation of RTV.

Subjects who do not reach the weight of ≥ 35 kg during Stage 1 continue on the powder formulation of ATV through the end of the 48-week period of Stage 1 and then move into Stage 2 while remaining on the powder formulation.

Subjects who did not have the opportunity to reach Week 48 during Stage 1 by the time the last treated subjects reaches Week 24 will have a final Stage 1 status assessment performed and will immediately move in Stage 2 while remaining on ATV powder. These subjects will follow the assessment and in-clinic study visits specified in Stage 2.

Stage 2

In-clinic study visits in Stage 2 will be conducted every 12 weeks through the end of study participation.

Dosing of ATV in Stage 2 may include subjects taking ATV powder and subjects taking ATV capsules, dosed according to weight, as outlined in Protocol Tables 3.1.1-1 and 3.1.1-2, respectively. When dosing with ATV powder, RTV oral solution is dosed at 80 mg for body weight less than 25 kg and is dosed at 100 mg RTV oral solution or tablets/capsules for body weight 25 kg to less than 35 kg; when dosing with ATV capsules, RTV (capsules/tablets) is dosed at 100 mg.

10% aspartame ATV powder to 4.2% aspartame ATV powder transition:

Subjects who remain on ATV powder formulation in Stage 2 must be switched to the new 4.2% aspartame ATV oral powder formulation at their next regular visit provided that IRB/IEC approval of the amended protocol has been received. Dose recommendation of new 4.2% aspartame ATV powder is the same as for the 10% aspartame ATV powder and will be determined by weight.

Subjects who reach the age of 12 years or weight of ≥ 35 kg during Stage 2 must be switched from the powder formulation of ATV to the capsule formulation of ATV.

Powder-to-Capsule Transition:

Subjects who are transitioning from powder to capsule, either at entry to Stage 2 or at any point during Stage 2, will be required to return to the clinic for two subsequent powder-to-capsule transition visits 4 weeks and 8 weeks after the switch is initiated.

- Dose of the ATV capsule will be determined by weight, according to Protocol Table 3.1.1-2; RTV is dosed at 100 mg (capsules or tablets) when dosing with the ATV capsule;
- Subjects who are unable to swallow the capsule by the end of the 8-week transition period will be required to be discontinued from the study;
- Subjects who complete a successful transition to capsules will continue in Stage 2 and will be dosed according to the recommendations provided in Protocol Table 3.1.1-2.

- Subjects are required to switch to capsule in Stage 2 when they reach 35 kg or 12 years of age. However, subjects who reach a weight of 25 kg or 6 years of age during Stage 2 may, at the discretion of the investigator and caregiver, choose to attempt switch to the solid dosage forms of ATV/RTV.

Stage 2 participation ends when:

- a subject reaches the age of 18 years, or
- a subject's country has an approved and available pediatric indication whose requirements are met by the subject; the subject will then transition off of the study and will be dosed according to those local guidelines.

If an approved pediatric indication for ATV capsule becomes available for a subject who is dosing with the powder formulation, the powder-to-capsule transition will occur within the study within an 8-week timeframe as described above. After the 8-week transition period, the subject will be discontinued from the study, regardless of tolerability of the capsule.

2.2 Treatment Assignment

At the start of the screening period, the investigative staff will call the Assignment Center via an Interactive Voice Response System (IVRS) designated by the Sponsor to enroll the subject and to obtain a subject/patient identification number (PID), which must be recorded on the Case Report Form (CRF). This unique subject number must be used on all further documentation and correspondence referring to this particular subject.

A minimum of 56 treated subjects on ATV powder with at least 24 weeks of follow-up are needed with a minimum number of subjects with at least 24 weeks of follow-up from the following weight bands:

- Minimum 5 subjects (on 150 mg ATV powder and 80 mg RTV) between 5 - < 10 kg,
- Minimum 6 subjects (on 200 mg ATV powder and 80 mg RTV) between 5 - < 10 kg,
- Minimum 10 subjects between 10 - < 15 kg,
- Minimum 10 subjects between 15 - < 25 kg,

In the event that the minimum number of subjects in any one weight band has been met while the other weight bands remain substantially under-enrolled, further enrollment in the fully enrolled weight band may be temporarily put on hold. Enrollment will continue for the under-enrolled groups until the minimum number of treated subjects has been achieved (except for 25 - < 35kg weight band). After this point, enrollment will continue for all weight bands until at least a total of 95 subjects started treatment in order to have a minimum number of 56 treated subjects with a minimum 24 weeks follow-up. In the event that the minimum number of subjects (overall and/or per weight band) with a minimum 24 weeks follow-up is projected not to be met due to higher than projected early discontinuation rate, then enrollment target will be re-adjusted during enrollment period or enrollment re-opened during the study to replace these subjects.

Subjects in a lower weight band who transition to the 25 - < 35 kg weight band during Stage 1 will have a Week 2 Intensive PK assessment completed.

A total of 30 ARV experienced subjects treated with ATV powder for minimum 24 weeks will be enrolled in this study, which will be tracked through the IVRS. Treatment experienced subjects are defined by a previous exposure to antiretroviral drugs (ARVs) through either prior treatment for their HIV disease or through a post natal treatment with ≥ 1 ARVs for prevention of MTCT. In the event that the minimum number of ARV experienced subjects remains substantially under-enrolled, then further enrollment of ARV-naïve subjects may be temporarily put on hold until the target of 30 ARV experienced is met. After this point, enrollment will continue for both ARV naïve and experienced subjects. and) and treated with ATV powder for minimum 24 weeks.

2.3 Blinding and Unblinding


Not applicable (This study is open label).

2.4 Protocol Amendments

This section describes protocol amendments that affect statistical analyses.

Amendment 2 allowed use of both brand and generic locally approved and available NRTIs by removing statements not intended to have been in protocol section 6.7.1.

Amendment 4 included the following changes:

- Allowed that also the Ritonavir Trough plasma concentration at each scheduled visit from Week 4 through Week 48 will be evaluated from the sample tube collected for the ATV Trough plasma concentration assessment as ATV/RTV can be assessed simultaneously.
- Clarified objective and aligned with the primary objective measurements used in the AI424397 sister study. The frequency of AEs and lab abnormalities will be summarized but is not part of the primary study objective analysis
- 
- Updated Section 8.0 to be aligned with the Statistical Analysis Plan.

Amendment 5 included the following changes:

- To change the whole treatment regimen, including ATV, in patients with confirmed virologic failure or virologic rebound above 1000 copies/mL based on the resistance profile at failure in accordance with the recommendations from guidelines as per FDA comments on sister study AI424397 amendment 05.
- To modify the definition of virologic failure in accordance with the updated 2011 DHHS pediatric guidelines and clarified the virologic failure criteria to discontinue a subject in the study.

Amendment 7 included the following changes:

- To increase the inclusion upper age limit to < 11 years of age and updated title, research hypothesis and objectives accordingly.
- Added palatability/taste as exploratory objective.
- Following the AI424-397 intensive PK analysis, added new 5 - < 10kg cohort with higher ATV dose (200 mg ATV and 80 mg RTV)
- Increased the sample size from 75 to 95 subjects in order to complete new cohort and have a minimum of 56 subjects with 48 weeks of follow-up on ATV powder overall and minimum number of subjects required per weight band.
- To switch all subjects in stage 2, who are still on the current atazanavir oral powder formulation (10% aspartame), to the new 4.2% aspartame atazanavir oral powder formulation and to collect palatability/acceptability data at the time of switch and after the switch.
- Clarified that subjects with a confirmed HIV RNA of ≥ 1000 copies/mL (after Week 24) should be discontinued.
- Added that subject diaries should be used for subjects switching to the new 4.2% aspartame ATV powder formulation in stage 2 and as long as the subject is on the new ATV powder or maximum duration of one year, whichever comes first.
- Added Adherence/Tolerability assessment procedures and note that the assessments only apply to subjects remaining on ATV powder in Stage 2 in Time and Event Table and described the palatability assessment and analyses.
- To allow use of RTV capsules or Tablets for subjects enrolled in the 25 - < 35 kg weight band.
- Added new assay (Abbott RealTime HIV-1 RNA) to be used when Roche Amplicor HIV RNA is discontinued.
- Updated the list of intensive PK steady state parameters in PK analyses.
- Removed upper age criterion as milestone from maximum study duration in stage 1 and changed the maximum age for powder to capsule transition from 8 to 12 years old.

Amendment 8 included the following changes:

- To remove the minimum number of 6 subjects required for the 25 - < 35kg weight band with 48 weeks of ATV powder.
- To modify primary endpoint study duration from 48 weeks to a minimum of 24 weeks and to modify key secondary objectives by adding Week 24 efficacy endpoint.
- To increase the blood volume collection from 1 up to 2 mL for HIV RNA testing when switching to the new Abbott RealTime HIV-1 assay after the Roche Amplicor assay is discontinued.

3 OBJECTIVES

3.1 Primary

To describe the safety of ATV powder formulation boosted with RTV based HAART regimens in pediatric subjects dosed through a minimum 24 weeks, as measured by the frequency of deaths, serious adverse events and discontinuation due to AEs.

3.2 Secondary

- To describe efficacy as measured by proportion of subjects with a virologic response as defined by HIV RNA levels < 50 copies/mL and < 400 copies/mL by Roche Amplicor[®] HIV-1 RNA Assay (version 1.5), or Abbott RealTime HIV-1 assay after the Roche Amplicor assay is discontinued, at Week 24 and Week 48 of ATV powder formulation.
- To describe the pharmacokinetic profile of ATV powder formulation with RTV in pediatric subjects weighing 25 - < 35 kg and/or 6 - < 11 years of age and for new 5 - < 10 kg cohort (200mg ATV and 80 mg RTV) in terms of ATV C_{max}, C_{min} and AUC.

[REDACTED]

4 ENDPOINTS

4.1 Primary Endpoint

- Safety, as measured by the frequencies of deaths, SAEs through Week 48 on ATV powder, and discontinuations due to AEs through Week 48 on ATV powder.

All safety data up through Week 48 on ATV powder regardless of stage will be included in the safety analysis.

4.2 Secondary Endpoints

- Proportions of subjects with HIV RNA < 50 c/mL and < 400 c/mL at Week 24 and Week 48 of ATV powder formulation;
- Summary statistics for PK parameters (C_{max}, C_{min} and AUC) of ATV powder.

5 SAMPLE SIZE AND POWER

Sample size is not based on power calculations. A total of Approximately 95 subjects are planned for this study in order to treat approximately 10-15 subjects in the new 5 - < 10 kg (200mg ATV and 80 mg RTV) cohort and have a minimum number of 56 treated subjects with minimum 24 weeks follow-up on ATV powder based on an expected drop-out rate of approximately 30%. This study plans to enroll approximately 160 subjects, which will result in approximately 95 treated subjects due to an expected screen failure rate of 40%.

A target sample size of 95 treated subjects can detect with 80% probability, a safety event that occurs at a per subject incident rate of 1.7%.

A target sample size of 95 treated subjects can produce an exact binomial 95% confidence interval (CI) within $\pm 10.5\%$ for a response rate of 50.5% for the modified intent-to-treat (ITT) analysis.

6 STUDY PERIODS, TREATMENT REGIMEN AND POPULATIONS FOR ANALYSES

6.1 Study Periods

6.1.1 *Pre-Treatment Period*

The pre-treatment period begins at the first visit until initiation of active study therapy (ie, ATV).

Measurements taken before Day 1 (ie, the first dose of active study therapy) are considered pre-treatment for all data domains. In addition, measurements taken on Day 1 are considered pre-treatment for the following data domains: demography, disease history, ECG, laboratory test results, medical history, physical examination, physical measurements, subject status, viral genotyping, viral phenotyping, virology and vital signs.

6.1.2 *On-Treatment Period*

The on-treatment period begins after Day 1 and ends on the last dose of study therapy. In addition, measurements taken on Day 1 are considered on-treatment for the following data domains: AEs, drug dispensation, exposure, inclusion/exclusion, non-study medications, sample collection, sample informed consent and sample reference.

For Stage 1, the on-treatment period ends on the visit date entered on the end of Stage 1 treatment subject status CRF. For Stage 2, the Stage 2 on-treatment period begins on the visit date plus 1 day.

Analyses of the following select endpoints extend the on-treatment period to include measurements through a specified number of days after the last dose of study therapy:

- Efficacy (HIV RNA and CD4; [Sections 7.5.1 through 7.5.3](#)): 4 days after the last dose of study therapy. The 4-day cut-off reflects the point at which minimal antiviral activity related to ATV is present. It is also expected that minimal drug exposure and undetectable drug levels will be present beyond 4 days post-dose.
- Resistance (viral genotyping and phenotyping; [Section 7.5.4](#)): 10 days after the last dose of study therapy. The 10-day cut-off reflects the point at which the virus reverts rapidly to wild type and resistant variants become minor variants that cannot be detected reliably.
- Safety (AEs, ECGs, vital signs and laboratory tests; [Section 7.6](#)): 30 days after the last dose of study therapy to account for safety reporting per protocol.

6.1.3 Off-Treatment Follow-up Period

The off-treatment follow-up period begins after the last dose of study therapy and ends at the last follow-up visit.

Measurements taken after the last dose of study therapy are considered follow-up.

6.2 Treatment Regimen

The treatment regimen is ATV powder with RTV liquid (or RTV capsules/tablets for 25 - < 35 kg weight band only) for subjects enrolled in this study. The dose will be determined by the subject's weight on the date of first dose (Day 1). Refer to Protocol Section 3.1 for the dosing guidelines. Subjects must be dose adjusted once they exceed the upper limit of their current weight band. Subjects reaching their 12th birthday or reaching a weight ≥ 35 kg should be transitioned to the capsule formulation of ATV.

6.3 Populations for Analyses

Populations consist of enrolled and treated subjects grouped according to baseline weight band:

- Enrolled subjects are those who signed an informed consent form and were assigned a Patient Identification number (PID). This cohort is used to assess subject status and deaths.
- Treated subjects are enrolled subjects who received at least 1 dose of active study therapy (ATV). This cohort is used to assess all data domains.
- **Week 24 ATV Powder Cohort** consists of treated subjects who did not switch to ATV capsule before analysis Week 24 or before their HIV RNA Week 24 assessment (see [Section 8.1](#)). This cohort is used to assess efficacy of ATV powder through Week 24.
- **Eligible Week 48 ATV Powder Cohort:** Subjects who initiated study therapy at least 48 weeks prior to LPLV date and did not switch to ATV capsule before analysis Week 48 or before their HIV RNA Week 48 assessment. This cohort is used to assess efficacy of ATV powder through Week 48.

7 STATISTICAL ANALYSES

Statistical analyses are performed using the version of UNIX SAS or S-Plus in production at BMS, unless specified otherwise.

Summaries are presented by baseline weight band (and ATV initial dose for 5 - < 10 kg) (5 - < 10 kg (ATV 150mg), 5- < 10 kg (ATV 200mg), 10 - < 15 kg, 15 - < 25 kg, 25 - < 35 kg) and total for treated subjects, unless specified otherwise.

7.1 General Methods

Categorical variables are summarized with counts and percents or with proportions (number with event divided by number evaluable) and percents, depending on the endpoint.

Continuous variables are summarized with univariate statistics (eg, n, mean, median, minimum, maximum, quartiles, standard deviation [SD]). Changes from baseline in continuous variables are summarized with univariate statistics (eg, n, mean, standard error [SE], median, interquartile range [IQR]).

Longitudinal summaries of efficacy and safety parameters use pre-defined visit week windows (see [Section 8.1](#)). In addition, analyses of HIV RNA use pre-defined analysis week windows (see [Section 8.1](#)).

Subjects must have a baseline measurement and at least 1 on-study measurement (ie, after the first dose of study therapy) to be evaluable for change from baseline analyses for observed values. In addition, subjects must have a baseline measurement to be evaluable for longitudinal summaries of parameter values and changes from baseline based on observed values.

Summaries of relevant protocol deviations, non-study medications, AEs (except multiple AEs in [Section 8.2.6](#)), and laboratory abnormalities present incidence rates, i.e., numbers of subjects with unique events. Thus, multiple occurrences of the same event are counted only once per subject.

By-subject listings sorted by baseline weight band and PID are provided for select endpoints (see [Section 9.2](#)). Listings display all events regardless of study period unless specified otherwise, and identify ATV formulation (powder or capsule).

For non-study medications, imputed start and end dates are used only for classification of medications into study periods for summary reporting purposes (ie, prior, concomitant, and post-treatment). The actual dates entered on the CRF are reported in by-subject listings.

For AEs, imputed onset dates are used only for classification of AEs into study periods for summary reporting purposes (ie, pre-treatment, on treatment and follow-up) and to calculate duration of events. The actual dates entered on the CRF are reported in by-subject listings.

Subjects who move to another investigative site during the study are classified according to original investigative site, country and region.

Formats of tables, listings and graphs are described in the AI424451 Data Presentation Plan.

7.2 Study Conduct

Relevant protocol deviations are summarized. Relevant protocol deviations are those that could potentially affect the interpretability of the study results, which is related, but not limited to:

- Some inclusion or exclusion criteria
- Subject management, such as:
 - Incorrect dosing or study treatment assignment;
 - Use of prohibited concomitant medications;
 - Subjects not withdrawn from treatment or study despite having met specified criteria for withdrawal.

A subject is considered to have a deviation of an inclusion or exclusion criterion only if all pre-treatment measurements fail the criterion. [Appendix 1](#) describes the relevant protocol deviations that can be programmed from the database.

7.3 Study Population

7.3.1 Disposition of Subjects

7.3.1.1 Pre-Treatment Subject Status and Accrual

Pre-treatment subject status is summarized. This presents the number of subjects enrolled, treated and not treated. Reasons for not treated are also included (eg, AE, death, lost to follow-up).

Enrollment at each investigative site by country is summarized for enrolled subjects and treated subjects pooled across baseline weight band.

7.3.1.2 End of Stage 1 Treatment Subject Status

End of Stage 1 treatment subject status is summarized. This presents the number of subjects treated, completed the Stage 1 treatment period, not completed the Stage 1 treatment period, continuing in the study, and not continuing in the study. Reasons for not completing the Stage 1 treatment period are also included (eg, lack of efficacy, AE, death, lost to follow-up). For subjects continuing in the study, the next phase entered is also shown (ie, Stage 2 transition to capsule; Stage 2; safety follow-up).

See [Section 7.4.2](#) for indentifying subjects who discontinued ATV powder.

7.3.1.3 End of Stage 2 Treatment Subject Status

End of Stage 2 treatment subject status is summarized for treated subjects who entered Stage 2. This presents the number of subjects who entered Stage 2, completed the Stage 2 treatment period, not completed the Stage treatment period, continuing in the study to safety follow-up, and not continuing in the study. Reasons for not completing the Stage 2 treatment period are also included (eg, lack of efficacy, AE, death, lost to follow-up).

7.3.1.4 End of Study Subject Status

End of study subject status is summarized for treated subjects who entered safety follow-up. This presents the number of subjects who entered safety follow-up, completed the study, and not completed the study. Reasons for not completing the study are also included (ie, subject withdrew consent, death, lost to follow-up, other). Percentages are based on subjects with end of study subject status CRFs.

7.3.2 Demographic and Other Baseline Characteristics

Summaries identify the number and percent of subjects with missing measurements as ‘NOT REPORTED’.

Baseline is the last value measured pre-treatment (see [Section 6.1.1](#)).

Demographics and baseline disease characteristics are also summarized by prior ARV use (ARV naive, ARV experienced).

7.3.2.1 Demographics

The following demographics are summarized: age at consent (months), age at first dose of study therapy (months), gender, race, ethnicity (Hispanic/Latino, not Hispanic/Latino), geographic region and country.

7.3.2.2 Baseline Disease Characteristics

The following baseline HIV disease characteristics are summarized:

- HIV RNA (\log_{10} c/mL), HIV RNA categories (< 30,000, 30,000 - 100,000, > 100,000 c/mL);
- CD4 (cells/mm³), CD4 categories (< 50, 50 - < 200, 200 - < 350, 350 - < 500, 500 - < 750, 750 - < 1000, 1000 - < 1500, 1500 - < 2000 and \geq 2000 cells/mm³);
- CD4 percent (%) and CD4 percent categories (< 15, 15 - < 25, \geq 25).
- Prior ARV use (ARV naive, ARV experienced).

7.3.2.3 Other Baseline Characteristics

Laboratory Tests at Baseline

Laboratory tests at baseline are summarized by toxicity grade (normal; grade 1, 2, 3, 4; see [Section 7.6.6.1](#)).

ECG at Baseline

See [Section 7.6.7](#).

Physical Measurements at Baseline

Physical measurements are summarized: height (cm), weight (kg), body mass index (BMI; kg/m²), body surface area (BSA; m²), head circumference (cm). See also [Section 7.6.8](#).

Vital Signs at Baseline

Vital signs are summarized: systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (bpm).

Pre-Treatment Events

All grades pre-treatment events are summarized within system organ class.

Pre-Treatment CDC Class C AIDS Events

Pre-treatment acquired immunodeficiency syndrome (AIDS) events are summarized. Documented clinical diagnoses are used to define AIDS (see Protocol Appendix 3).

Prior Treatments

Prior medications are summarized. Prior medications are those taken before the first dose of study therapy. Medications are presented alphabetically by anatomic class, therapeutic class and generic name using the World Health Organization (WHO) dictionary.

7.4 Extent of Exposure

Extent of exposure is presented for treated subjects.

7.4.1 Study Therapy

Time on therapy is summarized for each study drug formulation (ATV powder, ATV capsule, RTV oral solution, RTV capsule, lamivudine oral solution, zidovudine tablets, etc.). Time on therapy is defined as the number of days between the first dose date and last dose date of the drug formulation.

Average daily dose is summarized for each study drug formulation. Average daily dose is the total amount of drug formulation in dose units divided by time on therapy.

7.4.2 Discontinuation of Study Therapy

Time on ATV powder is described by a Kaplan-Meier curve and life table. Discontinuations of ATV powder are considered events in this analysis, and are identified by subjects with (a) non-missing first dose date of ATV capsule, or (b) missing first dose date of ATV capsule and non-missing last dose date of study therapy. For subjects who have not discontinued ATV powder, time on ATV powder is censored at the last dose date of ATV powder.

See [Section 8.2.1.1](#) for additional conventions.

7.4.3 Interruption or Delay of Study Therapy

Interruptions of ATV and RTV (ATV powder, ATV capsule, RTV oral solution, RTV capsule) greater than 3 consecutive days are summarized. Reasons for interruption are also identified (ie, AE, dosing error, other).

See [Section 8.2.1.2](#) for additional conventions.

7.4.4 Measures of Treatment Compliance

See [Section 7.9](#) for the palatability survey and [Appendix 1](#) for relevant protocol deviations that address treatment compliance.

[REDACTED]

7.5 Efficacy

All efficacy endpoints are secondary and focus on the ATV powder formulation using the extended on-treatment period (see [Section 6.1.2](#)). Values after the first dose date of ATV capsule

are excluded. HIV RNA viral loads are based on results by Roche Amplicor[®] HIV-1 RNA Assay (version 1.5), or Abbott RealTime HIV-1 assay after the Roche Amplicor assay is discontinued.

Longitudinal summaries are presented through Week 48 on ATV powder for the primary analysis and through stages combined for the final analysis.

Efficacy endpoints are also summarized by prior ARV use (ARV naive, ARV experienced).

7.5.1 HIV RNA < 50 c/mL and < 400 c/mL Over Time

Secondary endpoints are the proportions of subjects with HIV RNA < 50 c/mL and < 400 c/mL at each scheduled analysis week on ATV powder over time. Response rates are presented with exact binomial 95% CIs.¹

Response rates are assessed using following approaches with the snapshot algorithm, which uses the last HIV RNA in the pre-defined analysis week window to determine response:

Proportions of subjects with HIV RNA < 50 c/mL and < 400 c/mL through Week 24 (Week 24 ATV Powder Cohort):

- Modified intent-to-treat (ITT): The numerator is based on subjects meeting the response criteria, ie, on-treatment HIV RNA < 50 (< 400) c/mL at the analysis week through Week 24. The denominator is based on all treated subjects in the Week 24 ATV Powder Cohort.

Proportions of subjects with HIV RNA < 50 c/mL and < 400 c/mL through Week 48 (Eligible Week 48 ATV Powder Cohort):

- Modified intent-to-treat (ITT): The numerator is based on subjects meeting the response criteria, ie, on-treatment HIV RNA < 50 (< 400) c/mL at the analysis week through Week 48. The denominator is based on all treated subjects in the Eligible Week 48 ATV Powder Cohort.

Proportions of subjects with HIV RNA < 50 c/mL and < 400 c/mL through Week 48 (Treated Subjects):

- Observed values: Similar to modified ITT, the numerator is based on subjects meeting the response criteria. However, the denominator is based on treated subjects with on-treatment HIV RNA at the analysis week.

Response rates and CIs are presented at baseline and each analysis week over time on ATV powder as follows:

- Through Week 24 for the Week 24 ATV Powder Cohort using modified ITT and observed values;
- Through Week 48 for the Eligible Week 48 ATV Powder Cohort using modified ITT and observed values; Through Week 48 for treated subjects using observed values.
- Through stages combined for treated subjects using observed values.

Longitudinal plots displays response rates using modified ITT versus analysis week through Week 48 by baseline weight band with error bars representing CIs of the reported statistic for the Week 48 ATV powder cohort.

Outcomes

Outcomes for HIV RNA < 50 c/mL and < 400 c/mL are summarized using the snapshot algorithm on modified ITT as follows:

- At Week 24 for the Week 24 ATV Powder Cohort;
- At Week 48 for the Eligible Week 48 ATV Powder Cohort.

Outcomes, other than virologic successes, are based on the primary reason for treatment failure at the analysis week.

Outcome categories are virologic success, virologic failure (HIV RNA ≥ 50 [400] c/mL; discontinued due to virologic failure; discontinued due to other reasons and HIV RNA ≥ 50 [400] c/mL at time of discontinuation; OBT changed), no virologic data in analysis week window (discontinued due to AE or death; discontinued due to other reasons and HIV RNA < 50 [400] c/mL at time of discontinuation; missing data in window but on treatment). See [Appendix 2](#) for more details about the snapshot algorithm.

7.5.2 HIV RNA Changes from Baseline

HIV RNA \log_{10} observed values and changes from baseline are summarized at baseline and each analysis week on ATV powder through Week 48 and stages combined. The last HIV RNA in the pre-defined analysis week window is used.

Longitudinal plots display mean value versus analysis week and mean change from baseline versus analysis week through Week 48 by baseline weight band with error bars representing 1 SE of the reported statistic.

7.5.3 CD4 Changes from Baseline

Observed values and changes from baseline in CD4 cell counts and percents are summarized at baseline and each visit week on ATV powder through Week 48 and stages combined.

Longitudinal plots display CD4 cell count median value versus visit week and median change from baseline versus week on ATV powder through Week 48 by baseline weight band with error bars representing 1 SE of the reported statistic.

CD4 cell counts and changes from baseline are also summarized using last observation carried forward (LOCF) and baseline observation carried forward (BOCF) methods on ATV powder through Week 48. For LOCF, missing values are replaced with the last on-treatment value in the previous visit window; if a subject did not have any on-treatment value, then the baseline value is carried forward. For BOCF, missing values are replaced with the baseline value.

7.5.4 Resistance Profiles

Viral genotypic and phenotypic resistance profiles are assessed for virologic failures. Virologic failures are subjects who meet the criteria for resistance testing per Protocol Section 4.5.1. Only

samples with a confirmed HIV RNA level ≥ 400 c/mL will be tested for genotypic and phenotypic resistance. Note that the threshold of 400 c/mL reflects the limitations of resistance tests used in this study.

HIV 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™ HIV assay (Monogram Biosciences, Inc., CA). HIV substitutions in the reverse transcriptase and protease genomes are determined using the GeneSeq™ HIV assay (Monogram Biosciences, Inc., CA).

Genotypic substitutions at baseline are summarized for virologic failures. This presents subjects with genotypable isolates, those with PI substitutions from genotypable isolates, and those with selected RT substitutions from genotypable isolates using the most current version of the International AIDS Society-USA (IAS-USA) list and Stanford HIV Drug Resistance Database (see [Appendix 3](#)).

Newly emergent genotypic substitutions are summarized analogously for virologic failures without baseline phenotypic resistance to ATV or RTV, using all on-treatment isolates. Newly emergent substitutions are on-treatment substitutions that were not detected at baseline.

Phenotypic resistance at baseline is summarized for virologic failures. This presents subjects with phenotypable isolates and those with phenotypic resistance. Resistance to a drug is defined as a fold change (ie, ratio of the 50% inhibitory concentration [IC50] of the clinical isolate to the IC50 of the reference strain) $>$ the cut-off for reduced susceptibility (see [Appendix 3](#)). Cut-offs may change based on the availability of clinical data

Newly emergent phenotypic resistance is summarized analogously for virologic failures using all on-treatment isolates. This presents subjects with phenotypable isolates and those with phenotypic resistance. Newly emergent phenotypic resistance to a drug is defined as a baseline fold change \leq the cut-off for reduced susceptibility, and an on-treatment fold change $>$ the cut-off for reduced susceptibility.

7.6 Safety

Safety endpoints are assessed using the extended on-treatment period (see [Section 6.1.2](#)), unless specified regardless of onset.

For the primary analysis, key on-treatment summaries are presented for treated subjects on ATV powder through Week 48 (ie, ≤ 54 weeks, the mid-point between Stage 1 Week 48 and Stage 2 Week 12; see [Section 8.1](#)). In addition, the following on-treatment summaries are also presented for treated subjects on ATV powder through Stages 1 and 2 combined: SAEs; AEs leading to discontinuation of study therapy; all grades AEs; grade 2 - 4 related AEs; grade 2 - 4 related AEs occurring with overall incidence $\geq 5\%$; grade 3 - 4 laboratory abnormalities.

For the final analysis, key on-treatment summaries are presented for treated subjects on ATV powder through Stages 1 and 2 combined.

In summaries, values are excluded after the first dose date of ATV capsule (for AEs, values on the first dose date of ATV capsule are also excluded) unless specified otherwise.

Longitudinal summaries are presented through Week 48 on ATV powder for the primary analysis and through stages combined for the final analysis.

The investigators determine the intensity of AEs and the relationship of AEs to study therapy. The investigators' terms are coded and grouped by system organ class using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) in production at BMS.

In order to account for AEs with multiple occurrences in the same subject, AE records are collapsed for each subject and preferred term when records have the same onset date, or when records are contiguous or overlapping (see [Section 8.2.6](#)). All AE presentations are based on collapsed records.

AEs are presented by system organ class and preferred term, both in descending order of incidence of total, unless specified otherwise.

Summaries of AEs include both non-serious and SAEs as defined in the protocol, unless specified otherwise. AEs with missing intensity are included only in summaries of all grades (related or regardless of relationship to study therapy). If a subject had an AE with different intensities during the treatment period, then only the greatest intensity is reported. If relationship to study therapy is missing, the AE is included in summaries of AEs related to study therapy.

Select MedDRA preferred terms in [Section 7.6.4](#) may change according to the current version of MedDRA in production at BMS and review from a BMS physician prior to database lock.

7.6.1 Deaths

Deaths are listed for enrolled subjects regardless of onset. The death listing contains date of death, study days to death, source of information, and cause of death. Deaths from multiple sources of information are listed (ie, Status or AE/SAE CRF).

Deaths are identified from the following sources:

- Status data: study discontinuation reason of death.
- AE/SAE data: MedDRA higher level, lower level or preferred term contains 'death'; SAE outcome of death; SAE category of death; death date.

7.6.2 Other Serious Adverse Events

SAEs are summarized within system organ class for the following:

- Regardless of onset for enrolled subjects;
- ATV powder through Week 48;
- ATV powder through stages combined.

7.6.3 Adverse Events Leading to Discontinuation of Study Therapy

AEs that led to discontinuation of study therapy are summarized within system organ class for the following:

- Regardless of onset;
- ATV powder through Week 48;
- ATV powder through stages combined.

7.6.4 Other Significant Adverse Events

Other significant AEs are assessed as described in Sections 7.6.4.1 through [7.6.4.9](#).

7.6.4.1 Renal Toxicity

Renal toxicity AEs (all grades) are summarized within system organ class on ATV powder through Week 48 and stages combined. Renal toxicity AEs are identified from the following MedDRA preferred terms: acute prerenal failure, albuminuria, anuria, azotaemia, continuous haemodiafiltration, costovertebral angle tenderness, creatinine renal clearance abnormal, creatinine renal clearance decreased, crystalluria, crystal nephropathy, cylindruria, diabetic cystopathy, diabetic end stage renal disease, diabetic nephropathy, dialysis, dysuria, Fanconi syndrome, Fanconi syndrome acquired, fluid retention, focal glomerulosclerosis, glomerular filtration rate abnormal, glomerular filtration rate decreased, glomerulonephritis, glomerulonephritis acute, glomerulonephritis chronic, glomerulonephritis membranoproliferative, glomerulonephritis membranous, glomerulonephritis minimal lesion, glomerulonephritis proliferative, glomerulonephritis rapidly progressive, glomerulonephropathy, glomerulosclerosis, glycosuria, haematuria, haemodialysis, hypercreatininaemia, hyperkaliuria, hyperphosphaturia, hypophosphataemia, intercapillary glomerulosclerosis, ketonuria, kidney enlargement, kidney fibrosis, kidney small, leukocyturia, lipiduria, microalbuminuria, neonatal anuria, nephritic syndrome, nephritis, nephritis allergic, nephritis autoimmune, nephritis haemorrhagic, nephritis interstitial, nephrocalcinosis, nephrogenic diabetes insipidus, nephrolithiasis, nephropathy, nephropathy toxic, nephrosclerosis, nephrotic syndrome, oliguria, peritoneal dialysis, polyuria, proteinuria, renal colic, renal disorder, renal failure, renal failure acute, renal failure chronic, renal failure neonatal, renal glycosuria, renal impairment, renal impairment neonatal, renal osteodystrophy, renal pain, renal tubular acidosis, renal tubular atrophy, renal tubular disorder, renal tubular necrosis, tubulointerstitial nephritis, urea renal clearance decreased and urine abnormality.

7.6.4.2 Cardiac Disorders

Cardiac disorder AEs (all grades) are summarized within system organ class on ATV powder through Week 48 and stages combined. Cardiac disorders are identified from the following MedDRA preferred terms: angina pectoris, arrhythmia, atrial fibrillation, atrioventricular block, atrioventricular block first degree, atrioventricular block complete, atrioventricular block second degree, bradycardia, bundle branch block left, bundle branch block right, cardiac failure congestive, cardiomegaly, cor pulmonale, electrocardiogram abnormal, electrocardiogram PR

prolongation, electrocardiogram QRS complex prolonged, electrocardiogram QT prolonged, long QT syndrome, sinus bradycardia, tachycardia, cardiac function test abnormal, ventricular dysfunction, and cardiomyopathy.

7.6.4.3 Rash

Rash AEs (all grades; grade 2 - 4 related) are summarized within system organ class on ATV powder through Week 48 and stages combined. Rash is identified from the following MedDRA preferred terms: dermatitis allergic, dermatitis atopic, dermatitis exfoliative, drug eruption, drug rash with eosinophilia and systemic symptoms, erythema, erythema multiforme, exfoliative rash, prurigo, pruritus allergic, psoriasis, rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular, rosacea, skin exfoliation, skin toxicity, Stevens-Johnson syndrome, toxic skin eruption, urticaria and urticaria papular.

Time to first rash and duration of first rash are summarized for all grades and grade 2 - 4 related rash separately. The duration of rash is measured from the onset date to the resolution date (the last contact date is used if the resolution date is 'continuing'; the onset date is used if the resolution date is missing). The last contact date is the death date (if it exists), or the latest of the following: adverse event onset dates; adverse event resolution dates; last contact date if study discontinuation reason is lost to follow-up; HIV RNA draw dates; laboratory test dates; visit dates.

7.6.4.4 CDC Class C AIDS Events

CDC Class C AIDS AEs (all grades) are summarized within system organ class on ATV powder through Week 48 and stages combined. Documented clinical AIDS diagnoses are used to define AIDS (see Protocol Appendix 3).

7.6.4.5 Lipodystrophy-Related Adverse Events

Lipodystrophy-related AEs (all grades) are summarized within system organ class on ATV powder through Week 48 and stages combined. Lipodystrophy-related AEs are identified from the following MedDRA preferred terms: atrophy, breast enlargement, central obesity, congenital generalized lipodystrophy, facial wasting, fat atrophy, fat redistribution, gynaecomastia, lipoatrophy, lipodystrophy acquired, lipohypertrophy, lipomatosis, partial lipodystrophy and waist circumference increased.

7.6.4.6 Lactic Acidosis Syndrome (LAS) or Symptomatic Hyperlactatemia (SHL)

Potential cases of LAS/SHL are listed regardless of onset. Potential cases of LAS/SHL are identified from the following MedDRA preferred terms: acidosis, blood lactic acid increased, coma hepatic, cytolytic hepatitis, hepatic encephalopathy, hepatic failure, hepatic necrosis, hepatic steatosis, hepatitis, hepatitis acute, hepatitis chronic active, hepatitis chronic persistent, hepatitis fulminant, hepatitis toxic, hepatocellular damage, hepatomegaly, hepatotoxicity, hyperlactacidemia, lactic acidosis, metabolic acidosis and mitochondrial toxicity.

All terms are further reviewed for case definitions of LAS/SHL or hepatic steatosis by a BMS safety physician to validate the cases. In addition, subjects are included if supporting evidence of LAS or SHL was available (ie, hospital records, SAE comments, etc), which may not have been reflected in the AEs.

7.6.4.7 *Hyperbilirubinemia-Related Adverse Events*

Hyperbilirubinemia-related AEs (all grades; grade 2 - 4 related) are summarized within system organ class on ATV powder through Week 48 and stages combined. Hyperbilirubinemia-related AEs are identified by the following combination of MedDRA preferred terms: hyperbilirubinaemia combined (blood bilirubin abnormal, blood bilirubin conjugated increased, blood bilirubin increased, blood bilirubin unconjugated, blood bilirubin unconjugated increased, hyperbilirubinaemia), jaundice combined (jaundice or yellow skin) and ocular icterus. The summary also presents subjects who have at least 2 or more of hyperbilirubinaemia combined, jaundice combined or ocular icterus.

7.6.4.8 *Cholelithiasis*

Cholelithiasis AEs (all grades) are summarized within system organ class on ATV powder through Week 48 and stages combined. Cholelithiasis is identified from the following MedDRA preferred terms: bile duct stone, biliary colic, biliary dilatation, cholangitis, cholecystitis, cholecystitis acute, cholecystitis chronic, cholelithiasis, cholelithiasis obstructive, gallbladder disorder and hydrocholecystis.

7.6.4.9 *Nephrolithiasis*

Nephrolithiasis AEs (all grades) are summarized within system organ class on ATV powder through Week 48 and stages combined. Nephrolithiasis is identified from the following MedDRA preferred terms: calculus bladder, calculus ureteric, calculus urinary, crystalluria, crystal urine, nephrocalcinosis, nephrolithiasis and renal colic.

7.6.5 *Overall Adverse Events*

AEs are summarized within system organ class by intensity on ATV powder through Week 48 and stages combined: all grades; all grades related; grade 2 - 4 related; grade 3 - 4.

Grade 2 - 4 related AEs occurring with overall incidence $\geq 5\%$ are also summarized on ATV powder through Week 48 and stages combined.

Non-serious AEs (all grades) occurring with overall incidence $\geq 5\%$ are also summarized analogously on ATV powder through Week 48 and stages combined.

Multiple AEs (all grades) occurring with overall incidence $> 5\%$ are also summarized on ATV powder through Week 48 and stages combined, presenting the numbers of events and exposure-adjusted incidence rates (see [Section 8.2.6](#)).

Generic medication names are also summarized by preferred term for AEs that require treatment with concomitant medications on ATV powder through Week 48 and stages combined (see also [Section 7.4.5](#)).

All grades AEs on ATV powder through Week 48 and stages combined may be summarized for new onset AEs and AEs that are exacerbation of a pre-treatment event separately depending on data availability.

7.6.6 Clinical Laboratory Evaluations

Summaries are based on subjects with at least 1 laboratory measurement during the study period. Values are excluded after the first dose date of ATV capsule.

7.6.6.1 Laboratory Abnormalities by Toxicity Grade

Laboratory abnormalities (normal; grade 1 - 4; grade 3 - 4) are summarized on ATV powder through Week 48 and stages combined for the following tests:

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

Laboratory abnormalities are further summarized by baseline toxicity grade (normal; grade 1 - 4; grade 3 - 4).

Laboratory test results are graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, unless specified otherwise (see Protocol Appendix 2). Hematocrit, amylase, BUN/urea and chloride are graded using modified WHO criteria (see Protocol Appendix 5).

The highest toxicity grade on treatment is reported for each test.

7.6.6.2 Drug Induced Liver Injury (DILI)

Potential cases of DILI are listed on treatment regardless of ATV formulation. Potential DILI is defined as AT (ALT or AST) > 3 x upper limit of normal (ULN) concurrent with total bilirubin > 2 x ULN. Concurrent is defined as within \pm 30 days.

All cases are further reviewed by a BMS safety physician to validate the cases.

7.6.7 Electrocardiograms

7.6.7.1 ECG over Time

Longitudinal summaries of ECG parameters (HR, QTcB, QTcF, PR) present observed values and changes from baseline at baseline and each visit week on ATV powder through Week 48.

Categories of ECG parameters are summarized at baseline and each scheduled visit week on ATV powder through Week 48 using observed values:

1. QTcB and QTcF intervals $\leq 450, > 450 - 480, > 480 - 500, > 500$ msec;
2. PR interval ≤ 98 th percentile, borderline, prolonged (see table below).

Subject's Age	98 th Percentile for PR Interval (msec)	Borderline Range (msec)	Prolonged Range (msec)
3 - < 6 months	150	151 - 187	> 187
6 months - < 1 year	160	161 - 200	> 200
1 - < 3 years	150	151 - 187	> 187
3 - < 5 years	160	161 - 200	> 200
5 - < 8 years	160	161 - 200	> 200
8 - < 12 years	170	171 - 212	> 212
12 - < 13 years	180	181 - 225	> 225
≥ 13 years	200 ^a	201 - 250	> 250

^a Not the 98th percentile for PR interval, but the upper limit of normal for the PR interval in this age group
Source: Protocol PACTG 1020-A Version 6.0

The QT interval corrected for heart rate by the Bazett's formula, QTcB, is defined as

$$QTcB = \frac{QT}{\sqrt{RR}},$$

the QT interval corrected for heart rate by the Fridericia's formula, QTcF, is defined as

$$QTcF = \frac{QT}{\sqrt[3]{RR}},$$

where RR represents the RR interval of the ECG, in seconds.

Three ECG measurements are taken at Week 2 visit for subjects who have intensive PK taken at that visit. The worst (highest) value of these 3 measurements at Week 2 is used for those subjects in the analysis.

7.6.8 Physical Measurements

Longitudinal summaries of physical measurements (height, weight, age-adjusted percentiles and age-adjusted Z scores for height and weight) present observed values and changes from baseline at baseline and each visit week on ATV powder through Week 48 and stages combined.

7.7 Pharmacokinetics

The lower limit of quantification (LLOQ) for each analyte is determined by analytical laboratories and is subject to change:

- ATV: 10 ng/mL;
- RTV: 5 ng/mL.

Analyses are based on ATV powder and RTV. Values are excluded after the first dose date of ATV capsule.

7.7.1 PK Parameters in Stage 1

In Stage 1, intensive PK samples are taken for subjects weighing 25 - <35 kg and/or ≥ 6 to < 11 years of age and for subjects in the new 5 - < 10 kg cohort with 200 mg ATV and 80 mg RTV dose. The following steady state PK parameters of ATV and RTV are derived from plasma concentration versus time data at Week 2 by non-compartmental methods using a validated PK program:

- C_{max}: Maximum observed concentration;
- T_{max}: Time of maximum observed concentration;
- C_{min}: Plasma concentration 24 hours post observed dose. Pre-observed dose concentration is used as an estimate of C_{min} if sample 24 hours post dose is not collected;
- AUC(TAU): Area under the concentration-time curve, in 1 dosing interval from time 0 to 24 hours post observed dose. This is calculated by log- and linear-trapezoidal summations using a mixed log-linear method. Pre-observed dose concentration is used as an estimate of concentration 24 hours post observed dose if sample is not collected.
- IQ: Ratio of C_{min} at Week 2 to Protein Binding Adjusted EC₉₀ derived from individual subject clinical isolates at screening (ATV only, For ARV naive subjects, a population mean protein binding adjusted EC₉₀ for wild-type virus (14 ng/mL) may be used if individual EC₉₀ was not collected).
- CLT/F: apparent oral clearance from plasma
- CLT/F/kg: apparent oral clearance from plasma adjusted for body weight

PK parameters of ATV and RTV at Week 2 are summarized (eg, n, mean, SD, geometric mean, coefficient of variation [CV], median, quartiles, minimum, maximum) by baseline weight bands. IQ is a PK/PD parameter that will be reported separately in a combined PK/PD analysis of data from AI424397 and AI424451.

7.7.2 Trough Concentrations in Stage 1

Analyses are based on trough concentrations that meet the following criteria: complete sampling and dosing times; collected within 20-28 hours (inclusive) of the previous day's dose; collected before the next dose; concentrations < LLOQ imputed as LLOQ/2.

ATV trough concentrations are collected pre-dose at each scheduled visit week on treatment through a minimum 24 weeks and up to a maximum of 48 weeks and are summarized (eg, n, mean, SD, geometric mean, CV, median, quartiles, minimum, maximum). ATV IQ, defined as the ratio of C_{min} at the visit week to Protein Binding Adjusted EC₉₀ derived from individual subject clinical isolates at baseline, is summarized analogously.

ATV composite trough concentration, defined as the geometric mean of a subject's ATV trough concentrations through a minimum 24 weeks and up to a maximum of 48 weeks, is summarized.

ATV composite IQ, defined as the geometric mean of a subject's ATV IQ through a minimum 24 weeks and up to a maximum of 48 weeks, is also summarized.

RTV trough concentrations are collected similarly. RTV trough concentration and RTV composite trough are assessed analogously.

Trough concentration data will be included in a separate report and combined with data from study AI424397 for PK/PD analyses.

7.8 Pharmacodynamics

The relationship between endpoints of safety or efficacy and ATV trough and composite trough concentration (see [Section 7.7.2](#)) may be summarized and/or explored graphically, depending on the observed safety and efficacy profiles:

- Efficacy on ATV powder using the Week 24 ATV Powder Cohort and Eligible Week 48 ATV Powder Cohort
- Selected physiological and adverse events (eg, jaundice) on ATV powder through Week 48
- Selected laboratory parameters (eg, total bilirubin) on ATV powder through Week 48

Additional statistical methods may be used if appropriate.

Data will be combined with study AI424397 to perform PK/PD analyses in a separate report. Analyses are described in the Data Presentation Plan (DPP).

7.9 Taste Assessment

Palatability surveys are administered at each on treatment study visit in Stage 1 from Week 2 through Week 48 when a subject takes ATV 10% aspartame powder formulation. In Stage 2, the survey will be administered for subjects on ATV powder who switches to the new ATV 4.2% aspartame powder formulation. Assessment will be carried out at time of switch and after switch as long as the subject is on the new ATV powder formulation or maximum duration of one year, whichever comes first. The following are presented at each visit week while subjects are on ATV 10% aspartame powder formulation through Week 48 by weight band based on current weight:

- Proportions of subjects mixing ATV powder with food: milk, water, other, not reported.
- Proportion of subjects generally having trouble completing the dose of ATV. For those who have trouble completing, reasons are also included: does not generally like medicines or food; does not like the taste of ATV; child generally regurgitates (spits up) after meals; other; not reported.
- Proportion of subjects generally having trouble completing the dose of RTV. For those who have trouble completing, reasons are also included: does not generally like medicines or food; does not like the taste of RTV; child generally regurgitates (spits up) after meals; other; not reported.

Proportions are based on the number of subjects with at least 1 survey response at the visit week.

For the new ATV 4.2% aspartame powder formulation, proportions of subjects in each category of each question on the palatability survey will be tabulated similarly at each visit since they switch to the new formulation in Stage 2. In addition, 5-point Facial Hedonic Scale will be summarized at each visit for subjects who take it (i.e. ≥ 3 years old in Stage 2 on ATV powder formulation) since they switch to the new formulation in Stage 2. The visit windows on ATV 4.2% aspartame powder formulation (4.2% POU) are provided in section 8.1.

8 CONVENTIONS

Presentations follow BMS general global standards for all data domains.² This document is available upon request.

8.1 Windows for Analysis Weeks and Visit Weeks

Time is measured from the first dose of study therapy. For longitudinal presentations of data, windows around planned measurement times are based on the midpoint between planned study visits.

Analysis week windows for HIV RNA are defined at baseline and on ATV powder through Stages 1 and 2 consistent with FDA correspondence about the snapshot algorithm (see table below). First, values are included through the extended on-treatment period (see [Section 6.1.2](#)), and are excluded after the first dose date of ATV capsule. Analysis week windows are created after value selection. Longitudinal summaries use the last value in the analysis week window.

Week	Label	Analysis Week Window on ATV Powder
-1	SCREENING	≤ 1 day not at baseline
0	BASELINE	≤ 1 day at baseline
4	WEEK 4	Day 2 - < 6
8	WEEK 8	6 - < 10
12	WEEK 12	10 - < 14
16	WEEK 16	14 - < 18
24	WEEK 24	18 - < 30
32	WEEK 32	30 - < 36
40	WEEK 40	36 - < 42
48	WEEK 48	42 - < 54
60	WEEK 60	54 - < 66
72	WEEK 72	66 - < 78
84	WEEK 84	78 - < 90
96	WEEK 96	90 - < 102
108	WEEK 108	102 - < 114
120	WEEK 120	114 - < 126
X	WEEK X	$(X - 6) - < (X + 6)$

Visit windows are defined in the following table for study periods. The on-treatment period is split into Stage 1 and 2. Visit labels appear in listings and in raw datasets.

Study Period Label	Visit Label	Target Day from Start of Study Period	Visit Windows
PRE-TREAT	PRE-TREAT	1	< 1 day ^a
ON-TRT ST1	DAY 1	1	1 - 4 days ^b
	WEEK 2	14	> Day 4 - 3 weeks
	WEEK 4	28	> 3 - 6 weeks
	WEEK 8	56	> 6 - 10 weeks
	WEEK 12	84	> 10 - 14 weeks
	WEEK 16	112	> 14 - 20 weeks
	WEEK 24	168	> 20 - 28 weeks
	WEEK 32	224	> 28 - 36 weeks
	WEEK 40	280	> 36 - 44 weeks
ON-TRT ST2	WEEK 48	336	> 44 - 54 weeks ^c
	WEEK 12 ST2	84	≤ 18 weeks
	WEEK 24 ST2	168	> 18 - 30 weeks
	WEEK 36 ST2	252	> 30 - 42 weeks
	WEEK 48 ST2	336	> 42 - 54 weeks
	WEEK 60 ST2	420	> 54 - 66 weeks
	WEEK 72 ST2	504	> 66 weeks - 78 weeks
FOLLOW-UP	WEEK X ST2	X * 7	> (X - 6) weeks - (X + 6) weeks
	F/U WEEK 2	10	> Day 4 - 3 weeks
	F/U WEEK 4	24	> 3 - 5 weeks
	F/U WEEK 6	38	> 5 - 7 weeks
	F/U WEEK 8	52	> 7 - 9 weeks
	...		
	F/U WEEK 48	332	> 47 - 49 weeks

^a See [Section 6.1](#) for classification of measurements on Day 1 (first dose of active study therapy) as pre-treatment or on-treatment depending on the data domain.

^b See [Section 6.1.2](#).

^c For primary analysis, Week 48 visit window in Stage 1 may include data from Stage 2.

Weeks are study days divided by 7.

Visit windows are rederived for longitudinal analyses of CD4, ECG, physical measurements and taste assessment. First, values are included through the extended on-treatment efficacy/safety period (see [Section 6.1.2](#)), and are excluded after the first dose date of ATV capsule. Visit week windows are created after value selection. Longitudinal summaries use the value closest to the target day of the visit week window, except for ECG at Week 2, which uses the worst (highest) value of the 3 measurements for subjects who have intensive PK at Week 2. The visit windows on ATV 4.2% aspartame powder formulation (4.2% POU) are provided in the table below.

Study Period Label	Visit Label	Target Day from Start of 4.2% POU ATV	Visit Windows
ON-TRT 4.2% POU	WEEK 12-4.2% POU	84	≤ 18 weeks
	WEEK 24 4.2% POU	168	> 18 - 30 weeks
	WEEK 36 4.2% POU	252	> 30 - 42 weeks
	WEEK 48 4.2% POU	336	> 42 - 54 weeks
	WEEK 60 4.2% POU	420	> 54 - 66 weeks
	WEEK 72 4.2% POU	504	> 66 weeks - 78 weeks
	WEEK X 4.2% POU	X * 7	> (X - 6) weeks - (X + 6) weeks

8.2 Domain Derivations

Refer to BMS internal documents for additional conventions on date imputation and derivation of parameters across study periods for standard data domains: AEs, demography, ECGs, human genotyping, laboratory test results, non-study medications, physical measurements, subject status, taste assessment and vital signs. [3,4,5,6,7,8,9,10,11,12,13,14](#) These documents are available upon request.

8.2.1 Exposure

8.2.1.1 Study Therapy

Derived exposure dates that are used commonly in analyses are defined as follows:

- First dose date of study therapy is the earliest start or stop date of ATV identified from dosing records with non-missing start or stop dates and non-zero dose. This date is used to identify treated subjects and to distinguish study periods.
- Last dose date of study therapy is the latest start or stop dates of ATV identified from dosing records with non-missing start or stop dates and non-zero dose. This date is derived only for subjects with valid dosing records and a subject status CRF page indicating whether the subject completed the study. It is used to exclude data in efficacy and safety analyses, and also to identify subjects who have discontinued study therapy.

First and last dose dates of study drug formulations (ie, ATV powder, ATV capsule, RTV oral solution) are derived analogously for subjects with valid dosing records. Last dose dates of study drugs are derived without regard to the end of treatment subject status.

Time on study therapy is the last dose date of study therapy - first dose date of study therapy + 1.

Time on therapy for an individual drug formulation is the last dose date - first dose date + 1.

The following conventions are applied to dosing calculations for each drug formulation:

- Distinct records with non-missing dose start date, total dose, generic drug name and formulation are selected.
- Missing dose end dates are imputed. The missing end date of a dosing record is set to 1 day before the start date of the next available dosing record. If there is no subsequent record, the missing end date is set to the start date.
- Duration for a dosing record is calculated as imputed end date - start date + 1.
- Total amount of drug taken is the sum of total daily dose x duration across dosing records.

8.2.1.2 Interruption or Delay of Study Therapy

Interruptions of ATV powder are identified from complete dosing records (ie, non-missing start date, generic drug name and formulation) in which the total dose is 0 and the start date is before the last dose date of ATV powder (see [Section 8.2.1.1](#)). Duration for an interruption is determined using the minimum (last dose date of ATV powder, imputed end date) - start date + 1.

Interruptions of ATV capsule, RTV oral solution and RTV capsule are identified analogously to those of ATV powder.

Interruptions with missing reasons are categorized as “NOT REPORTED”.

8.2.2 Laboratory Tests

Analyses of laboratory tests use values from the central or local laboratory.

Laboratory parameters are presented using US standard values and units.

Fasting glucose is identified by the laboratory test ‘GLUCF’, whereas non-fasting glucose is identified by ‘GLUC’.

Fasting triglycerides are identified by the laboratory test ‘TRIGF’, whereas non-fasting triglycerides are identified by ‘TRIG’. Fasting status for other lipids is determined by the fasting indicator.

8.2.3 Physical Measurements

For each baseline parameter (eg, BMI), if there are multiple records on the same measurement day, then the last record entered is selected.

8.2.4 Viral Genotyping and Phenotyping

For baseline HIV subtype, if there are multiple records on the same collection day, then the last record assayed is selected. Only records from the central laboratory are used.

8.2.5 Virology

Analyses of HIV RNA use values from the Roche Amplicor Version 1.5 ultrasensitive or standard assay, or Abbott RealTime HIV-1 assay after the Roche Amplicor assay is discontinued, from the central laboratory. The lower and upper limits of quantification (LOQ) are 50 c/mL and 100,000 c/mL for the Roche Amplicor ultrasensitive assay, 400 c/mL and 750,000 c/mL for the Roche Amplicor standard assay, and 40 c/mL and 10,000,000 c/mL for Abbott RealTime HIV-1 assay.

HIV RNA viral loads are reported by the central laboratory as follows:

Actual numeric values for detectable virus within lower and upper LOQ;

Upper LOQ with the inequality “>” for detectable virus above upper LOQ;

Lower LOQ with the inequality “<” for detectable virus below lower LOQ.

The following convention applies to analyses of HIV RNA as a continuous variable. First, HIV RNA values are assigned a value of 1 more (or 1 less) if an inequality “>” (“<”) is present. Values outside the upper (or lower) LOQ are assigned a value of 1 more (or 1 less) than the limit.

If there are multiple records on the same collection day, then the last record assayed is selected.

Modified ITT and observed values analyses use the last value in the analysis week window.

8.2.6 Adverse Events

In order to account for AEs with multiple occurrences in the same subject, AE records are collapsed for each subject and preferred term when:

- Records have the same onset date.
- The onset date of an event record is either the same day or 1 day later than the resolution date of a preceding event record (contiguous events).
- The onset date of an event record is after the onset date and prior to or on the resolution date of a preceding event record (overlapping events).

The collapsed record contains the earliest onset date (and time, if collected); latest resolution date (and time, if collected); highest intensity in the following order (highest to lowest: very severe, severe, moderate, or mild); AE type of SAE, if ever reported as a SAE, AE otherwise; latest causality, as determined by the last modification time stamp (highest causality in the following order [highest to lowest: related, not related], if records contain the same last modification time stamp with different causalities); treatment required of yes, if ever required; highest action taken in the following order (highest to lowest: drug discontinued, drug interrupted, dose reduced, dose increased, none); last reported term, as determined by the last modification timestamp. Medications and procedures used to treat AEs are merged with collapsed AE records for AEs requiring treatment.

Incidence rates per 100 person-years of exposure (IR/100 P-Y) are defined as event count * 100 / person-years of exposure (see [Section 7.6.5](#)). Exposure on ATV powder is defined as time on study therapy (see [Section 7.4.1](#)), plus 30 days for subjects who discontinued study therapy to account for on-treatment safety reporting.

9 CONTENT OF REPORTS

9.1 Planned Analyses

Two analyses are planned:

- The primary analysis is conducted after the last treated subject is treated for 24 weeks (Stage 1). Safety assessments focus on ATV powder through Week 48. Longitudinal assessments of efficacy and safety parameters are presented on ATV powder through Week 48.
- The final analysis is conducted after the last subject in Stage 2 completes the study. Safety assessments focus on ATV powder through stages combined. Longitudinal assessments of efficacy and safety parameters are presented on ATV powder through stages combined.

Additional analyses may be conducted at unscheduled intervals to support regulatory questions/interactions, and at the request of the DMC.

9.2 Listings

Reports also contain subject listings described in the DPP. Listings are based on treated subjects, unless specified otherwise. Listings may include, but are not limited to, the following:

- Batch numbers
- Subjects excluded from the efficacy analysis (ie, enrolled subjects not treated)
- Relevant protocol deviations
- End of Stage 1 subject status
- End of Stage 2 subject status
- Demographics (enrolled subjects)
- Exposure
- Non-study medications
- HIV RNA (enrolled subjects)
- Snapshot algorithm outcomes at Weeks 24 and 48
- CD4 cell count and percent (enrolled subjects)
- Viral genotyping (enrolled subjects)
- Viral phenotyping (enrolled subjects)
- Adverse events (enrolled subjects)
- AEs requiring treatment with concomitant medications
- Deaths (enrolled subjects; see [Section 7.6.1](#))
- SAEs (enrolled subjects)
- Adverse events leading to discontinuation of study therapy
- Renal Toxicity (see [Section 7.6.4.1](#))
- Cardiac Disorders (see [Section 7.6.4.2](#))
- Rash (see [Section 7.6.4.3](#))

- CDC Class C AIDS Events (see [Section 7.6.4.4](#))
- Lipodystrophy-related AEs (see [Section 7.6.4.5](#))
- Potential LAS/SHL (see [Section 7.6.4.6](#))
- Hyperbilirubinemia-related AEs (see [Section 7.6.4.7](#))
- Cholelithiasis (see [Section 7.6.4.8](#))
- Nephrolithiasis (see [Section 7.6.4.8](#))
- Laboratory tests (enrolled subjects; excluding CD4 cell count and percent)
- Potential DILI (see [section 7.6.6.2](#))
- Pregnancy tests
- ECGs
- Physical measurements
- PK parameters of ATV powder and RTV oral solution in Stage 1
- Trough concentrations of ATV powder and RTV oral solution in Stage 1
- Survey for palatability
- Facial Hedonic Scale (only subjects ≥ 3 years of age at time of switch to new 4.2% aspartame ATV powder)

APPENDIX 1 RELEVANT PROTOCOL DEVIATIONS

This appendix lists relevant protocol deviations that can be programmed from the database. The list would be updated as appropriate if, in the course of monitoring the study, additional protocol deviations are found and considered relevant.

Eligibility Deviations

Eligibility deviations (ie, protocol deviations of entry criteria) are listed below.

- Age < 3 months or ≥ 11 years at time of first treatment
- HIV RNA < 1,000 c/mL at screening
- CDC Class C AIDS events diagnosed between 30 days prior to screening and treatment (ie, informed consent date - $30 \leq$ onset date \leq first dose date of study therapy)
- Corrected QTcF interval > 440 ms at screening
- Weight < 5 kg or ≥ 35 kg at date of first dose
- > Grade 2 ALT or AST

Relevant Protocol Deviations during Treatment

Relevant protocol deviations during the treatment period through Week 48 on ATV powder include:

- [REDACTED]
- [REDACTED]
- Remain on treatment > 8 weeks after having met the following definition of virologic failure (meeting any of the following criteria):
 - Less than 1 \log_{10} decrease from baseline HIV RNA by Week 16, confirmed by a second HIV RNA redrawn within 2 and 4 weeks from original sample;
 - Confirmed HIV RNA of ≥ 1000 c/mL (after Week 24);
 - Confirmed HIV RNA ≥ 400 c/mL and showing Genotypic and/or phenotypic resistance to ATV/RTV and/or one or more assigned NRTI study drugs.Remaining on treatment > 8 weeks is defined as last dosing date > 8 weeks after the confirmed HIV RNA drawn date.

APPENDIX 2 SNAPSHOT ALGORITHM

This appendix describes the snapshot algorithm for a Week 24 and Week 48 analysis. The principal analysis includes all treated subjects. The algorithm uses the last HIV RNA in the Week 24 and Week 48 analysis week window (see [Section 8.1](#)) to determine response.

See [Section 7.4.2](#) for indentifying subjects who discontinued ATV powder. Discontinuations of ATV powder before Week 24 are identified by the (last dose date of ATV powder - first dose date of study therapy + 1)/7 < 18, the lower bound of the Week 24 analysis week window. Discontinuations of ATV powder before Week 48 are identified by the (last dose date of ATV powder - first dose date of study therapy + 1)/7 < 42, the lower bound of the Week 48 analysis week window.

Outcomes for HIV RNA < 50 c/mL at Week 24/48

Outcomes, other than virologic success, are based on the primary reason for failure through Week 24/48. Each subject's status is categorized as follows:

- **Virologic success** includes subjects with HIV RNA < 50 c/mL in the Week 24/48 analysis week window.
- **Virologic failure** includes subjects in the following subcategories:
 - **HIV RNA ≥ 50 c/mL:** subjects with HIV RNA ≥ 50 c/mL in the Week 24/48 analysis week window;
 - **Discontinued due to virologic failure:** subjects with missing HIV RNA in the Week 24/48 analysis week window who discontinued ATV powder before Week 24/48 due to lack of efficacy (regardless of last on-treatment HIV RNA);
 - **Discontinued due to other reasons and HIV RNA ≥ 50 c/mL at time of discontinuation:** subjects with missing HIV RNA in the Week 24/48 analysis week window who discontinued ATV powder before Week 24/48 for reasons other than AE, death or lack of efficacy with last on-treatment HIV RNA ≥ 50 c/mL, if no on-treatment HIV RNA are available, the subject baseline HIV RNA will be used;
 - **OBT changed:** subjects who changed optimized background therapy (OBT) to a new class or changed OBT not permitted per protocol before the Week 24/48 HIV RNA draw date.
- **No virologic data in Week 24/48 window** includes subjects with missing HIV RNA in the Week 48 analysis week window in the following subcategories:
 - **Discontinued due to AE or death:** subjects who discontinued ATV powder before Week 24/48 due to AE or death (regardless of last on-treatment HIV RNA);
 - **Discontinued due to other reasons and HIV RNA < 50 c/mL at time of discontinuation:** subjects who discontinued ATV powder before Week 24/48 for reasons other than AE, death and lack of efficacy with last on-treatment HIV RNA < 50 c/mL;
 - **Missing data in window but on treatment:** subjects who did not discontinue ATV powder before Week 24/48.

The snapshot algorithm for HIV RNA < 400 c/mL and for other analysis weeks is assessed analogously.

References:

1. FDA Correspondence. Comments on proposed labeling (SDN 316 dated 03/07/2011) for sNDA 21567/S-026. 17MAR2011.

APPENDIX 3 GENOTYPIC AND PHENOTYPIC RESISTANCE

Genotypic Resistance

Genotypic resistance is assessed by searching for (1) all PI substitutions, and (2) select RT substitutions in the most current version of the International AIDS Society-USA (IAS-USA) list and Stanford HIV Drug Resistance Database (HIVdb).^{1,2} The HIVdb mutation scoring algorithm has been compared and validated with other algorithms. In addition, it has been shown to predict clinical response and virologic failure in clinical trials and salvage ARV therapy.^{3,4,5,6}

PI substitutions are categorized as IAS-USA based on amino acid (aa) substitutions at a particular position of the HIV enzyme. PI substitutions not listed in IAS-USA are categorized as polymorphisms.

PI substitutions listed in IAS-USA are further categorized as major, minor or polymorphism using IAS-USA and HIVdb classifications. Note that aa substitutions at a specific position may have different classifications (eg, V82A is major, but V82I is a polymorphism). When there is a discrepancy between IAS-USA and HIVdb for major vs. minor or minor vs. polymorphism, the HIVdb classification takes precedence given its mutation scoring algorithm.

PI polymorphisms, majors and minors are defined as follows:

- Polymorphisms
 - PI substitutions listed as minor in IAS-USA that have mutation scores of 0 for all PIs, according to values assigned by HIVdb.
 - PI substitutions not listed in IAS-USA (HIV subtype B as reference).
- Majors
 - PI substitutions listed as major in IAS-USA, except Q58E, T74P, N83D (listed as minor in HIVdb).
 - I54ASTV (listed as minor in IAS-USA, but major in HIVdb).
- Minors: Q58E, T74P, N83D and PI substitutions listed as minor in IAS-USA, except those categorized previously as polymorphisms or majors.

The following table summarizes the PI and RT substitutions searched. All NRTI and NNRTI substitutions listed in IAS-USA are included. Also included in bold are RT substitutions not listed in IAS-USA that have at least 1 mutation score ≥ 5 according to values assigned by HIVdb.⁷

Drug	Substitutions
PI	
Any	At least 1 PI substitution.
IAS-USA	At least 1 of the following listed in IAS-USA: L10CFIRV, V11I, G16E, K20IMRTV, L24I, D30N, V32I, L33FIV, E34Q, M36ILV, K43T, M46IL, I47AV, G48V, I50LV, F53LY, I54ALMSTV, Q58E, D60E, I62V, L63P, I64LMV, H69KR, A71ILTV, G73ACST, T74P, L76V, V77I, V82AFILST, N83D, I84V,

Drug	Substitutions
	I85V, N88DS, L89IMV, L90M, I93LM. Substitutions are further tabulated at each codon. Major: D30N, V32I, M46IL, I47AV, G48V, I50LV, I54ALMSTV, L76V, V82AFLST, I84V, N88S, L90M. Minor: L10FIRV, V11I, K20IT, L24I, L33F, K43T, F53L, Q58E, A71ILTV, G73ACST, T74P, N83D, N88D, L89V. Polymorphism: L10C, G16E, K20MRV, L33IV, E34Q, M36ILV, F53Y, D60E, I62V, L63P, I64LMV, H69KR, V77I, V82I, I85V, L89IM, I93LM.
Non-IAS-USA (polymorphism)	At least 1 PI substitution not listed in IAS-USA. Substitutions are further tabulated at each codon.
RT	
Any	At least 1 of the following: NNRTI; NRTI. Substitutions are further tabulated at each codon.
NRTI	At least 1 of the following: E40F, E44AD, K65N, K66 insertion, K66 deletion, D67 insertion, D67 deletion, D67EGHST, S68 insertion, S68 deletion, T69DGN, T69 deletion, K70 insertion, K70 deletion, K70N, W71 insertion, W71 deletion, L74IV, Y115F, V118I, Q151L, N348I ; 69 insertion complex; 151 complex; TAMS; TDF/FTC; ZDV.
69 insertion complex	Substitution at codon 69 with a double amino acid insertion and at least 1 of the following: M41L, A62V, K70R, L210W, T215FY, K219EQ.
151 complex	Q151M and at least 1 of the following: A62V, V75AIMST, F77L, F116Y.
TAMS	At least 1 of the following: M41L, D67N, K70R, L210W, T215FY, K219EQ.
TDF/FTC	At least 1 of the following: K65R, K70EGQST, M184IV.
ZDV	At least 1 of the following: M41L, D67N, K70R, L210W, T215ACDEFILNSVY, K219 DEHNQRW .
NNRTI	At least 1 of the following: V90I, A98G, L100I, K101EHP, K103HNST, V106AIM, V108I, E138AGKQR, V179DEFLT, Y181CISV, Y188CHL, G190ACEQSTV, H221Y, P225H, F227CL, M230IL, K238NT, Y318F, N348I .
K103N	

TAMS = Thymidine analogue-associated mutations

Phenotypic Resistance

The phenotypic resistance to a drug is defined as a fold change (ie, ratio of the 50% inhibitory concentration [IC50] of the clinical isolate to the IC50 of the reference strain) greater than the cut-off for reduced susceptibility. The following table displays cut-offs used by Monogram Biosciences, Inc., CA to determine reduced susceptibility to each drug.

Drug	Reduced Susceptibility Cut-offs
PI	atazanavir (ATV) 2.2; atazanavir/ritonavir (ATV/R) 5.2; darunavir/ritonavir (DRV/R) 10; fosamprenavir (AMP) 2; fosamprenavir/ritonavir (AMP/R) 4; indinavir/ritonavir (IDV/R) 10; lopinavir/ritonavir (LPV/R) 9; nelfinavir (NFV) 3.6; ritonavir (RTV) 2.5; saquinavir (SQV) 1.7; saquinavir/ritonavir (SQV/R) 2.3; tipranavir/ritonavir (TPV/R) 2
NNRTI	delavirdine (DLV) 6.2; efavirenz (EFV) 3; etravirine (ETR) 2.9; nevirapine (NVP) 4.5
NRTI	abacavir (ABC) 4.5; didanosine (ddI) 1.3; emtricitabine (FTC) 3.5; lamivudine (3TC) 3.5; stavudine (d4T) 1.7; tenofovir (TFV) 1.4; zidovudine (ZDV) 1.9

DOCUMENT HISTORY

Version Number	Author(s)	Description
■	■	Original version
■	■	See AI424451 SAP Amendment 1