Protocol Number: AI424451
IND Number: 56,897
Ex-US Non-IND
EUDRACT Number 2010-024537-23
Date: 08-Feb-2011
Revised Date: 15-Apr-2014

Clinical Protocol AI424451

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)

Revised Protocol Number: 05

Incorporates amendment(s) 08, Administrative letter 02

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Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

SYNOPSIS

Clinical Protocol AI424451

Title of Study: Protocol AI424451: 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)

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): ATV oral powder with RTV liquid (or RTV capsules/tablets for 25 to < 35 kg weight band only) at doses recommended per protocol.

Subjects will receive ATV powder with RTV liquid (or RTV capsules/tablets for 25 to < 35 kg weight band only) once a day with food.

Duration of treatment is dependent on a subject's age, weight, and the timing with which a country receives approval and has availability for the pediatric indication of a formulation whose requirements are met by the subject.

ATV/RTV should be taken orally with food at approximately the same time of each day.

Two NRTIs must be locally approved for pediatric use and should be dosed as per the local country label. Study physicians will prescribe NRTIs based on viral resistance results, the local guidelines for ARV treatment and subject's treatment history. Tenofovir is prohibited.

Study Phase: 3b

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 yrs who are ≥ 5 kg to < 35 kg.

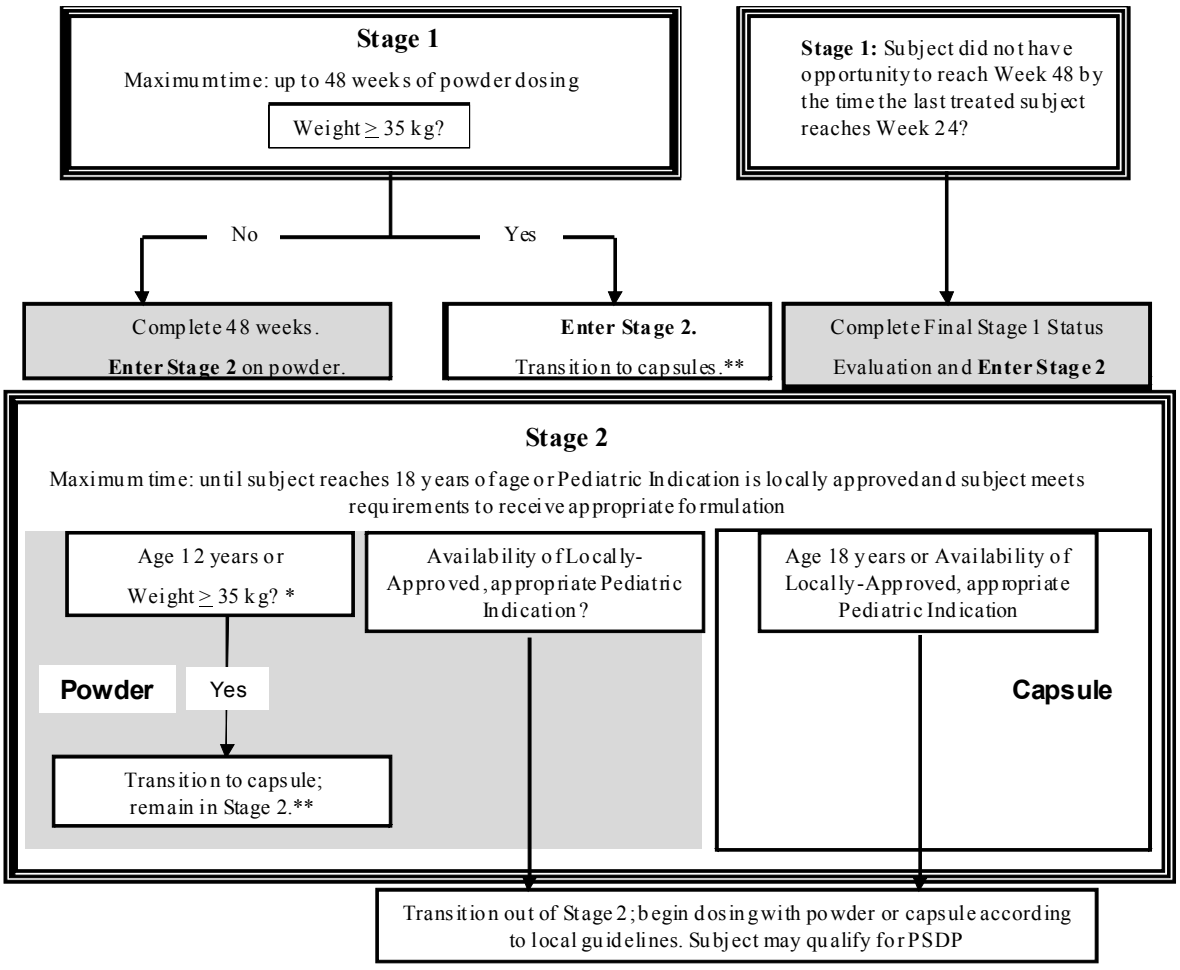
Primary Objective: To describe the safety of ATV powder formulation boosted with RTV based HAART regimens in pediatric subjects dosed through a minimum of 24 weeks, as measured by the frequency of deaths, serious adverse events and discontinuation due to AEs.

Secondary Objectives:

1) To describe efficacy as measured by proportions 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
2) To describe the pharmacokinetic profile of ATV powder formulation boosted with RTV in pediatric subjects weighing ≥ 25 to < 35 kg and/or who are ≥ 6 to < 11 years of age, and for subjects enrolling in the new ≥ 5 - <10 kg cohort (200mg ATV and 80 mg RTV) in terms of ATV Cmax, Cmin and AUC.

Study Design:

Age ≥ 3 months to < 11 years: Minimum 56 subjects treated with ATV powder formulation for 24 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	No Minimum	300	100	
The study will commit to enroll a minimum of 30 ARV experienced patients treated with ATV powder for a minimum of 24 weeks.				



* Subjects are required to switch to capsules when they reach 35 kg and/or 12 years of age. However, subjects who reach a weight of 25 kg and/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. Careful consideration should be given to the time of switch as subjects who are unable to swallow capsule after an 8-week transition period must be discontinue from Stage 2.

** Subjects who are unable to swallow the capsule formulation after an 8 week transition period must be discontinued from the study.

Study Population:

Key Inclusion Criteria:

- Confirmed HIV 1 infection diagnosed by protocol criteria
- ≥ 5kg to < 35kg, and ≥ 3 months to < 11 years of age at the time of first treatment
- Antiretroviral naive or treatment-experienced. 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 the prevention of mother to child transmission (PMTCT). For the purposes of this study, subjects exposed to ARVs in utero or intra-partum are eligible for the study, but will be considered 'treatment naive'.
- Screening HIV RNA ≥ 1000 copies/mL by Roche Amplicor HIV-RNA Assay (version 1.5), or Abbott RealTime HIV-1 assay after the Roche Amplicor assay is discontinued.
- Antiretroviral naive subjects must have genotypic sensitivity at screening to ATV and at least 2 NRTIs (excluding TDF). NRTIs must be approved for pediatric use at the local country level.
- Antiretroviral experienced subjects (as defined above) must have documented genotypic *and* phenotypic sensitivity at screening to ATV (Fold Change in susceptibility < 2.2) and at least 2 NRTIs (excluding TDF). NRTIs must be approved for pediatric use at the local country level.

Key Exclusion Criteria:

- Experienced subjects who received ATV or ATV/RTV at any time prior to study enrollment or who have prior history of 2 or more PI failures
- Antiretroviral-naive or experienced HIV-1 infected subjects with contraindication to study medications
- Documented cardiac conduction abnormality(ies) or significant cardiac dysfunction, or a history of syncope
- Family history of QTc interval syndrome, Brugada syndrome or right ventricular dysplasia or with a corrected QTc interval at screening of > 440 ms
- One of the following cardiac rhythm abnormalities documented on the screening ECG: First degree atrioventricular (AV) block
- Type I second degree AV block while awake, type II second degree AV block at any time, complete AV block at any time, or age-adjusted heart rate < 2nd percentile)
- Need for Tenofovir
- Coinfection with either HBV or HCV

Study Assessments and Primary Endpoint: Safety assessments include vital signs and physical measurements, deaths, adverse events, serious and non-serious, including Centers for Disease Control (CDC) Class C AIDS events, concomitant medication, laboratory measurements, and ECGs. Efficacy assessments include HIV RNA and CD4 cell counts. Intensive pharmacokinetic assessment in subjects weighing ≥25 kg to < 35 kg or ≥ 6 to < 11 years old, and subjects enrolling in the new ≥ 5 - <10 kg cohort (200mg ATV and 80 mg RTV) receiving the ATV powder formulation will be conducted. Palatability assessments includes a palatability survey for all subjects and Facial Hedonic Scale (only for subjects who are ≥ 3 years old in Stage 2 on ATV powder formulation and switching to new 4.2% aspartame ATV powder formulation).

Statistical Methods: Values after transition from ATV powder to ATV capsules (i.e. Stage 2) will be excluded from all analyses through week 48 (Stage 1). Efficacy, safety and PK will be summarized by weight band on ATV powder through a minimum of 24 weeks for treated subjects.

The primary safety endpoints are the frequency of deaths, SAEs and AEs leading to discontinuation of study therapy.

The principal efficacy endpoints are the proportions of subjects with HIV RNA < 50 c/mL and < 400 c/mL at Week 24 and Week 48.

For intensive PK, ATV and RTV PK parameters (e.g. Cmax, Cmin, AUC, etc.) will be summarized for subjects weighing ≥25 - <35 kg and/or aged ≥ 6 - to < 11 years receiving the powder ATV formulation and for subjects enrolling in the new ≥ 5 - <10 kg cohort (200mg ATV and 80 mg RTV). Trough PK of ATV and RTV will be summarized over time

There will be an independent data monitoring committee (DMC) for this study.

TABLE OF CONTENTS

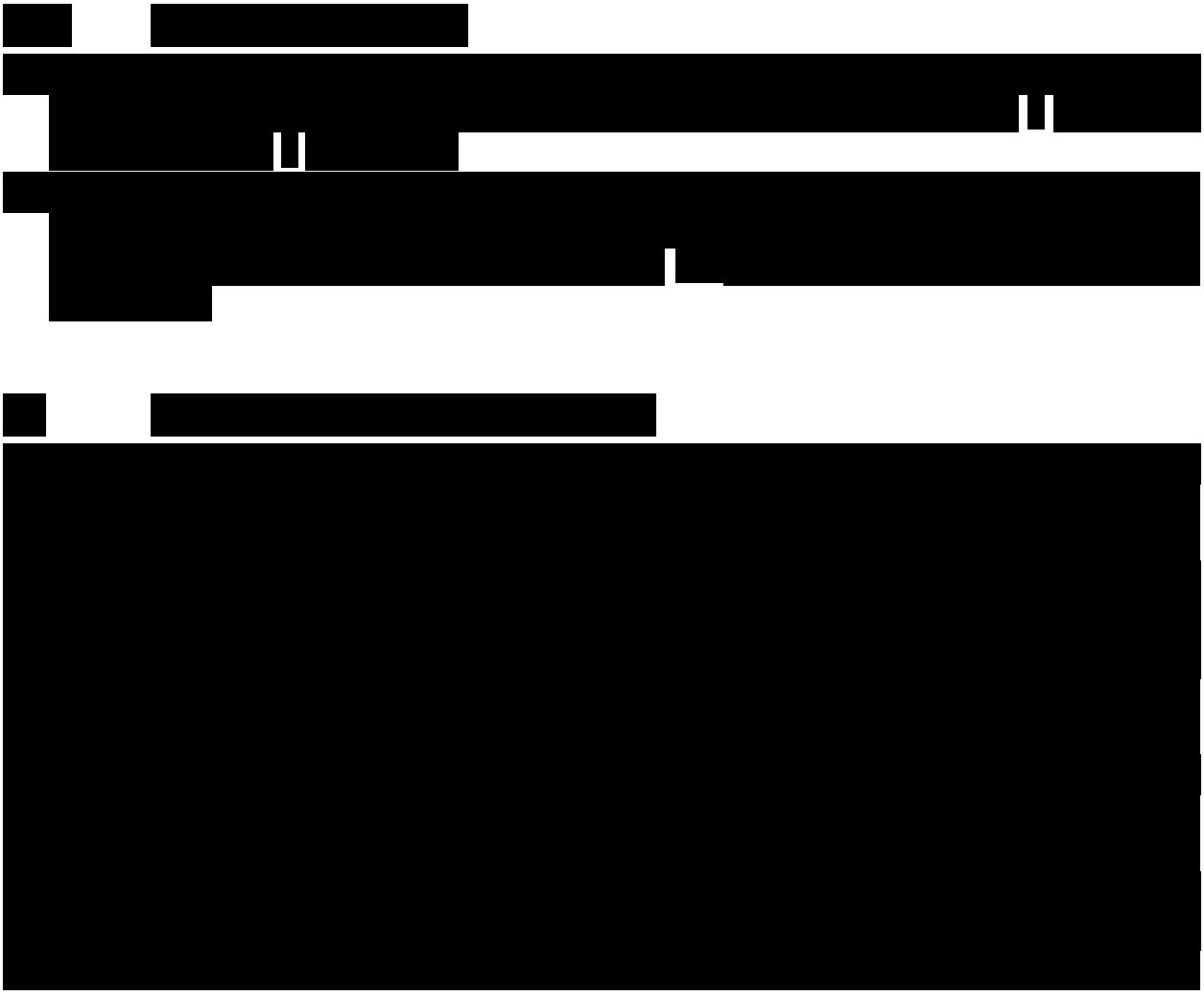
1.3 Objectives

1.3.1 Primary Objectives

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

1.3.2 Secondary Objectives

1) To describe efficacy as measured by proportions 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.
2) To describe the pharmacokinetic profile of ATV powder formulation with RTV in pediatric subjects weighing ≥ 25 - < 35 kg and/or ≥ 6 to < 11 years of age and for new ≥ 5 - < 10 kg cohort (200 mg ATV and 80 mg RTV) in terms of ATV Cmax, Cmin and AUC.



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2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s).

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (eg, advertisements), and any other written information to be provided to subjects. The investigator or sponsor should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling, information to be provided to subjects and any updates.

The investigator or sponsor should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments and administrative letters) according to regulatory requirements or institution procedures.

2.3 Informed Consent

Investigators must ensure that subjects, or, in those situations where consent cannot be given by subjects, their legally acceptable representatives, are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study
3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4) Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating their informed consent during the study, then consent must additionally be obtained from the subject.
6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

For minors, according to local legislation, one or both parents or a legally acceptable representative must be informed of the study procedures and must sign the informed consent form approved for the study prior to clinical study participation. The explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

Minors who are judged to be of an age of reason must also give their written assent.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

3.1.1 Study Design

This study is a 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.

Subjects can be antiretroviral naive or experienced (without prior exposure to ATV). 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 as part of a prevention of mother to child transmission (PMTCT) program (in accordance with multiple guidelines: WHO, DHHS and South Africa PMTCT guidelines). For the purposes of this trial, subjects exposed to ARVs intra-uterine or peri-partum will not be considered treatment experienced (but are still eligible for the study).

Nucleoside backbone therapy will be determined by the investigator on the basis of the viral resistance profile and local guidelines according to the subject's treatment history. It will consist of 2 NRTIs approved for pediatric use and dosed as per the local country label (tenofovir will be excluded). Background NRTIs should remain unchanged through the duration of the study unless changes are required for treatment-limiting NRTI toxicity.

The choice of the switched NRTI backbone has to be locally approved for pediatric use and dosed as per the local country label and will be determined by the investigator on the basis of the viral resistance profile of the subject, susceptibility profile of the NRTIs being considered, and local guidelines for treatment of HIV infected children.

A total of approximately 95 subjects will be treated with the ATV powder formulation boosted with RTV oral solution (or RTV capsules/tablets for 25 to < 35 kg weight band only) in order to have a minimum number of 56 treated subjects with at least 24 weeks follow-up on ATV powder formulation. In the event that the minimum number of subjects (overall and/or per weight band) with at least 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.

The study consists of two stages (see Figure 3.1.1-1):

STAGE 1

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. A "visit" done via the telephone is conducted after the first week of study participation, primarily to check in with the caregiver to ask how the subject is tolerating the study drug regimen.

Important assessments done during Stage 1 include but are not limited to:

- A Week 2 Intensive 24 hour PK samples will be collected only for subjects in Stage 1 who either enter the study weighing ≥ 25 - < 35 kg and/or ≥ 6 to < 11 years of age or those who grow into that weight or age range during Stage 1, or for subjects enrolling in a new ≥ 5 - < 10 kg cohort with 200 mg ATV and 80 mg RTV dose, (see Section 5.5.1)
  - Malfunctions to the venous catheter, poor venous access, or other difficulties which would cause time point sample delays may be cause for the reschedule of the Intensive PK visit;
- A PK Trough sample (Ctrough) will be collected for all subjects for ATV and RTV (see Section 5.5.2) at each scheduled visit from Week 4 through a minimum of 24 weeks up through Week 48,
- ECGs will be collected at each scheduled in-clinic visit for all subjects, and during the Intensive PK portion at Week 2 (pre-dose, 2.5, 4 hours post-dose) for subjects weighing ≥ 25 - < 35 kg and/or ≥ 6 to < 11 years of age or those who grow into that weight or age range during Stage 1, or for subjects enrolling in a new ≥ 5 - < 10 kg cohort with 200 mg ATV and 80 mg RTV dose.

It is important to note that all visits in Stage 1 (with the exception of Week 2 and Transition Visits) include a PK trough assessment, so it is of critical importance to instruct the caregivers that study medication should NOT be administered on the day of a study visit, rather at the clinic after the blood draw has been completed. An elapsed time from the previous dose of study medication to the draw of the blood for PK must be within a 20-28-hour window.

Dosing of ATV in Stage 1 is performed only with the powder formulation, dosed according to weight, as outlined in Table 3.1.1-1. When dosing with ATV powder, RTV oral solution is dosed at 80 mg for subjects weighing ≥ 5 to < 25 kg, and 100 mg RTV oral solution or 100 mg RTV tablets/capsules for subjects weighing ≥ 25 to < 35 kg.

Once a subject has qualified by weight to move to a higher weight band/higher dose, they will remain at that new dose regardless of any subsequent weight loss.

BMS will require extra monitoring of subjects each time they transition to a higher weight band/higher dose of ATV. If a subject is moved to a higher weight band during Stage 1 on or after Week 16 (beyond which study visits occur every 8 weeks), the subject will be required to

return to the clinic for a weight band transition visit 4 weeks later. If they moved to the ≥ 25 to < 35 weight range or reach 6 years of age during Stage 1, a 24-hr intensive PK will be taken 2 weeks after the dose change for the new weight band. If the subject becomes 6 years of age but without a dose change then the intensive PK visit can occur at the next regular Stage 1 visit. Intensive PK collection for the age range (≥ 6 to < 11 years), but not fulfilling the ≥ 25 to < 35 weight range, will be stopped when PK samples from approximately 10 subjects have been collected. All subjects from the weight cohorts (≥ 25 - < 35 kg, ≥ 5 - < 10kg on 200 mg ATV and 80 mg RTV dose) will be evaluated for Intensive PK.

Subjects who reach the weight ≥ 35kg during Stage 1: Subjects 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 ≥ 35kg during Stage 1: Subjects 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 or weight ≥ 35kg during Stage 1 by the time the last treated subject reaches Week 24 will have a final Stage 1 status assessment performed and will immediately move into Stage 2 while remaining on ATV powder. These subjects will follow then the assessments 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 Table 3.1.1-1 and Table 3.1.1-2, respectively. When dosing with ATV powder, RTV oral solution is dosed at 80mg if weight < 25 kg and is dosed at 100 mg RTV oral solution or 100 mg RTV tablets/capsules when weight is ≥ 25 - < 35 kg. When dosing with ATV capsules, RTV (capsules/tablets) is dosed at 100mg.

Once a subject has qualified by weight to move to a higher weight band/higher dose, they will remain at that new dose regardless of any subsequent weight loss.

BMS will require extra monitoring of subjects each time they transition to a higher weight band/higher dose of powder and capsules. If a subject is moved to a higher powder or capsule weight band during Stage 2, the subject will be required to return to the clinic for a weight band transition visit 4 weeks later.

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 regularly scheduled visit that occurs after the IRB/IEC approval of the amended protocol and informed consent 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 according to Table 3.1.1-1.

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

ATV Powder-to-Capsule Transition:

Subjects who are transitioning from powder to capsules, 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 Table 3.1.1-2; RTV is dosed at 100mg (capsules or tablets) when dosing with the ATV capsule;
- Subjects who are unable to swallow the ATV and RTV capsules/tablets 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 ATV and RTV capsules/tablets will continue in Stage 2 and will be dosed according to the recommendations provided in Table 3.1.1-2.
- Subjects are *required* to switch to capsules in Stage 2 when they reach 35 kg and/or 12 years of age. However, subjects who reach a weight of 25 kg and/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. Careful consideration should be given to the time of switch as subjects who are unable to swallow capsules after an 8-week transition period must be discontinued from Stage 2.

Stage 2 participation ends when:

- A subject reaches the age of 18 years
- 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 capsules 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.
  - Subjects who are medically stable may be eligible for a post-study drug program to ensure continuity of care (for greater detail regarding the post-study drug program, please see Section 3.2).

Table 3.1.1-1: ATV Powder/RTV Oral Solution Dosing Table

Body Weight (kg)	Target # Subjects with at least 24 weeks Follow-up	ATV Dose (mg)[a]	RTV Dose (mg)
5 to less than 10	Minimum of 5	150	80
5 to less than 10	Minimum of 6	200[b]	80

Table 3.1.1-1: ATV Powder/RTV Oral Solution Dosing Table

Body Weight (kg)	Target # Subjects with at least 24 weeks Follow-up	ATV Dose (mg)[a]	RTV Dose (mg)
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[c]	No Minimum	300	100[d]

[a] ATV powder will be dosed in 50 mg sachet packets.

[b] After reviewing the AI424397 interim intensive PK report[19], a new cohort for the ≥ 5 to < 10 kg weight band will be added to assess if exposures could potentially be enhanced with a higher dose (200mg ATV powder, 80 mg RTV) in this weight band.

[c] 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.

[d] RTV oral solution, capsules or tablets is allowed for the 25 - < 35 kg weight band.

Table 3.1.1-2: Dosage for Pediatric Patients (12[a] to less than 18 years of age) for REYATAZ Capsules with Ritonavir Capsules or Tablets

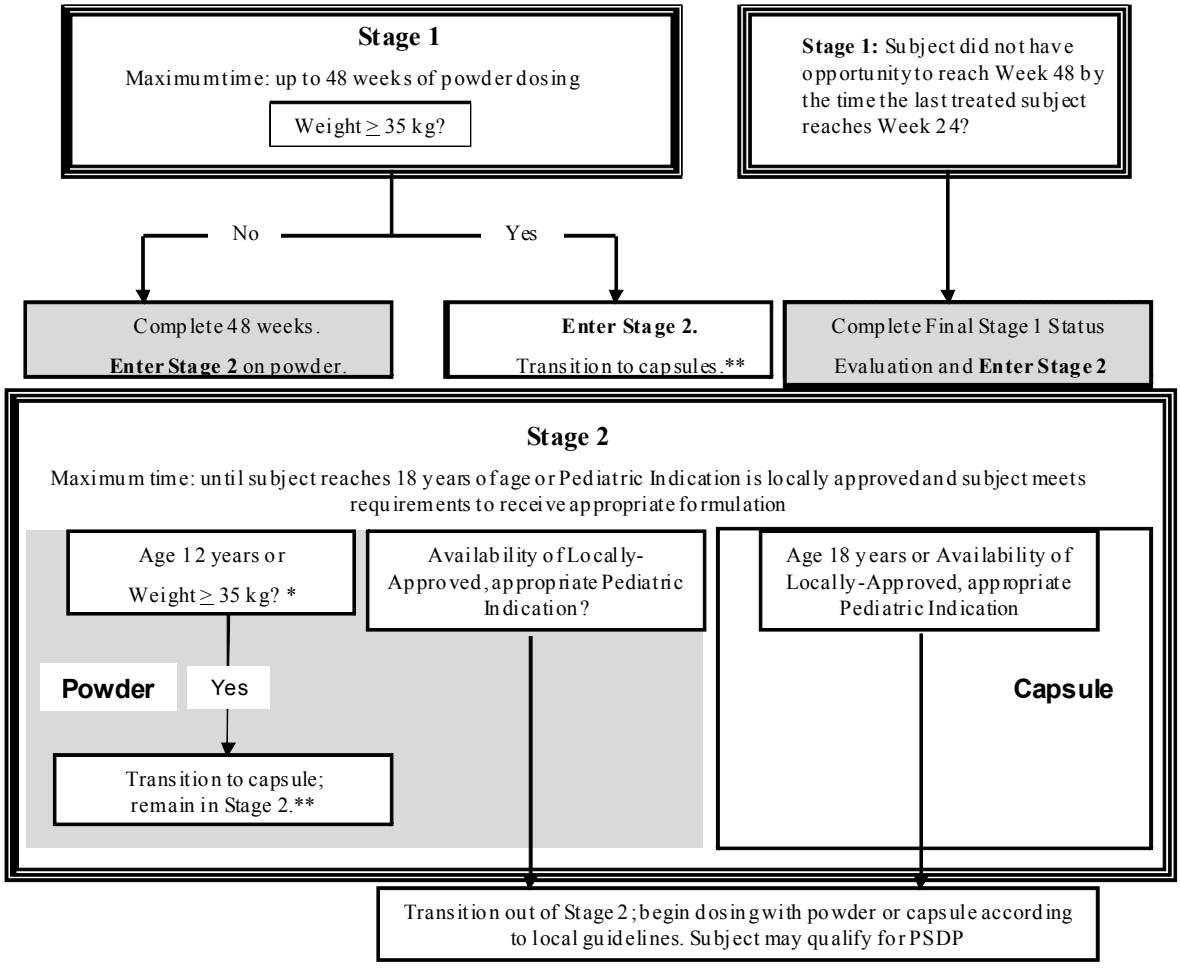
Body Weight		REYATAZ Dose[b]	Ritonavir Dose
(kg)	(lbs)	(mg)	(mg)
15 to less than 20	33 to less than 44	150	100
20 to less than 40	44 to less than 88	200	100
at least 40	at least 88	300	100

[a] Subject who reach 6 years of age during Stage 2 may, at the discretion of the investigator and caregiver, choose to attempt to switch to the solid dosage forms of ATV/RTV.

[b] The recommended dosage of REYATAZ can be achieved using a combination of commercially available capsule strengths. NOTE: The capsule dose of ATV is lower than the highest powder dose for subjects ≥ 25 to < 35 kg because of the lower bioavailability of the ATV powder as compared with ATV capsules.

Figure 3.1.1-1: Study Schematic

Age ≥ 3 months to < 11 years: Minimum 56 subjects treated with ATV powder formulation for 24 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	No Minimum	300	100	
The study will commit to enroll a minimum of 30 ARV experienced patients treated with ATV powder for a minimum of 24 weeks.				



* Subjects are required to switch to capsules when they reach 35 kg and/or 12 years of age. However, subjects who reach a weight of 25 kg and/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. Careful consideration should be given to the time of switch as subjects who are unable to swallow capsule after an 8-week transition period must be discontinue from Stage 2.

** Subjects who are unable to swallow the capsule formulation after an 8 week transition period must be discontinued from the study.

3.1.2 Study Duration

STAGE 1

Duration of study participation in Stage 1 is dependent on weight milestone:

- Subjects who do not reach a weight of ≥ 35kg while in Stage 1 will complete the full 48 weeks of dosing with ATV powder, at which point they will transition to Stage 2 and continue on ATV powder.
- Subjects reaching the weight of ≥ 35kg at any point during Stage 1 will immediately transition to Stage 2 and begin the transition to the ATV capsule formulation.

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

STAGE 2

Duration of study participation in Stage 2 is dependent on an age milestone, or by the timing of approval of a local pediatric indication (whichever is first):

- Subjects will end study participation in Stage 2 when they reach the age of 18 years, or when there is approval and availability of a locally-approved pediatric indication whose requirements are met by the subject.

The sponsor reserves the right to terminate Stage 2 if any of the following occur: a) the marketing application is rejected by responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; or d) therapeutic alternatives become available in the local market.

3.2 Post Study Access to Therapy

At the conclusion of the study, subjects who complete the study and continue to demonstrate clinical benefit will be eligible to receive study drug. In countries where the study drug is not approved and available, study drug will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of the sponsor. The sponsor reserves the right to terminate access to study drug if any of the following occur: a) the marketing application is rejected by responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; or d) therapeutic alternatives become available in the local market.

In countries where the regimen is approved and available, subjects who are not able to receive drug reimbursement through a private or government sponsored health program and are in financial need may be eligible to continue to receive medication they received on study through the BMS Post Study Drug Program. This program will provide only medicines that 1) were used

in the subject's regimen in this trial and 2) are locally marketed. The drugs provided to a subject will be limited to drugs made available in the clinical trial in which the subject was treated. If a newer formulation of marketed product is not available, an earlier formulation may be provided. Safety monitoring and evaluation will be the sole responsibility of the investigator.

3.3 Study Population

HIV infected pediatric subjects ≥ 3 months to < 11 years of age and ≥ 5 kg to < 35 kg. Subjects can be antiretroviral naive or experienced (without prior exposure to ATV). 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 the prevention of MTCT (in accordance with multiple guidelines: WHO, DHHS and South Africa PMTCT guidelines). For the purposes of this study, subjects exposed to ARVs in utero or intra-partum may be included in the study but will be considered 'treatment naive'.

A total of 30 ARV experienced subjects treated with ATV powder for a minimum of 24 weeks will be enrolled in this study. Study enrollment will remain open until a minimum of 30 ARV experienced subjects treated with ATV powder for a minimum of 24 weeks are enrolled. Weight designation will be based upon the child's weight at the time of first treatment (Day 1 Visit). Subjects ≥ 2 months and < 3 months are eligible to be screened as long the date of first treatment does not occur until reaching the age of ≥ 3 months AND ≥ 5 kg in weight.

For entry into the study, the following criteria MUST be met.

3.3.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Informed consent from a parent/legal guardian must be obtained prior to screening. Minors who are judged to be of an age of reason must also give their written assent (see Section 2.3).

2) Target Population

Confirmed HIV-1 infection diagnosed by positive virologic test results on 2 separate occasions by any of the following:

a) HIV DNA PCR.

b) HIV RNA with values ≥ 1,000 copies/mL will be considered evidence of infection.

c) Positive HIV ELISA at ≥ 18 months of age, with confirmatory Western blot or indirect immunoflourescence antibody.

Note: At least one diagnostic result may have been prior to the Screening visit.

3) Age and Sex

a) Infants and children of either gender, ≥ 3 months to < 11 years of age at the time of first treatment.

4) Other Inclusion Criteria

a) Antiretroviral naive or treatment-experienced subjects. 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 the prevention of mother to child transmission (PMTCT). For the purposes of this study, subjects exposed to ARVs in utero or intra-partum are eligible for the study, but will be considered 'treatment naive'.

b) Antiretroviral naive subjects must have genotypic sensitivity at screening to ATV and at least 2 NRTIs (excluding tenofovir). NRTIs must be approved for pediatric use at the local country level.

c) Antiretroviral experienced subjects (as defined above) must have documented genotypic *and* phenotypic sensitivity at screening to ATV (Fold Change in susceptibility < 2.2) and to at least 2 NRTIs (excluding TDF). NRTIs must be approved for pediatric use at the local country level.

3.3.2 Exclusion Criteria

1) Target Disease Exceptions

a) Experienced subjects who received ATV or ATV/RTV at any time prior to study enrollment or who have prior history of 2 or more PI failures will not be allowed in the study.

b) Antiretroviral-naïve or experienced HIV-1 infected subjects with contraindication to study medications.

c) Subjects with genotypic resistance at screening to ATV or either component of the local NRTI backbone based upon the following criteria:

i) Any Major Mutations: I50L, I84V, N88S.

ii) ≥ 2 of the following minor or cross resistant mutations:

(1) M46I/L, G48V, I54L/V/M/T/A, V82A/T/FI, L90M, V32I

d) The use of any investigational agent within 30 days of enrollment.

e) History of psychiatric or cognitive/developmental impairment that could compromise subject safety or the ability of the subject to comply with the protocol.

f) Premature infants (less than 37 weeks gestation at birth) will not be eligible to enter the study until they are over 6 months of age.

g) The need for Tenofovir.

2) Medical History and Concurrent Diseases

a) Any active CDC Category C clinical condition.

b) Not applicable as per protocol amendment 04.

c) Coinfection with either HBV or HCV

i) Coinfection with HBV as documented* by the presence of HBsAg and/or HBV DNA by a PCR assay in infants < 18 months and HBsAg for children ≥ 18 months of age

ii) Coinfection with HCV as documented* by the presence of HCV RNA by a PCR assay in infants < 18 months and HCV ELISA positive for children ≥ 18 months of age

iii) HBV or HCV infection in mothers for children in whom HBV or HCV infection can not be excluded.

*: HBV and HCV serologies for all ages and PCR for infants < 18 months are to be performed locally.

d) Documented cardiac conduction abnormality(ies) or significant cardiac dysfunction, or a history of syncope.

e) Family history of QTc interval syndrome, Brugada syndrome or right ventricular dysplasia or with a corrected QTc interval at screening of > 440 ms.

f) One of the following cardiac rhythm abnormalities documented on the screening ECG: First degree atrioventricular (AV) block; type I second degree AV block while awake, type II second degree AV block at any time, complete AV block at any time, or age-adjusted heart rate < 2nd percentile).

g) History of pancreatitis, peripheral neuropathy, malignancy that requires systemic therapy, or any medical condition which, in the opinion of the investigator, adds undue risk to trial participation.

h) Malabsorption syndrome.

i) Presence of a newly diagnosed HIV-related opportunistic infection or any medical condition requiring acute therapy at the time of enrollment.

3) Physical and Laboratory Test Findings

a) Weight < 5 or ≥ 35 kg at date of first dose (Day 1)

b) > Grade 2 transaminase (AST, ALT) abnormalities.

4) Allergies and Adverse Drug Reaction

a) Hypersensitivity to any component of the study medication formulations (ATV/RTV, or a locally prescribed NRTI with a pediatric indication).

5) Sex and Reproductive Status

a) Infants and children of either gender, < 3 months or ≥ 11 years at the time of first treatment.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

3.3.3 Women of Childbearing Potential

Women of childbearing potential include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Post menopause is defined as:

- Amenorrhea ≥ 12 consecutive months without another cause and a documented serum follicle stimulating hormone (FSH) level >35 mIU/mL or
- Women with irregular menstrual periods and a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL or

  NOTE: FSH level testing is not required for women ≥ 62 years old with amenorrhea of ≥ 1 year
- Women on hormone replacement therapy (HRT)

Women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or are practicing abstinence or where their partner is sterile (eg, vasectomy) should be considered to be of childbearing potential.

[redacted]

3.4.2 Other Restrictions and Precautions

3.4.2.1 Restrictions

Grapefruit Juice: Due to the known interaction of grapefruit juice with the cytochrome P450 isoform CYP3A4 (the metabolizing enzyme for atazanavir), it is suggested that subjects not consume grapefruit or grapefruit juice for the duration of the study.

3.5 Discontinuation of Subjects from Treatment

Subjects MUST discontinue investigational product (and noninvestigational product at the discretion of the investigator) for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Subject requires a medication prohibited by the protocol as outlined in Sections 3.4.1 and 3.4.2.
- Virologic failure or disease progression which, in the investigator's opinion, precludes the subject's continued participation in the study or meets any of the following criteria:
  - Subjects with an incomplete virologic response defined as less than a 1 log10 drop from baseline in plasma HIV RNA level by Week 16 (using the Amplicor® v1.5 PCR assay for measuring HIV RNA), confirmed by a second plasma HIV RNA level redrawn within 2 and 4 weeks from original sample; or
  - Subjects with a confirmed HIV RNA of ≥ 1000 copies/mL (after Week 24); or
  - Subjects with a confirmed HIV RNA of ≥ 400 copies/mL and showing Genotypic and / or Phenotypic resistance to ATV/RTV and/or one or more assigned NRTI study drugs
- Non-compliance by the subject with the requirements of the protocol, treatment or monitoring.
- Inability to swallow capsule after an 8-weeks transition period from powder to capsule in Stage 2.
- Any of the following cardiac findings:
- Clinical symptoms potentially related to heart block,
- QTc interval > 440 msec seen on EKG,
- Third degree AV heart block.

All subjects who discontinue should comply with protocol specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If a subject was withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate case report form (CRF) page.

3.5.1 Premature Termination

With the exception of subjects who did not have the opportunity to reach 48 weeks of treatment by the time that the last treated subject reaches week 24, premature termination is defined as discontinuing the study prior to 48 weeks of treatment.

- If premature termination is due to toxicity or occurs while the subject is experiencing ≥ Grade 3 toxicities, these should be followed with appropriate clinical and/or laboratory monitoring until resolved to ≤ Grade 2.
- Subjects who fail to comply with the study requirements (in taking study medications or in showing up for scheduled visits) may be terminated by the investigator.
- Subjects who discontinue the study early for reasons other than withdrawn consent will be asked to participate in an early discontinuation study visit.
- Subjects who discontinue study medications due to virologic failure, and subjects who discontinue study treatment for any other reason except withdrawal of consent, will be asked to provide a sample for HIV genotypic and phenotypic resistance testing at their early discontinuation study visit. If a subject withdraws consent to participate, no additional study blood draws will be performed.
- When a subject is "lost to follow-up", eg, does not return for clinic visits, a reasonable effort should be made (and documented) to have the subject return for end-of-treatment evaluation.
- Subjects unable to tolerate 2 NRTIs in addition to ATV/RTV will be terminated from the study.

Subjects who did not have the opportunity to reach week 48 by the time the last patient reaches week 24, they will be considered to have completed Stage 1.

4 TREATMENTS

All protocol-specified investigational and non-investigational products are considered study drug.

4.1 Study Treatments

Table 4.1-1: Product Description: AI424451 Study Medication

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
Atazanavir (ATV) powder[a] for oral use	50 mg/sachet	1.5 g sachet/open label with text and symbols printed directly on sachet and cross-referencing to outer carton	Outer carton containing 30 sachets/open label booklet label cross-referencing to the sachet label	Sachet: aluminum foil with text and symbols printed directly on the sachet Outer carton: white cardboard with booklet label attached	15° - 25°C (59° - 77°F)
Norvir (RTV) Oral Solution	80 mg/ml	90 ml (EU-sourced) or 240 ml (US-sourced) bottle/open label booklet label	NA	A practically clear, orange solution in amber-colored, multi-dose bottles	Store below 25°C (77°F); Do not refrigerate or freeze. Store in a tightly closed container. Protect from excessive heat.
Atazanavir Capsule	150 mg	60 capsules per bottle/open label	NA	Blue cap and powder blue body with “BMS 150 mg” and “3624” markings.	Store at 25°C (77°F); excursions permitted to 15°- 30°C (59°- 86°F)
Atazanavir Capsule	200 mg	60 capsules per bottle/open label	NA	Blue cap and blue body with “BMS 200 mg” and “3631” markings.	Store at 25°C (77°F); excursions permitted to 15°- 30°C (59°- 86°F)
Atazanavir Capsule	300 mg	30 capsules per bottle/open label	NA	Red cap and blue body with “BMS 300 mg” and “3622” markings.	Store at 25°C (77°F); excursions permitted to 15°- 30°C (59°- 86°F)
Ritonavir Capsule	100 mg	30 capsules (US sourced) or 84 capsules (EU-sourced) per bottle/open label	NA	White soft gelatin capsules imprinted with the Abbott corporate logo and “100”, and “DS” markings.	Store at 2° - 8°C (36° - 46°F); protect from light.

Table 4.1-1: Product Description: AI424451 Study Medication

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
Ritonavir Tablet	100 mg	30 tablets (US sourced) or 30 or 60 tablets (EU-sourced)/open label	NA	White film-coated ovaloid tablets debossed with the corporate logo and the Abbo-Code NK providing 100 mg ritonavir.	Store at 20°- 25°C (68°- 77°F); excursions permitted to 15°- 30°C (59°- 86°F). Storage in original container. Protect from moisture.

[a] ATV powder for oral use containing 10% aspartame is used in stage 1 and 2. Subjects remaining on ATV powder in stage 2 will be switched to the new 4.2% aspartame ATV powder for oral use after the amendment 07 has been approved by the IRB/IEC of the subject's site.

4.1.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as follows:

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, investigational product(s) is/are: Atazanavir, and Ritonavir. Both will be provided as part of the study. Please refer to Table 4.1-1 for details regarding these 2 medications.

4.1.2 Noninvestigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as noninvestigational products.

In this protocol, noninvestigational product(s) is/are: Any antiretroviral medication from the NRTI class. NRTIs must be approved for pediatric use and should be dosed as per the local country label. Study physicians will prescribe NRTIs based on viral resistance results and subject's treatment history. In cases where NRTI backbone therapy is not covered by private insurance, government programs, etc, Bristol-Myers Squibb will provide treatment or reimburse for the cost of prescription therapy.

4.1.3 Handling and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the sponsor. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor immediately.

Storage facilities for controlled substances must be securely locked and substantially constructed, with restricted access to prevent theft or diversion, as applicable by local regulations.

4.2 Method of Assigning Subject Identification

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.

For subjects who meet the protocol eligibility criteria, the investigative staff will call the IVRS on Day 1 and subjects will be assigned to a dose of ATV/RTV appropriate to weight. It is the responsibility of the principal investigator to ensure that the subject is eligible for the study prior to a second call to the assignment center for confirmation of the appropriate dosage. It is important that the investigative staff reconfirm the subject's willingness to continue in the trial prior to treatment administration. Once the dosage has been confirmed, study medication should be initiated within 3 days, with the first dose being given in the clinic at the Day 1 visit. Note: if, in order to allow for timely provisioning of study medication by the site investigational pharmacy, it is necessary to call IVRS in advance of the subject's Day 1 visit (within 1 day prior), this is acceptable and will not be considered a protocol deviation. All efforts should be made to call IVRS on Day 1, however, to limit the possibility of enrolling subjects that do not start treatment. If a subject is enrolled but does not receive study medication, the study team must be notified immediately.

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 3 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 of 24 weeks follow-up. In the event that the minimum number of subjects (overall and/or per weight band) with a minimum of 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 of 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-naive 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 naive and experienced subjects. Enrollment will remain open until a minimum of 30 ARV experienced subjects are enrolled (regardless of weight band) and treated with ATV powder for minimum of 24 weeks.

4.3 Selection and Timing of Dose for Each Subject

Dosing information for RTV oral solution and ATV powder is provided in Table 3.1.1-1; dosing information for RTV and ATV capsules is provided in Table 3.1.1-2.

Initial dose will be determined by the subject's weight on the day of the first on-treatment study visit (Day 1).

Dosing changes are driven by weight band thresholds provided in Table 3.1.1-1 and Table 3.1.1-2.

Transitioning from the powder to the capsule formulation of ATV is driven by reaching the age of 12 or weight of ≥ 35 kg.

Please refer to Section 3.1.1 Study Design for specific details of dosing changes.

4.3.1 Dosing Instructions

The prescriber should instruct the caregiver to tap the sachet to settle the contents. Use scissors to cut open the sachet on the dotted line.

The powder may be mixed with a small amount of food or beverage (eg, water, milk, chocolate milk, liquid infant formula, applesauce or yogurt). If water is used, the mixture must be taken with food. The entire contents of the mixture must be consumed to obtain the full dose. The mixture should be consumed within one hour and may be stored at room temperature 20° - 25°C (68° - 77°F) during this time.

Ritonavir oral solution should be taken immediately after the ATV powder preparation.

ATV capsules should be ingested with food and stored at 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F).

Ritonavir capsules should be ingested with food immediately before or after ATV intake.

Ritonavir tablets should be ingested with food immediately before or after ATV intake. The tablets should be swallowed whole and not chewed, broken or crushed.

4.3.2 Specific Dosing Instructions on Days of Pharmacokinetic Assessments

Intensive PK

Intensive 24 hour PK samples will be collected in Stage 1 only on subjects who:

- Enter the study weighing ≥ 25 - < 35 kg and/or ≥ 6 to < 11 years of age at scheduled Week 2 visit or
- Subjects moving into the ≥ 25 - < 35 kg weight range or becoming 6 years old during Stage 1, the intensive PK visit will occur two weeks after the dose change for the new weight band. If the subject becomes 6 years of age but without a dose change then the intensive PK visit can occur at the next regular Stage 1 visit.
- Subjects enrolling a new ≥ 5 - <10 kg cohort with 200mg ATV and 80 mg RTV dose.

Intensive PK collection for the age range (≥ 6 to < 11 years), but not fulfilling the ≥ 25 to < 35 weight range, will be stopped when PK samples from approximately 10 subjects have been collected. All subjects from the weight cohorts (≥ 25 - < 35 kg, ≥ 5 - < 10kg on 200 mg ATV and 80 mg RTV dose) will be evaluated for Intensive PK.

- Subjects must be instructed to take their dose of study medication such that the last dose (dose on the day prior to the PK visits) of ATV/RTV is approximately 24 hours prior to the pre-dose sample collection.
- Subjects must be instructed not to take any dose of study medication prior to the study visit on the day of the PK assessment.
- The investigative site should ensure that the atazanavir powder is administered either mixed with a food substance or water and taken with a light meal and should ensure the NRTIs are dosed according to the local label, but after the pre-dose sample collection.

ATV/RTV Trough PK (All subjects at scheduled visits Week 4 through a minimum of 24 weeks and up through 48 weeks, except transition visits)

Trough PK will be collected at scheduled study visits through a minimum of 24 weeks and up to a maximum of 48 weeks. Trough PK collection will be stopped for ongoing subjects in Stage 1 when the last treated subject reaches Week 24.

- Subjects must be instructed to take their dose of study medication such that the last dose of ATV/RTV is approximately 24 hours prior to the trough sample collection. Subjects must be able to provide the date and time of the meal and dose prior to the trough sample collection.
- Subjects must be instructed not to take their dose of study medication prior to the study visit on the day of the trough PK assessment, and must not take their dose prior to the trough sample collection. Subjects may take their dose at the investigative site after the trough sample collection.

4.3.3 Dose Modifications

There will be no dose modifications for toxicity or PK. Dose modifications will be made to ATV/RTV or the NRTI backbone as needed to compensate for weight gain only (see Table 3.1.1-1 and Table 3.1.1-2).

4.4 Blinding/Unblinding

Not applicable.

4.5 Treatment Compliance

Subject adherence to the treatment regimen will be critical in the conduct of this study. Subjects will be required to complete study medication diaries through Stage 1 of the study. Caregivers should be provided with the medication diary at the Day 1 visit, instructed on its completion, including the importance of making daily entries and bringing the diary at each visit throughout Stage 1. Where feasible, the study coordinator should make a telephone call to the caregiver in the interim period (eg, at Week 1) to provide further adherence support. Adherence will be evaluated by the investigative staff at every treatment visit through direct interviews with the subject's caregivers, a sachet count and the review of a diary. In addition, periodic contact with the caregivers between study visits is strongly encouraged in order to confirm compliance with the study regimen. The caregiver should be instructed to bring all unused study medication back in the original container to each visit. Use of the study medication diaries; will be used for all subjects.

Subjects remaining on ATV powder in Stage 2 are encouraged to continue using the study medication diaries. After the switch from the 10% aspartame ATV powder to the new 4.2% aspartame ATV powder in Stage 2, study medication diaries will be used as long as the subject is on the new 4.2% aspartame ATV powder or maximum duration of one year, whichever comes first. The caregiver should be instructed to continue bringing the diary at each visit.

4.5.1 Guidelines for the Management of Subjects with Rebound HIV RNA Levels Greater Than or Equal to 50 copies/mL

This section provides clinical guidance for the management of subjects with virologic failure during the study. Laboratory results must be confirmed with repeated testing before a final assessment of virologic treatment failure is made.

Virologic failure occurs as an incomplete virologic response to therapy or as a viral rebound after virologic suppression is achieved.

Incomplete virologic response to therapy is defined as:

- Less than a 1 log10 drop from baseline in plasma HIV RNA level by Week 16 (using the Amplicor® v1.5 PCR assay, or Abbott RealTime HIV-1 assay after the Roche Amplicor assay is discontinued, for measuring HIV RNA), confirmed by a second plasma HIV RNA level redrawn within 2 and 4 weeks from original sample; or

- 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
- Repeated plasma HIV RNA level ≥ 50 copies/mL (using the Amplicor® v1.5 PCR assay, or Abbott RealTime HIV-1 assay after the Roche Amplicor assay is discontinued, for measuring HIV RNA) after Week 48.

Viral rebound is defined as:

- 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 is 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.
- Subjects with a plasma HIV RNA level ≥ 50 copies/mL and < 1000 copies/mL (using the Amplicor® v1.5 PCR assay, or Abbott RealTime HIV-1 assay after the Roche Amplicor assay is discontinued, for measuring HIV RNA) followed by return to virologic suppression will be considered a viral blip and not a viral rebound.

The subjects meeting the criteria for viral rebound or virologic failure at any time during the study will be managed as follows:

- Those with a confirmed HIV RNA of < 400 copies/mL may continue on their assigned treatment and must have a repeat confirmatory HIV RNA checked every study visit.
- Those with a confirmed HIV RNA of ≥ 400 copies/mL and < 1000 copies/mL may remain on assigned treatment at the discretion of the investigator, in consultation with the BMS Medical Monitor.
  - A viral resistance test will be conducted automatically and the result forwarded to the site investigator.
  - Subjects with Genotypic and / or Phenotypic resistance to ATV/RTV and/or one or more assigned NRTI study drugs must be discontinued.
  - Further management will be at the discretion of the investigator in consultation with the BMS Medical Monitor.
  - Those with a confirmed HIV RNA of ≥ 1000 copies/mL must be discontinued from the study.
- Those subjects with an incomplete virologic response defined as less than a 1 log10 drop from baseline in plasma HIV RNA level by Week 16 (using the Amplicor® v1.5 PCR assay, or Abbott RealTime HIV-1 assay after the Roche Amplicor assay is discontinued, for measuring HIV RNA), confirmed by a second plasma HIV RNA level redrawn within 2 and 4 weeks from original sample, must be discontinued from the study.

Plasma samples for resistance testing will be collected at screening and at, or immediately after, a rebound or virologic failure. Samples will be submitted for immediate testing and the results

conveyed to the investigator. Only samples with a confirmed HIV RNA level ≥ 400 copies/mL will be tested for genotypic and phenotypic resistance. Investigators may also send an ATV trough PK sample for subjects with virologic rebound. See Table 5.1-2 and Section 5.5.2.

4.6 Destruction and Return of Study Drug

4.6.1 Destruction of Study Drug

If study drugs (those supplied by the sponsor or sourced by the investigator) are to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for the disposal, procedures for proper disposal have been established according to applicable regulations, guidelines and institutional procedures, and appropriate records of the disposal have been documented. The unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor.

4.6.2 Return of Study Drug

Study drug will not be returned. All unused and/or partially used study drug may be destroyed on site providing the site has an applicable standard operating procedure on file.

4.7 Retained Samples for Bioavailability / Bioequivalence

Not applicable

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedural Outline (AI424451)

Procedure	Screening Visit	Notes
Eligibility Assessments		
Demography	X	
Informed Consent	X	
Eligibility(Inclusion/Exclusion Criteria)	X	
Medical History	X	
Safety Assessments		
Full Physical Examination	X	
Vital Signs	X	
Medication Review (Prior ARV Treatment)	X	
Physical Measurements	X	
ECG	X	
Assessment of Pre-Treatment Events	X	
AIDS Defining Pre-Treatment Events	X	
Clinical Laboratory		
HIV RNA	1 mL	
Viral Resistance	2 mL	For treatment-experienced subjects, a sample for genotype and phenotype will be collected at Screening. Treatment-naive subjects will only have a sample collected at Screening for genotype testing.
Hematology	1 mL	

Table 5.1-1: Screening Procedural Outline (AI424451)

Procedure	Screening Visit	Notes
Serum Chemistry	1 mL	Up to 4ml additional blood volume will be collected in the event that HBV and HCV serologies for all ages and PCR for infants < 18 months is unknown and testing will be performed locally.
Urinalysis	X	
Total Blood Volumes	5 mL	Blood Volumes do not exceed NIH Clinical Center Guidelines of 3 mL/Kg at a single draw (ie, 15 mL for a 5 Kg infant, the smallest weight that would be enrolled in the study) or 7 mL/Kg over 6 weeks (ie, 35 mL for a 5 kg infant). These volumes represent SOC for HIV infected pediatric subjects except for the PK sampling.

Table 5.1-2: Treatment Phase (Stage 1) Procedural Outline (AI424451)

Procedure	Start of Treatment Day 1 (Baseline)[a]	Week 1[b]	Week 2 (also Intensive PK Visit[c] for some subjects) Day 14 (+4 days)	Weeks 4, 8, 12, 16, 32, and 40[d] (± 5 days)	Week 24 and 48 (final Stage 1 Visit)[d] (± 5 days)	Transition Visit for Weight Band change[e] (± 5 days)	Notes
Eligibility Assessments							
Eligibility (Inclusion/Exclusion Criteria)	X						
Safety Assessments							
Drug Tolerability Assessment		X	X	X	X	X	
Full Physical Examination					X		
Targeted Physical Examination	X		X	X		X	
Vital Signs	X		X	X	X	X	
Concomitant Medication Assessment	X		X	X	X	X	
Physical Measurements	X		X	X	X		
ECG	X		X	X	X	X	Recorded 3 times at intensive PK visit (pre-dose, 2.5 hrs, and 4 hrs (Cmax)
Adverse Events Assessment	X		X	X	X	X	
AIDS Defining Adverse Events	X	X	X	X	X	X	

Table 5.1-2: Treatment Phase (Stage 1) Procedural Outline (AI424451)

Procedure	Start of Treatment Day 1 (Baseline)[a]	Week 1[b]	Week 2 (also Intensive PK Visit[c] for some subjects) Day 14 (+4 days)	Weeks 4, 8, 12, 16, 32, and 40[d] (± 5 days)	Week 24 and 48 (final Stage 1 Visit)[d] (± 5 days)	Transition Visit for Weight Band change[e] (± 5 days)	Notes
Central Laboratory							
HIV RNA	1 mL			1-2 mL	1-2 mL	1-2 mL	Up to 2mL of blood will be required when Abbott RealTime HIV RNA-1 assay will be used after Roche Amplicor HIV-1 assay (1mL) will be discontinued. If a VL ≥ 400 c/mL is reported, a confirmation sample is to be taken between 2-4 weeks of the original sample date.
CD4 Count and Percent	1 mL			1 mL	1 mL		
Viral Resistance							Additional 2 ml samples for both genotype and phenotype resistance testing will be collected in the instance of virologic failure or rebound.
Intensive ATV Pharmacokinetics			11.7 mL				only for subjects weighing ≥ 25 - < 35 kg and/or aged ≥ 6 to < 11 years or enrolling in a new ≥ 5 - < 10 kg cohort with 200 mg ATV powder and 80 mg RTV

Table 5.1-2: Treatment Phase (Stage 1) Procedural Outline (AI424451)

Procedure	Start of Treatment Day 1 (Baseline)[a]	Week 1[b]	Week 2 (also Intensive PK Visit[c] for some subjects) Day 14 (+4 days)	Weeks 4, 8, 12, 16, 32, and 40[d] (± 5 days)	Week 24 and 48 (final Stage 1 Visit)[d] (± 5 days)	Transition Visit for Weight Band change[e] (± 5 days)	Notes
ATV PK Plasma Trough[f]				1 mL	1 mL		To be collected pre-dose. ATV should be administered following the PK plasma trough sample collection. Will not require a fasting state except when fasting lipids are drawn. Will only be collected for a minimum of 24 weeks up through the Week 48 visit.
Hematology	1 mL			1 mL	1mL		
Serum Chemistry	1 mL			1 mL	1mL	1mL	
Lipids	X				X		Fasting for subjects ≥ 3 years of age (ie, NPO except for water and medications for at least 12 hours). Subjects < 3 years of age may be non-fasting.
Urinalysis					X		Conducted yearly after the Screening visit.
Clinical Drug Supplies							
Register Study Treatment	X			X	X		
Dispense Study Treatment	X			X	X		ATV powder, RTV oral solution or RTV capsules/Tablets (when weight is ≥ 25 - < 35 kg, NRTIs)

Table 5.1-2: Treatment Phase (Stage 1) Procedural Outline (AI424451)

Procedure	Start of Treatment Day 1 (Baseline)[a]	Week 1[b]	Week 2 (also Intensive PK Visit[c] for some subjects) Day 14 (+4 days)	Weeks 4, 8, 12, 16, 32, and 40[d] (± 5 days)	Week 24 and 48 (final Stage 1 Visit)[d] (± 5 days)	Transition Visit for Weight Band change[e] (± 5 days)	Notes
Education of Study Treatment	X						
Record Study Medication Compliance			X	X	X	X	
Adherence/Tolerability							
Dispense/Review Subject Diary	X	X	X	X	X	X	
Conduct Dosing Assessment		X	X	X	X	X	
Total Blood Volumes	4 mL		11.7 mL	5-6 mL	5-6 mL	2-3 mL	Blood Volumes do not exceed NIH Clinical Center Guidelines of 3 mL/Kg at a single drawn (ie, 15 mL for a 5 Kg infant, the smallest weight that would be enrolled in the study) or 7 mL/Kg over 6 weeks (ie, 35 mL for a 5 kg infant). These volumes represent SOC for HIV infected pediatric subjects except for the PK sampling. To avoid sample dilution, when PK sampling through an IV catheter, approximately an additional 1 mL (blood and saline mix) should be withdrawn and discarded prior to collecting the 0.8 mL for the blood PK sample (ie, to discard the catheter saline flush).

[a] The Baseline visit must be within 30 days of the screening visit. In cases where the test or re-test results are not available after 30 days, the timeline to the Baseline visit (Day 1) may be extended to 50 days. The IVRS can be called up to 72 hours prior to the Baseline (Day 1) visit. The first dose must be taken in the clinic at the Baseline (Day 1) visit.

[b] Telephone call or brief clinic visit to ensure that subject is tolerating the study medication.

[c] All subjects will have a week 2 visit. Only subjects weighing ≥ 25 - < 35 kg and/or aged ≥ 6 to < 11 years or subjects enrolling in a new ≥ 5 - < 10 kg cohort (with 200mg ATV and 80 mg RTV) will have Intensive PK performed at this visit. Intensive PK visit may take place from Day 14 - Day 18 following the first study dose of ATV. Subjects who move into the ≥ 25 - < 35 kg weight range or becoming 6 years old **during Stage 1**, will also have the Intensive PK performed (approximately 2 weeks or 14 - 18 days) after switching to the new doses. If the subject becomes 6 years of age but without a dose change then the intensive PK visit can occur at the next regular Stage 1 visit. Intensive PK collection for the age range (≥ 6 to < 11 years), but not fulfilling the ≥ 25 to < 35 weight range, will be stopped when PK samples from approximately 10 subjects have been collected. All subjects from the weight cohorts (≥ 25 - < 35 kg, ≥ 5 - < 10kg on 200 mg ATV and 80 mg RTV dose) will be evaluated for Intensive PK.

[d] Subjects who did not have the opportunity to reach Week 48 by the time the last treated subject reaches Week 24 will have a final Stage 1 status assessment performed and will immediately move into Stage 2.

[e] If a subject moved to a higher weight band during Stage 1 on or after Week 16 (beyond which study visits occur every 8 weeks), a transition visit will be scheduled 4 weeks following the change in dose. Study visits will then follow per the regular schedule.

[f] Trough ATV levels may be sent for analysis at the discretion of the investigator as a component of a clinical evaluation of subjects with virologic rebound, or failure to achieve virologic suppression in the timeframe expected by the investigator.

Table 5.1-3: Treatment Phase (Stage 2) Procedural Outline (AI424451)

Procedure	Visit every 3 months until Early D/C or local ATV pediatric approval (± 5 days)	Transition Visit for powder-to-capsule switch[a] (± 5 days)	Transition Visit for Weight Band change[b] (± 5 days)	Notes
Safety Assessments				
Full Physical Examination	X			A full physical exam must be performed with vital signs for Final and Early D/C visits.
Targeted Physical Exam		X	X	
Vital Signs	X	X	X	
Concomitant Medication Assessment	X	X	X	
Physical Measurements	X			
Adverse Events Assessment	X	X	X	
AIDS Defining Adverse Events	X	X	X	
ECG		X	X	
Central Laboratory				
HIV RNA	1-2 mL	1-2 mL	1-2 mL	Up to 2mL of blood will be required when Abbott RealTime HIV RNA-1 assay will be used after Roche Amplicor HIV-1 assay (1 mL) will be discontinued. If a VL ≥ 400 c/mL is reported, a confirmation sample is to be taken between 2-4 weeks of the original sample date.
CD4 Count and Percent	1 mL			
Viral resistance				Additional 2 ml samples for both genotype and phenotype resistance testing will be collected in the instance of virologic failure or rebound.
Hematology	1 mL			
Serum Chemistry	1 mL	1 mL	1 mL	

Table 5.1-3: Treatment Phase (Stage 2) Procedural Outline (AI424451)

Procedure	Visit every 3 months until Early D/C or local ATV pediatric approval (± 5 days)	Transition Visit for powder-to-capsule switch[a] (± 5 days)	Transition Visit for Weight Band change[b] (± 5 days)	Notes
Lipids	X			Fasting for subjects ≥ 3 years of age (ie, NPO except for water and medications for at least 12 hours). Subjects < 3 years of age may be non-fasting.
Urinalysis	X			Conducted yearly after the Screening visit.
Pregnancy[c]	X			Local urine pregnancy testing is preferred. In case of doubt, serum pregnancy testing will be done.
Clinical Drug Supplies				
Dispense Study Treatment	X	X		Unless final or Early Discontinuation visit.
Record Study Medication Compliance	X	X	X	
Adherence/Tolerability				
Dispense/Review Subject Diary	X	X	X	Only for subjects on ATV powder and switching to new 4.2% aspartame ATV powder. At time of switch and each visit after as long as the subject is on the new ATV powder formulation or maximum duration of one year, whichever comes first.
Conduct Dosing Assessment	X	X	X	Only for subjects on ATV powder and switching to new 4.2% aspartame ATV powder. Assessed at time of switch and each visit after as long as the subject is on the new ATV powder formulation or maximum duration of one year, whichever comes first

Table 5.1-3: Treatment Phase (Stage 2) Procedural Outline (AI424451)

Procedure	Visit every 3 months until Early D/C or local ATV pediatric approval (± 5 days)	Transition Visit for powder-to-capsule switch[a] (± 5 days)	Transition Visit for Weight Band change[b] (± 5 days)	Notes
Facial Hedonic Scale	X	X	X	5-point scale only to be completed by subjects ≥ 3 years of age on ATV powder and switching to new 4.2% aspartame ATV powder. At time of switch and after as long as the subject is on the new ATV powder formulation or maximum duration of one year, whichever comes first.
Total Blood Volumes	4-5 mL	2-3 mL	2-3 mL	Blood Volumes do not exceed NIH Clinical Center Guidelines of 3 mL/Kg at a single drawn (ie, 15 mL for a 5 Kg infant, the smallest weight that would be enrolled in the study) or 7 mL/Kg over 6 weeks (ie, 35 mL for a 5 kg infant). These volumes represent SOC for HIV infected pediatric subjects except for the PK sampling.

[a] For those subjects switching to the ATV capsule formulation, follow-up visits will be scheduled at 4 and 8 weeks following the indication to switch. Study visits will then follow 4 weeks later, then every 12 weeks until local pediatric ATV approval or until 18 years of age. Subjects who are not able to swallow the capsule after an 8-week transition period will have to discontinue from the study.

[b] When a subject moves to a higher powder or capsule weight band, a follow-up visit will be scheduled 4 weeks following the change in dose. Study visits will then follow per the regular schedule

[c] Started when applicable and more frequent testing can be done if required per local guidelines.

Table 5.1-4: Safety Follow-Up Procedural Outline for Subjects who discontinue the study for any reason, and have hyperbilirubinemia and/or jaundice or ocular icterus at the time of discontinuation

Procedure	Safety Follow-up Visit every 2 Weeks[a]	Notes
Safety Assessments		
Targeted Physical Examination	X	
Concomitant Medication Assessment	X	
Adverse Events Assessment	X	
AIDS Defining Adverse Events	X	
Central Laboratory		
Serum Chemistry	1 mL	
Total Blood Volumes	1 mL	Blood Volumes do not exceed NIH Clinical Center Guidelines of 3 mL/Kg at a single draw (ie, 15 mL for a 5 kg infant, the smallest weight that would be enrolled in the study) or 7 mL/kg over 6 weeks (ie, 35 mL for a 5 kg infant). These volumes represent SOC for HIV infected pediatric subjects except for the PK sampling.

[a] Additional visits every 2 weeks until bilirubin levels are back to Grade 0 or until in the opinion of the investigator, the hyperbilirubinemia is no longer an effect of study medication (eg, it is attributable to other medication or concomitant illness). (See Section 6.7.1.1)

5.2 Study Materials

The sponsor will provide each investigative site with the following:

- ATV (BMS-232632) IB and any relevant safety addenda
- Protocol and any Amendments to the Protocol
- Instructions for completing case report forms (CRFs)
- Investigator Manual from the central laboratory
- Instructions for processing and shipping PK and resistance samples
- SAE and pregnancy forms
- Worksheets for calling the IVRS Assignment Center to enroll, register study treatment, and discontinue subjects
- Investigational Product inventory and assignment logs
- Subject Medication Diary
- Facial Hedonic Scale

5.3 Safety Assessments

Safety assessments include vital signs, physical measurements, deaths, adverse events (serious and non-serious), including Centers for Disease Control (CDC) Class C AIDS events, concomitant medication, laboratory measurements, and ECGs.

Toxicities will be graded according to the Division of AIDS (DAIDS) of the US National Institutes of Health, Toxicity Tables for Grading Severity of Adult and Pediatric (> 3 months of age) Adverse Experiences [December 2004; clarification August 2009] (Appendix 2). The modified WHO grades will be used if DAIDS grading are not available (Appendix 5). Harriet Lane laboratory normals will be used to grade toxicities when laboratory normal ranges are not available.[29] Electrocardiogram (ECG) changes and symptoms related to cardiac conduction abnormalities will be monitored as per protocol (see Section 5.1 for a schedule of ECGs).

5.3.1 Vital Signs and Physical Examinations

The schedule of vital signs, physical examinations, and targeted physical examinations is provided in Section 5.1 (Flow Chart/Time and Events Schedule). Vital signs (blood pressure, heart rate, respiration rate, and temperature) should be measured after the subject has been sitting/resting for at least 5 minutes. Targeted physical examinations will include an examination of the heart, lungs, skin, abdomen, any symptomatic organ system, and general appearance.

5.3.2 Adverse Events

Subjects will be closely monitored throughout the study for any new or ongoing HIV-related diagnoses (Appendix 3) and/or adverse events. Events that occur from the Screening Visit through Day 1 (prior to dosing) will be recorded as Pre-treatment Events. All events that occur

after dosing on Day 1 will be recorded on the appropriate Adverse Event eCRF. Additional information on Adverse Events is provided in Section 6.

[redacted]

5.3.4 Electrocardiograms

The schedule of electrocardiograms (ECGs) is provided in Section 5.1 (Flow Chart/Time and Events Schedule). ECGs will be read by a central vendor to monitor for evidence of arrhythmias, ischemia, or AVB at Screening to determine eligibility, including PR prolongation, QTc increase, QRS widening and any other abnormalities occurring on treatment. A complete report will be generated for each ECG, including all standard measurements and an interpretation.

5.3.5 Physical Measurements

Physical measurements (measured without shoes, without diapers, and wearing minimal clothing) include height, weight, head circumference (for subjects < 3 years of age at the visit), and BSA.

5.4 Efficacy Assessments

5.4.1 Primary Efficacy Assessment

All efficacy assessments address secondary study objectives.

5.4.2 Secondary Efficacy Assessments

Efficacy analysis will include: proportions of subjects with HIV RNA < 50 c/mL and < 400 c/mL at each scheduled visit through Week 24 and up to Week 48; (see Section 8.3 for further detail).

- Change from baseline in HIV RNA, CD4 cell count and CD4 percentage will be assessed.
- Results from Stage 2: Efficacy will be assessed only to ensure subjects maintain virologic and immunologic control.

Subjects who did not have the opportunity to reach Week 48 by the time the last treated subject reaches Week 24 will have a final Stage 1 status assessment performed and will immediately move into Stage 2 while remaining on ATV powder.

5.5 Pharmacokinetic Assessments

5.5.1 Intensive Pharmacokinetic Assessment

Intensive 24 hour PK samples will be collected in Stage 1 only for subjects who:

- Enter the study weighing ≥ 25 - < 35 kg and/or ≥ 6 to < 11 years of age at scheduled Week 2 visit or
- Subjects moving into the ≥ 25 - < 35 kg weight range or becoming 6 years old during Stage 1, the intensive PK visit will occur two weeks after the dose change for the new weight band. If the subject becomes 6 years of age but without a dose change then the intensive PK visit can occur at the next regular Stage 1 visit.
- Subjects enrolling a new ≥ 5 - < 10 kg cohort with 200mg ATV and 80 mg RTV dose

An intensive PK assessment will be conducted at Week 2 (Day 14). Serial plasma concentrations will be collected over a 24-hour period in order to assess the steady state PK of ATV and RTV. Table 5.5.1-1 lists the sampling schedule to be followed for the assessment of PK over a 24 hour period at Week 2. For subjects moving into the ≥ 25 to < 35 kg weight range or becoming 6 years old during Stage 1, the intensive PK visit will occur 2 weeks after the dose change for the new weight band. If the subject becomes 6 years of age but without a dose change then the intensive PK visit can occur at the next regular Stage 1 visit.

Intensive PK collection for the age range (≥ 6 to < 11 years), but not fulfilling the ≥ 25 to < 35 weight range, will be stopped when PK samples from approximately 10 subjects have been collected. All subjects from the weight cohorts (≥ 25 - < 35 kg, ≥ 5 - < 10 kg on 200 mg ATV and 80 mg RTV dose) will be evaluated for Intensive PK.

Table 5.5.1-1: Intensive PK Sample Schedule

Sample Collection Time		**Time (Relative To Dosing) hours:min**	**PK Blood Sample for ATV/RTV**
Study Week	Time (Event)		
Week 2	0 h (pre-dose)[a]	00:00 (pre-dose)	X
	1.5 h (post-dose)	01:30	X
	2.5 h (post-dose)	02:30	X
	4 h (post-dose)	04:00	X
	6 h (post-dose)	06:00	X
	8 h (post-dose)	08:00	X
	12 h (post-dose)	12:00	X
	24 h(post-dose)	24:00	X

[a] Samples to be obtained prior to study drug(s) administration

Steady state PK parameters to be assessed include ATV and RTV Cmax, Tmax, AUC(TAU), Cmin, apparent oral clearance from plasma (CLT/F) and apparent oral clearance from plasma adjusted for body weight (CLT/F/kg).

5.5.1.1 Data Collection (Intensive PK- only for subjects weighing ≥ 25 - < 35 kg and/or aged ≥ 6 to < 11 years; subjects enrolling in a new ≥ 5 - <10 kg cohort with 200mg ATV and 80 mg RTV)

There are several important dates and times to record relative to the Intensive PK visit at Week 2, not only on the day of the actual visit, but also on the day prior to the visit, as well as the day after the visit is initiated.

PK data is viable only if the time elapsed between the dose taken prior to the sampling (taken on the day before the sampling) and the actual start of the Intensive PK blood sampling (the 0-hr blood draw) is between 20 - 28 hours. In order to determine adherence to this window, data points collected on the CRF and on the laboratory requisition are analyzed to calculate the elapsed time.

Important Lab Requisition data points

1. Date and Time* of Blood Sampling on the day of the Intensive PK visit

Important CRF data points

1. Date and Time* of Dose PRIOR TO the 0-hr PK blood draw
   a) This date and time should be the day prior to the visit (20 - 28 hours before the PK blood sampling is started). If the subject was mistakenly dosed on THE DAY OF the Intensive PK visit before they came to the clinic, then the 20 - 28-hour window cannot be applied and the Intensive PK visit should be rescheduled to occur as quickly as possible. (Immediately notify your BMS Site Manager.)
2. Date and Time* of Dose and *light* Meal AFTER the 0-hr PK blood draw
   a) This is the date and time of the dose on THE DAY OF the Intensive PK visit. This dose must not be taken at home, rather AT the clinic visit and AFTER the 0-hr blood draw is taken.
3. All concomitant medication taken by the subject within 24 hours of the 0-hr PK blood draw
4. Date and Time* of Dose AFTER the 24-hr PK blood draw
   a) This is the date and time on the day AFTER the PK sampling began. Once the 24-hr PK sample has been drawn, the subject may be administered the dose for the day.

** Time will be captured in the 24-hour clock format.*

5.5.2 Trough Plasma Concentration (for all subjects)

Trough PK will be evaluated at each scheduled visit from Week 4 through a minimum of 24 weeks up to a maximum of 48 weeks. Trough PK collection will be stopped for ongoing subjects in Stage 1 when the last subject reaches week 24. These samples will be collected at 24 hours after the last dose for ATV and RTV (acceptable window from prior ATV dose: 20 - 28 hours).

Trough ATV levels may be sent for analysis at the discretion of the investigator as a component of a clinical evaluation of subjects with virologic rebound, or failure to achieve virologic suppression in the timeframe expected by the investigator.

5.5.2.1 Data Collection (Trough PK - for all subjects)

There are several important dates and times to record relative to all of the Trough PK visits, not only on the day of the actual visit, but also on the day prior to the visit. Trough PK collection will be stopped for ongoing subjects in Stage 1 when the last subject reaches week 24.

PK data is viable only if the time elapsed between the dose taken prior to the sampling (taken on the day before the sampling) and the actual time of the Trough PK blood sampling is between 20 - 28 hours. In order to determine adherence to this window, data points collected on the CRF and on the laboratory requisition are analyzed to calculate the elapsed time.

Important Lab Requisition data points

1. Date and Time* of Blood Sampling on the day of the Trough PK visit

Important CRF data points:

1. Date and Time* of Dose and *light* Meal PRIOR TO the Trough PK blood draw
   a) This date and time should be the day prior to the visit (20 - 28 hours before the PK blood draw). If the subject was mistakenly dosed on THE DAY OF the Trough PK visit before they came to the clinic, then the 20 - 28-hour window cannot be applied and the sample should not be drawn. Depending on the visit, it may be possible to reschedule the Trough PK visit. (Immediately notify your BMS Site Manager.)
2. All concomitant medication taken by the subject within 24 hours of the Trough PK blood draw.

* *Time will be captured in the 24-hour clock format.*

5.5.3 Blood Collection and Processing (Intensive and Trough Samples)

Blood samples will be collected from an indwelling catheter or by direct venipuncture. If a catheter is used for blood collection then approximately 1 mL of blood/saline should be withdrawn initially and discarded. Malfunctions to the venous catheter, poor venous access, or other difficulties which would cause time point sample delays may be cause for the reschedule of the intensive PK visit. Note: 1 sample tube is collected as ATV/RTV is assayed simultaneously.

5.5.3.1 Collection Instructions

One (1) Polyethylene Terephthalate (PET) tube of 0.8 mL of blood for ATV/RTV will be collected from an indwelling catheter or by direct venipuncture. The blood samples will be collected into an evacuated collection tube containing EDTA (K2EDTA) as the anticoagulant. Immediately after collection, each blood sample will be gently inverted a few times for complete mixing with the anticoagulant (K2EDTA) and then placed on chipped ice. Within 60 minutes of

collection, each blood sample will be centrifuged (using a refrigerated centrifuge) for 10 minutes at approximately 1000 x g at about 5°C to separate the cellular elements from plasma. The separated plasma will be transferred within 30 minutes to a labeled screw-capped polypropylene cryotube and stored at -20°C until shipped to the analytical laboratory for analysis. At a minimum, times of sample collection, centrifugation, plasma harvest, and sample storage should be recorded on a sample harvest log. Each blood sample will be labeled appropriately and the date for each sample will be entered on the blood collection requisition form for the central laboratory. The status of sample collection for each PK time point (yes or no) will be entered on the blood collection eCRF page.

Alternatively, if there is no refrigerated centrifuge available at the clinical site, samples should be centrifuged as follows. After collection, samples should be gently inverted a few times for mixing with the anticoagulant and placed on chipped ice or in a refrigerator for 20 minutes prior to centrifugation. The centrifuge tube buckets(s) should be placed on chipped ice or in a refrigerator for 15 - 20 minutes prior to blood sample centrifugation. Each sample will then be centrifuged for 10 - 15 minutes at approximately 1000 x g to separate cellular elements from plasma. The separated plasma should be transferred within 60 minutes of collection to a polypropylene cryotube and stored at - 20°C until shipped to the central laboratory. At a minimum, times of sample collection, centrifugation, plasma harvest, and sample storage should be recorded on a sample harvest log. Each blood sample will be labeled appropriately and the actual, precise time and date for each sample will be entered on the blood collection requisition form for the central laboratory. The status of sample collection for each PK time point (yes or no) will be entered on the blood collection eCRF page. Samples should not be batched and should be shipped as soon as possible to the central laboratory.

5.5.4 Labeling and Shipping of Biological Samples (Intensive and Trough Samples)

Pre printed computer labels will be supplied along with sample collection kits for each pharmacokinetic sample.

All tubes will be clearly and indelibly labeled with the following information:

- Study
- Subject Number
- Study Week/Study Hour
- Period
- Sample Type
- Label Type
- Barcode

For plasma pharmacokinetic samples, the sampling time is written as Week(W) hour(h) minute(m). For example, the Week 2, 1.5 hour post-dose sample will be written as 2W 1h 30m; and the Week 2, 4 hour post-dose sample will be written as W2 4h 0m.

The samples should be shipped to the designated Central Laboratory by overnight air express using insulated containers with enough dry ice to maintain the samples in a frozen state until they are received at the analytical site. The shipment of biospecimens (human samples) must comply with the appropriate regulations as specified by the carrier. At a minimum, all samples must be packaged within 2 containers with absorbent material between containers to control any spill or leakage. The outer container must be puncture resistant (eg, cardboard mail tube, corrugated cardboard box). In addition to the name and address of the person responsible for receiving the samples, a fluorescent, orange-red BIOHAZARD label with the appropriate symbol must be affixed to the inner container.

The arrangements for shipping are to be made by the Study Coordinator. The Coordinator should contact the Central Laboratory (contact name to be provided) by telephone and/or fax at least 1 day prior to the sample shipment to ensure proper receipt.

SAMPLES SHOULD NOT BE SHIPPED TO ARRIVE OVER WEEKENDS OR HOLIDAYS.

5.6 Pharmacodynamics Assessments

Not applicable.

5.7 Pharmacogenomic/Pharmacogenetic Assessments

Not applicable.

5.8 Outcomes Research Assessments

Not applicable.

5.9 Other Assessments

5.9.1 Palatability Assessments

Subjects who are still on ATV powder formulation in Stage 2 will be switched to the new 4.2% aspartame ATV powder at their next regular study visit. The palatability assessment will be conducted by completion of a palatability survey and 5-point Facial Hedonic Scale.[30,31,32,33] The 5-point Facial Hedonic Scale will be completed by subjects ≥ 3 years of age on ATV powder and switching to the new ATV powder formulation. Subjects that cannot complete the assessment will be exempted from the Facial Hedonic Scale palatability assessment. Specific instructions for the Facial Hedonic Scale assessment tool and source documents will be provided to the sites.

The palatability assessments should be completed at the time of switch to the new 4.2% aspartame ATV powder formulation and after as long as the subject is on the new 4.2% aspartame ATV powder formulation or maximum duration of one year, whichever comes first.

The first dose on the new 4.2% aspartame ATV powder should be administered at the clinic and immediately followed by first 5-point Facial Hedonic Scale assessment. Subjects are encouraged not to take their dose of new study medication prior to the study visit as long as subject is on new ATV powder and Facial hedonic Scale palatability will be assessed. Subjects will take their dose at the clinic followed by Facial Hedonic Scale administration.

5.9.2 Laboratory Test Assessments

Please refer to Section 5.1 as to when these tests are required.

The tests will be performed by a central laboratory that is licensed and meets Clinical Laboratory Improvement Amendments (CLIA) regulations or equivalent by country. A copy of the current laboratory license and CLIA certification or equivalent must be kept on file at the study site. Laboratory test kits and a manual will be provided by the central laboratory.

Fasting lipids for subjects ≥ 3 years of age (ie, NPO except for water and medications for at least 12 hours). Subjects < 3 years of age may be non-fasting.

- Hematology will consist of CBC, cell differential (including absolute neutrophils + absolute bands), and platelet count, CD4 cell count, and percentage.
- Serum Chemistry will consist of sodium, potassium, chloride, bicarbonate, calcium, glucose, BUN, creatinine, urate (uric acid), total protein, albumin, LDH, ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin, amylase, and lipase.
- Fasting lipids - The following analytes will be evaluated: total cholesterol, HDL, LDL, and triglycerides. Subjects in ≥ 3 years of age will be NPO for 12 hours prior to draw except for water and medication. Subjects in < 3 years may have samples for these laboratory tests drawn non-fasting.
- Record the time of the most recent meal on the CRF.
- Urinalysis will comprise pH, specific gravity, protein, glucose, ketones, blood, and microscopy.
- HIV-1 RNA PCR by Roche Amplicor® Assay (version 1.5), or Abbott RealTime HIV-1 assay after the Roche Amplicor assay is discontinued.
- Pregnancy test (when applicable in stage 2). Urine pregnancy testing is preferred. In case of doubt, serum pregnancy testing (FSH, hCG) can be done.

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

6.1 Serious Adverse Events

A ***serious AE (SAE)*** is any untoward medical occurrence that at <u>any dose</u>:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

Suspected transmission of an infectious agent (eg, any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs for data transmission purposes (See Section 6.1.1 for reporting pregnancies).

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered "important medical event" or event life threatening)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)

- medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

6.1.1 Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 30 days of discontinuation of dosing. The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs must be recorded on the BMS SAE Report Form; pregnancies on a BMS Pregnancy Surveillance Form. These original BMS Forms are to remain on site. SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours via confirmed facsimile (fax) transmission, or scanned and reported via electronic mail to:

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: See Contact Information list.

SAE Telephone Contact (required for SAE and pregnancy reporting): See Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.3 Laboratory Test Abnormalities

The following laboratory abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical, rather than the laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

6.4 Pregnancy

Females who may become sexually active women of childbearing potential (WOCBP) must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized. The definition of WOCBP is addressed in protocol Section 3.3.3.

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to the sponsor. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

Specific Information Related to ATV and Pregnancy

Atazanavir is classified by the US FDA as Pregnancy "Category B" (Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.)

At maternal doses producing the systemic drug exposure levels equal to (in rabbits) or 2 times (in rats) those at the human clinical dose (400 mg once daily), ATV did not produce teratogenic effects. In the pre- and post-natal development assessment in rats, ATV, at maternally toxic drug exposure levels 2 times those at the human clinical dose, caused body weight loss or weight gain suppression in the offspring. Offspring were unaffected at a lower dose that produced maternal exposure equivalent to that observed in humans given 400 mg once daily. ATV had no effect on reproductive performance of the offspring. In conclusion, ATV demonstrated no selective developmental toxicity and no effects on reproductive function or fertility in rats and/or rabbits at exposures that were at least equal to or slightly greater than that observed in humans given 400 mg once daily.

Atazanavir has been evaluated in a limited number of women during pregnancy and postpartum. In clinical trial AI424-182, ATV/RTV (300/100 mg or 400/100 mg) in combination with zidovudine/lamivudine was administered to 41 HIV-infected adult pregnant women during the second or third trimester. The study also assessed 40 infants who received antiretroviral prophylactic treatment (which did not include ATV) and were negative for HIV-1 DNA at the time of delivery and/or during the first 6 months postpartum. PK and safety results were evaluated and detailed information is available in the U.S. Package insert for Reyataz and in the Summary of Medicinal Product Characteristics in the EU. Available human and animal data suggest that atazanavir does not increase the risk of major birth defects overall compared to the background rate. However, because the existing studies in humans cannot rule out the possibility of harm, atazanavir should be used during pregnancy only if the potential benefit justifies the potential risk. There are no studies and adequate clinical data in pregnant teenager females.

The CDC recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Studies in lactating rats have demonstrated that ATV is secreted in milk. It is not known whether ATV is secreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving ATV.

Pregnancy testing must also be performed throughout the study as specified in Section 5.1 (see flow chart/time and events schedule) and the results of all pregnancy tests (positive or negative) recorded on the CRF or transferred electronically.

In addition, all WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual period) at any time during study participation.

6.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 6.1.1 for reporting details.).

6.6 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1. for reporting details).

Potential drug induced liver injury is defined as

1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

6.7.1 Toxicity Management

There will be no dose reductions for study drug toxicities. Additionally, there will be no substitutions for ATV/RTV. On-study substitutions of nucleoside analog therapy with one or more other nucleoside analogs approved for use by infants/children will be permitted for toxicity at the discretion of the investigator. The BMS medical monitor or designee should be contacted prior to the substitution, if possible.

The cost of "alternative" NRTI agents not provided per protocol will be defrayed by the sponsor. Alternative nucleoside analogs, if used, must be administered according to labeled dosing recommendations. Subjects must receive 2 nucleoside analogs in addition to ATV/RTV throughout the study.

If it becomes necessary to temporarily interrupt any study medication for toxicity, all antiretrovirals must be stopped and restarted at the same time (on the same day), at full dose. If either NRTI is replaced with an alternative nucleoside analog all, new drugs should be started on the same day with ATV/RTV; sequential restarting of study medications is not allowed.

Symptomatic therapy for toxicity (eg, analgesics, anti-emetics, anti-diarrhea agents, or other medications) is permitted as long as it is not an exclusionary medication, but must be recorded in the CRF.

The Division of AIDS (DAIDS) standardized toxicity table for grading severity of pediatric adverse experiences (Appendix 2) will be used for grading toxicities. The supplemental toxicity tables supersede the DAIDS toxicity table when grading skin rash, triglyceride, and cholesterol toxicities.

In general, for abnormal treatment-related, or possibly treatment-related, clinical or laboratory observations of:

- Grade 1 severity - Continue study medications; routine monitoring.
- Grade 2 severity - Continue study medications; monitor closely with more frequent visits; work-up to exclude other causes.
- Grade 3 severity (with the exception of hyperbilirubinemia)- Repeat observation within 72 hours for confirmation. Subjects should continue taking study medications pending receipt of the confirmatory laboratory tests. However, the clinician has the option of immediately interrupting the study medications if a repeat confirmatory laboratory test cannot be performed within 72 hours, or if the clinician determines that the continuation of study medications is unsafe while awaiting test results. For all confirmed Grade 3 toxicities, stop all study medications until toxicity resolves to ≤ Grade 2. Subjects will be allowed to interrupt study treatment for up to 14 days. If toxicity persists at Grade 3 for more than 14 days or recurs on re-challenge, study medications generally should be discontinued permanently.
- Grade 4 severity* (with the exception of hyperbilirubinemia) - Hold study medications and notify the BMS medical monitor or designee. Obtain confirmatory laboratory results within 72 hours and notify the BMS medical monitor or designee of those results. For all confirmed Grade 4 toxicities, stop all study medications until toxicity resolves to < Grade 2. Subjects will be allowed to interrupt study treatment for up to 14 days. If toxicity persists at Grade 4 for more than 14 days or recurs on re-challenge, discontinue study medications permanently.

***Note**: For all Grade 4 toxicities (with the exception of hyperbilirubinemia)-, telephone the BMS medical monitor or designee within 24 hours of the event.

Specific recommendations for management of pancreatitis, hyperlipasemia, hyperamylasemia, abnormal liver enzymes, CNS symptoms, lipid abnormalities, hyperglycemia, and rash are outlined in Appendix 4.

6.7.1.1 Management of Hyperbilirubinemia

Many subjects taking ATV experience asymptomatic elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl transferase (UGT). Hepatic transaminase elevations that occur with hyperbilirubinemia should be evaluated for alternative etiologies. Dose modification of ATV is not permitted. Subjects who experience unacceptable jaundice/ocular icterus should be discussed with the BMS Medical Monitor to determine if subjects are to be discontinued from study.

The investigator must contact the BMS Medical Monitor prior to discontinuing any subject due to hyperbilirubinemia.

A post-study follow up will be required for the following discontinued subjects:

- Subjects who discontinue for hyperbilirubinemia and/or jaundice or ocular icterus (regardless of the grade of either)
- Subjects who discontinue for other reasons unrelated to hyperbilirubinemia or jaundice or ocular icterus but have a total bilirubin of ≥ Grade 2 at the time of discontinuation

The post-study follow up will consist of additional visits every 2 weeks until the hyperbilirubinemia decreases back to Grade 0 or until in the opinion of the investigator the hyperbilirubinemia is no longer an effect of study medication (eg, it is attributable to other medication or concomitant illness).

Follow-up visit procedures will include laboratory evaluation of liver function, assessments of concomitant medications and adverse events (and jaundice or ocular icterus resolution if applicable), and a targeted physical exam as needed (see Table 5.1-4).

6.7.1.2 Criteria for Treatment Interruption

Study medications may be interrupted either for medication toxicity, as detailed previously, or for an intercurrent illness, for up to 14 days. Therapy or prophylaxis for opportunistic infections requiring use of concomitant medications not allowed in the protocol should be discussed with the BMS medical monitor or designee.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

There will be an independent data monitoring committee (DMC) for this study. The DMC shall have access to data on at least an annual basis, including but not limited to following: the frequency and spectrum of serious adverse events; Grades 3 to 4 laboratory abnormalities; occurrence of malignancies; and other select adverse events of interest. The DMC shall act as an

advisor to the sponsor and have responsibility for safeguarding the subjects' interests. The DMC shall bring any safety concerns to the attention of the sponsor so that the sponsor can review the data and prepare appropriate communications to the Regulatory Authorities. A separate charter shall be developed for the DMC; this will describe the membership and activities of the DMC.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

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 (200 mg ATV and 80 mg RTV) cohort and have a minimum number of 56 treated subjects with 48 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 intervals (CI) within ± 10.5% for a response rate of 50.5% for modified intent-to-treat (ITT) analysis.

8.2 Populations for Analyses

- Enrolled subjects are those whose informed consent form were signed by a parent/legally acceptable representative and were assigned a subject identification number (PID).
- Treated subjects are enrolled subjects who received at least 1 dose of study therapy (ATV).

8.3 Endpoint Definitions

8.3.1 Safety Endpoints

Primary safety endpoints are:

- the number of subjects who died (regardless of onset)
- frequency of SAEs in Stage 1 through Week 48 on ATV powder
- frequency of AE leading to discontinuation in Stage 1 through Week 48 on ATV powder.

All safety data in Stage 1 through Week 48 on ATV powder will be included in the safety analysis.

8.3.2 Efficacy Endpoints

All efficacy endpoints are secondary. The principal efficacy endpoints are the proportions of subjects with HIV RNA < 50 c/mL and HIV RNA < 400 c/mL at Week 24 and Week 48 of ATV powder formulation.

The efficacy analysis at Week 48 of ATV powder formulation will include only those subjects who had the opportunity to reach week 48 by the time that the last treated subjects reaches week 24.

8.4 Analyses

When summarizing Stage 1 data, values after transitioning from powder to capsules will be excluded.

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 (e.g., n, mean, median, standard error).

Efficacy and safety parameters are assessed on ATV powder in Stage 1 through Week 48 (i.e., values after the first dose of ATV capsule are excluded), unless specified otherwise.

Analyses of HIV RNA use pre-defined analysis week windows based on both regulatory correspondence and the study visit schedule, while analyses of other parameters (e.g., laboratory tests, ECGs) use pre-defined visit week windows based on the study visit schedule.

Laboratory parameters are assessed using US values and units.

Efficacy is presented by baseline weight band (5 - < 10 (ATV 150 mg), 5 - < 10 (ATV 200 mg), 10 - < 15 kg, 15 - < 25 kg, 25 - < 35 kg), prior ARV use (naive, experienced) and total (pooled). All other summaries are presented by baseline weight and total. All summaries are presented for treated subjects unless otherwise noted.

8.4.1 Demographics and Baseline Characteristics

The following will be summarized for treated subjects:

- Demographics: age, race, ethnicity, gender, geographic region;
- Disease characteristics at baseline: HIV RNA, CD4 cell count, CD4 percentage, prior ARV use (naive, experienced);
- Vital signs and physical measurements at baseline;
- Laboratory tests at baseline;
- Pre-treatment CDC Class C AIDS events;
- Prior medications.

8.4.2 Efficacy Analyses

The following efficacy endpoints will be summarized on treatment:

- Proportions of subjects with HIV RNA < 50 c/mL and < 400 c/mL at Week 24:
  - Modified intent-to-treat (ITT): The numerator is based on subjects with HIV RNA < 50 (400) c/mL at Week 24. The denominator is based on treated subjects.
  - Observed values: Similar to modified ITT, the numerator is based on subjects with HIV RNA < 50 (400) c/mL at Week 24. However, the denominator is based on subjects with HIV RNA at Week 24.
- Proportions of subjects with HIV RNA < 50 c/mL and < 400 c/mL at Week 48:
  - Modified intent-to-treat (ITT): The numerator is based on subjects with HIV RNA < 50 (400) c/mL at Week 48. The denominator is based on treated subjects who had the opportunity to be assessed at Week 48.
  - Observed values: Similar to modified ITT, the numerator is based on subjects with HIV RNA < 50 (400) c/mL at Week 48. However, the denominator is based on subjects with HIV RNA at Week 48.

Response rates will be presented with exact binomial 95% CIs using modified ITT and observed values.

- HIV RNA $\log_{10}$ values and changes from baseline at each analysis week in Stage 1 through Week 48 on ATV powder;
- CD4 cell count and CD4 percentage: values and changes from baseline at each visit week in Stage 1 through Week 48 on ATV powder;
- Resistance in Stage 1 through Week 48 on ATV powder for virologic failures (defined in Section 4.5.1):
  - Newly-emergent genotypic substitutions, i.e., on-treatment substitutions that were not detected at baseline;
  - Newly-emergent phenotypic resistance, i.e., baseline fold change ≤ the cut-off for reduced susceptibility and an on-treatment fold change > the cut-off for reduced susceptibility.

Stage 2 data will be summarized at each visit week through the end of the study.

8.4.3 Safety Analyses

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

Adverse events will be presented by system organ class and preferred term. Summaries will include both non-serious and serious adverse events, unless specified otherwise. If a subject had

an adverse event with different intensities over time, then only the greatest intensity will be reported on treatment.

Deaths will be listed for enrolled subjects without regard to onset.

The frequencies of the following safety endpoints will be summarized on treatment in Stage 1 through Week 48 on ATV powder:

- Serious adverse events;
- Adverse events leading to discontinuation of study therapy;
- Adverse events by intensity;
- CDC Class C AIDS events;
- Laboratory abnormalities by toxicity grade and overall. The highest toxicity grade on treatment will be reported for each test.
- ECG categories at each visit week;
- Physical measurements (age-adjusted percentiles and age-adjusted Z scores for height and weight): values and changes from baseline at each visit week.

Stage 2 data will be summarized using freq of SAEs, AEs leading to disc, grade 3 to 4 AEs, grade 3 to 4 laboratory abnormalities.

8.4.4 Pharmacokinetic Analyses

Intensive PK (only for subjects weighing ≥ 25 - < 35 kg and/or aged ≥ 6 to < 11 years and subjects enrolling in the new ≥ 5 - < 10 kg cohort (200mg ATV and 80mg RTV).

An intensive PK assessment for ATV and RTV will be conducted. Serial plasma concentrations will be collected over a 24-hour period at Week 2 in order to assess the steady state PK of ATV and RTV. For subjects moving into the ≥ 25 to < 35 kg weight range or becoming 6 years old during Stage 1, the intensive PK visit will occur two weeks after the dose change for the new weight band. If the subject becomes 6 years of age but without a dose change then the intensive PK visit can occur at the next regular Stage 1 visit. Pharmacokinetic parameters of ATV and RTV will be derived from plasma concentration versus time data by a non-compartmental method using a validated pharmacokinetic program. Steady state parameters to be assessed include:

- Cmax: Maximum observed concentration;
- Tmax: Time of maximum observed concentration;
- Cmin: Plasma concentration 24 hours post observed dose;
- AUC (TAU): Area under the concentration-time curve, in 1 dosing interval from time 0 to 24 hours post observed dose;
- IQ: Ratio of Cmin at Week 2 to Protein Binding Adjusted EC90 derived from individual subject clinical isolates at baseline (ATV only);

- CLT/F: apparent oral clearance from plasma
- CLT/F/kg: apparent oral clearance from plasma adjusted for body weight.

Summary statistics for all the relevant PK parameters of ATV will be presented by weight bands. Additional summaries may be presented by age group. In addition, geometric means and coefficients of variation (CV) will be presented for Cmax, AUC (TAU), Cmin, and IQ. Medians, minima, and maxima will be reported for Tmax.

Similar analyses will be performed for RTV.

Trough Concentrations (for all subjects, Weeks 4 through a minimum of 24 weeks and up through 48 weeks in Stage 1, except transition visits)

Trough plasma concentrations (Ctrough) of ATV and RTV and IQ of ATV will be summarized by visit week.

8.4.5 Pharmacodynamic Analyses

The relationship between ATV PK parameters and efficacy and/or safety endpoints and ATV composite trough concentration and IQ versus efficacy endpoints following administration of the powder formulation will be explored graphically. Efficacy endpoints may include proportion of subjects with HIV RNA < 50 c/mL, proportion with HIV RNA < 400 c/mL, HIV RNA changes from baseline, CD4 cell count changes from baseline, and CD4 percentage changes from baseline. Safety endpoints may include selected AEs and changes from baseline in laboratory tests.

8.4.6 Pharmacogenomic Analyses

Not applicable.

8.4.7 Outcomes Research Analyses

Not applicable.

8.4.8 Other Analyses

8.4.8.1 Palatability

For ATV 10% aspartame powder formulation, proportions of subjects in each category of each question on the palatability survey will be tabulated at each visit when they are taking this formulation by weight band.

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 by weight band at each visit since they switch to the new formulation in Stage 2. In addition, 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).

8.5 Interim Analyses

- The primary analysis will be conducted when Week 24 data of all treated subjects are available (Stage 1).
- The final analysis will be conducted when Stage 2 data of all treated subjects are available.
- Additional safety updates and summaries of efficacy may be conducted at unscheduled intervals to support regulatory questions/interactions; and at the request of the DMC.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- Bristol-Myers Squibb
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent.

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the sponsor, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by the sponsor) and the following noninvestigational product(s): all NRTI backbone therapy, is maintained at each study site where study drug is inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label ID number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- non-study disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to the sponsor

- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product (IP) dispensing/accountability, as per the Delegation of Authority Form.

The sponsor will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by the sponsor.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by a qualified physician who is an investigator or sub-investigator. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by the sponsor. User accounts are not to be shared or reassigned to other individuals.

9.3 Publications

The data collected during this study are confidential and proprietary to the sponsor. Any publications or abstracts arising from this study require approval by the sponsor prior to publication or presentation and must adhere to the sponsor's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to the sponsor at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. Sponsor shall have the right to delete any

confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

10 GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or the sponsor as related to the investigational product
Expedited Safety Report	Rapid notification to investigators of all SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the Investigator Brochure), or that could be associated with the study procedures.
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator Brochure for an unapproved investigational product)

11 LIST OF ABBREVIATIONS

Term	Definition
3TC	lamivudine/Epivir
AE	adverse event
ALT	alanine transaminase (SGPT)
ARV	Antiretroviral
AST	aspartate transaminase (SGOT)
ATV	Atazanavir
AUC	area under the curve
AUC(TAU)	area under the curve (over the dosing interval)
AV	Atrioventricular
BSA	body surface area
c/mL	copies per milliliter
CBC	complete blood count
CD4	antigenic marker of helper/inducer T cells
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CLT/F	Apparent oral clearance from plasma
CLT/F/kg	Apparent oral clearance from plasma adjusted for body weight
Cmax	maximum concentration of drug
Cmin	minimum concentration of drug
CRF	case report form, paper or electronic
CSR	Clinical Study Report
DAIDS	Division of AIDS
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
eCRF	electronic CRF
EDC	electronic data capture
FDA	Food and Drug Administration
GCP	good clinical practice
h	Hour

Term	Definition
HAART	highly active antiretroviral therapy
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high density lipoprotein
HIV RNA	human immunodeficiency virus ribonucleic acid
ICH	International Council on Harmonization (of technical requirements for registration of pharmaceuticals for human use)
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent To Treat
IVRS	Interactive voice response system
Kg	Kilogram
L	Liter
LDL	low density lipoprotein
LPV	Lopinavir
mL	milliliter
NRTI	nucleoside reverse transcriptase inhibitor
NPO	nothing by mouth
PD	Pharmacodynamic
PI	protease inhibitor
PK	Pharmacokinetic
PMTCT	Prevention of mother to child transmission
PPK	Population pharmacokinetics
PSDP	Post Study Drug Program
QD	Once daily
RNA	ribonucleic acid
RTV	Ritonavir
SAE	serious adverse event
SOC	Standard of care
TAO	trial access online, the BMS implementation of an EDC capability
TDF	Tenofovir

Term	Definition
ULN	upper limit of normal
VR	Virologic response
WOCBP	women of child-bearing potential

APPENDIX 1 LISTINGS OF PROHIBITED AND PRECAUTIONARY THERAPIES DURING THE STUDY

General Notes:

- Guidelines for the use of drugs with established or other potentially significant drug interactions listed in the Package Inserts of the marketed ARV agents used by subjects participating in this study (Reyataz®, Norvir®) should be followed.
- Medications listed in the Package Inserts as contra-indicated with the other marketed ARV agents used by subjects participating in this study are not permitted.
- Prophylaxis for Pneumocystis carinii pneumonia (PCP) is strongly recommended for subjects who may develop during the study an absolute CD4 cell count ≤ 200 cells/mm^3 or who have had a prior episode of PCP.
- Guidelines regarding immunization:
  - Subjects on study and treated for > 12 weeks: Any immunizations deemed appropriate by the subject's physician are permitted provided that the immunization is given ≥ 4 weeks from any HIV RNA measurement; i.e. immunization should be given immediately after the HIV RNA sample is collected for purpose of the study visit
  - Subjects ≤ week 12 visit: The immunization program can be performed while keeping the visits schedule.
- For bone-marrow suppression emerging on study, the use of erythropoietin and/or G CSF and/or blood transfusions are allowed.
- A subject may not be co-enrolled in a concomitant trial prior to randomization.

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Drugs that may prolong the QT Interval and/or induce Torsades de Pointes:

amiodarone	mesoridazine
arsenic trioxide	mexiletine
chlorpheniramine	moexipril/HCTZ
chlorpromazine	moxifloxacin
clarithromycin	naratriptan
disopyramide	nicardipine
dofetilide	octreotide
dolasetron	paroxetine
droperidol	procainamide
erythromycin	quetiapine
felbamate	risperidone
fluoxetine	salmeterol
foscarnet	sertraline
fosphenytoin	sotalol
gatifloxacin	sparfloxacin
halofantrine	sumatriptan
haloperidol	tamoxifen
ibutilide	thioridazine

indapamide	tizanidine
isradipine	venlafaxine
levofloxacin	ziprasidone
levomethadyl	zolmitriptan
lidocaine (systemic)	

APPENDIX 2 DAIDS TOXICITY GRADES

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
Version 1.0, December, 2004; clarification AUGUST 2009

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE Grading Table") is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

This clarification of the DAIDS Table for Grading the Severity of Adult and Pediatric AE's provides additional explanation of the DAIDS AE Grading Table and clarifies some of the parameters.

I. Instructions and Clarifications

Grading Adult and Pediatric AEs

The DAIDS AE Grading Table includes parameters for grading both Adult and Pediatric AEs. When a single set of parameters is not appropriate for grading specific types of AEs for both Adult and Pediatric populations, separate sets of parameters for Adult and/or Pediatric populations (with specified respective age ranges) are given in the Table. If there is no distinction in the Table between Adult and Pediatric values for a type of AE, then the single set of parameters listed is to be used for grading the severity of both Adult and Pediatric events of that type.

> **Note:** In the classification of adverse events, the term "**severe**" is not the same as "**serious**." Severity is an indication of the intensity of a specific event (as in mild, moderate, or severe chest pain). The term "**serious**" relates to a participant/event outcome or action criteria, usually associated with events that pose a threat to a participant's life or functioning.

Addenda 1-3 Grading Tables for Microbicide Studies

For protocols involving topical application of products to the female genital tract, male genital area or rectum, strong consideration should be given to using Appendices I-III as the primary grading scales for these areas. The protocol would need to specifically state that one or more of the Appendices would be primary (and thus take precedence over the main Grading Table) for items that are listed in both the Appendix and the main Grading Table.

- Addendum 1 - Female Genital Grading Table for Use in Microbicide Studies - PDF
- Addendum 2 - Male Genital Grading Table for Use in Microbicide Studies - PDF
- Addendum 3 - Rectal Grading Table for Use in Microbicide Studies - PDF

Grade 5

For any AE where the outcome is death, the severity of the AE is classified as Grade 5.

Estimating Severity Grade for Parameters Not Identified in the Table

In order to grade a clinical AE that is not identified in the DAIDS AE grading table, use the category "Estimating Severity Grade" located on Page 3.

Determining Severity Grade for Parameters "Between Grades"

If the severity of a clinical AE could fall under either one of two grades (e.g., the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE. If a laboratory value that is graded as a multiple of the ULN or LLN falls between two grades, select the higher of the two grades for the AE. For example, Grade 1 is 2.5 x ULN and Grade 2 is 2.6 x ULN for a parameter. If the lab value is 2.53 x ULN (which is between the two grades), the severity of this AE would be Grade 2, the higher of the two grades.

Values Below Grade 1

Any laboratory value that is between either the LLN or ULN and Grade 1 should not be graded.

Determining Severity Grade when Local Laboratory Normal Values Overlap with Grade 1 Ranges
In these situations, the severity grading is based on the ranges in the DAIDS AE Grading Table, even when there is a reference to the local lab LLN.

For example: Phosphate, Serum, Low, Adult and Pediatric > 14 years (Page 20) Grade 1 range is 2.50 mg/dL - < LLN. A particular laboratory's normal range for Phosphate is 2.1 – 3.8 mg/dL. A participant's actual lab value is 2.5. In this case, the value of 2.5 exceeds the LLN for the local lab, but will be graded as Grade 1 per DAIDS AE Grading Table.

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II. Definitions of terms used in the Table:

Basic Self-care Functions	Adult Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding. Young Children Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).
LLN	Lower limit of normal
Medical Intervention	Use of pharmacologic or biologic agent(s) for treatment of an AE.
NA	Not Applicable
Operative Intervention	Surgical OR other invasive mechanical procedures.
ULN	Upper limit of normal
Usual Social & Functional Activities	Adult Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc. Young Children Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
ESTIMATING SEVERITY GRADE				
Clinical adverse event NOT identified elsewhere in this DAIDS AE Grading Table	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
SYSTEMIC				
Acute systemic allergic reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/ malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7 – 38.6°C	38.7 – 39.3°C	39.4 – 40.5°C	> 40.5°C
Pain (indicate body site) DO NOT use for pain due to injection (See Injection Site Reactions: Injection site pain) See also Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than emergency room visit) indicated

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Unintentional weight loss	NA	5 – 9% loss in body weight from baseline	10 – 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
INFECTION				
Infection (any other than HIV infection)	Localized, no systemic antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (e.g., septic shock)
INJECTION SITE REACTIONS				
Injection site pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than emergency room visit) indicated for management of pain/tenderness
Injection site reaction (localized)				
Adult > 15 years	Erythema OR Induration of 5x5 cm – 9x9 cm (or 25 cm^2 – 81cm^2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pediatric ≤ 15 years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (e.g., upper arm/thigh)	Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (e.g., upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pruritis associated with injection See also Skin: Pruritis (itching - no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 hours treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA
SKIN – DERMATOLOGICAL				
Alopecia	Thinning detectable by study participant (or by caregiver for young children and disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous reaction – rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
CARDIOVASCULAR				
Cardiac arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children > 10 cc/kg) indicated
Hypertension				
Adult > 17 years (with repeat testing at same visit)	140 – 159 mmHg systolic OR 90 – 99 mmHg diastolic	160 – 179 mmHg systolic OR 100 – 109 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Correction: in Grade 2 to 160 - 179 from > 160-179 (systolic) and to ≥ 100 -109 from > 100-109 (diastolic) and in Grade 3 to ≥ 180 from > 180 (systolic) and to ≥ 110 from > 110 (diastolic).				
Pediatric ≤ 17 years (with repeat testing at same visit)	NA	91st – 94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life threatening physiologic consequences OR Effusion with non-urgent intervention indicated	Life-threatening consequences (e.g., tamponade) OR Urgent intervention indicated
Prolonged PR interval				
Adult > 16 years	PR interval 0.21 – 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
Pediatric ≤ 16 years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Prolonged QTc				
Adult > 16 years	Asymptomatic, QTc interval 0.45 – 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 – 0.49 sec OR Increase in interval 0.03 – 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤ 16 years	Asymptomatic, QTc interval 0.450 – 0.464 sec	Asymptomatic, QTc interval 0.465 – 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/embolism	NA	Deep vein thrombosis AND No intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Embolic event (e.g., pulmonary embolism, life-threatening thrombus)
Vasovagal episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular dysfunction (congestive heart failure)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic congestive heart failure	Life-threatening congestive heart failure
GASTROINTESTINAL				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
Comment: Please note that, while the grading scale provided for Unintentional Weight Loss may be used as a guideline when grading anorexia, this is not a requirement and should not be used as a substitute for clinical judgment.				
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (e.g., diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea				
Adult and Pediatric ≥ 1 year	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 – 6 stools over baseline per 24-hour period	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Pediatric < 1 year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake
Mucositis/stomatitis (clinical exam) Indicate site (e.g., larynx, oral) See Genitourinary for Vulvovaginitis See also Dysphagia-Odynophagia and Proctitis	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (e.g., aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 – 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than emergency room visit)	Symptomatic AND Hospitalization indicated (other than emergency room visit)	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Proctitis (functional-symptomatic) Also see Mucositis/stomatitis for clinical exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
NEUROLOGIC				
Alteration in personality-behavior or in mood (e.g., agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (e.g., suicidal and homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions
Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
CNS ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit
Developmental delay – **Pediatric ≤ 16 years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than emergency room visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social & functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Seizure: (new onset) **– Adult ≥ 18 years** See also Seizure: (known pre-existing seizure disorder)	NA	1 seizure	2 – 4 seizures	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure: (known pre-existing seizure disorder) **– Adult ≥ 18 years** For worsening of existing epilepsy the grades should be based on an increase from previous level of control to any of these levels.	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR Infrequent break-through seizures while on stable medication in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (e.g., severity or focality)	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure **– Pediatric < 18 years**	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5 – 20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions
RESPIRATORY				
Bronchospasm (acute)	FEV1 or peak flow reduced to 70 – 80%	FEV1 or peak flow 50 – 69%	FEV1 or peak flow 25 – 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or respiratory distress				
Adult ≥ 14 years	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pediatric < 14 years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 – 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated
MUSCULOSKELETAL				
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss				
Adult ≥ 21 years	BMD t-score -2.5 to -1.0	BMD t-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Pediatric < 21 years	BMD z-score -2.5 to -1.0	BMD z-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
GENITOURINARY				
Cervicitis (symptoms) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Cervicitis (clinical exam) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Minimal cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption < 25% of total surface	Moderate cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption of 25 – 49% total surface	Severe cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption 50 – 75% total surface	Epithelial disruption > 75% total surface
Inter-menstrual bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic examination	Inter-menstrual bleeding not greater in duration or amount than usual menstrual cycle	Inter-menstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary tract obstruction (e.g., stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences
Vulvovaginitis (symptoms) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Vulvovaginitis (clinical exam) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Minimal vaginal abnormalities on examination OR Epithelial disruption < 25% of total surface	Moderate vaginal abnormalities on examination OR Epithelial disruption of 25 - 49% total surface	Severe vaginal abnormalities on examination OR Epithelial disruption 50 - 75% total surface	Vaginal perforation OR Epithelial disruption > 75% total surface
OCULAR/VISUAL				
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)
ENDOCRINE/METABOLIC				
Abnormal fat accumulation (e.g., back of neck, breasts, abdomen)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes mellitus	NA	New onset without need to initiate medication OR Modification of current medications to regain glucose control	New onset with initiation of medication indicated OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy (e.g., fat loss from the face, extremities, buttocks)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
HEMATOLOGY	***Standard International Units are listed in italics***			
Absolute CD4+ count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	300 – 400/mm^3 *300 – 400/µL*	200 – 299/mm^3 *200 – 299/µL*	100 – 199/mm^3 *100 – 199/µL*	< 100/mm^3 *< 100/µL*
Absolute lymphocyte count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	600 – 650/mm^3 *0.600 x 10^9 – 0.650 x 10^9/L*	500 – 599/mm^3 *0.500 x 10^9 – 0.599 x 10^9/L*	350 – 499/mm^3 *0.350 x 10^9 – 0.499 x 10^9/L*	< 350/mm^3 *< 0.350 x 10^9/L*
Comment: Values in children ≤ 13 years are not given for the two parameters above because the absolute counts are variable.				
Absolute neutrophil count (ANC)				
Adult and Pediatric, > 7 days	1,000 – 1,300/mm^3 *1.000 x 10^9 – 1.300 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	500 – 749/mm^3 *0.500 x 10^9 – 0.749 x 10^9/L*	< 500/mm^3 *< 0.500 x 10^9/L*
Infant*†, 2 – ≤ 7 days	1,250 – 1,500/mm^3 *1.250 x 10^9 – 1.500 x 10^9/L*	1,000 – 1,249/mm^3 *1.000 x 10^9 – 1.249 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	< 750/mm^3 *< 0.750 x 10^9/L*
Infant*†, ≤1 day	4,000 – 5,000/mm^3 *4.000 x 10^9 – 5.000 x 10^9/L*	3,000 – 3,999/mm^3 *3.000 x 10^9 – 3.999 x10^9/L*	1,500 – 2,999/mm^3 *1.500 x 10^9 – 2.999 x 10^9/L*	< 1,500/mm^3 *< 1.500 x 10^9/L*
Comment: Parameter changed from "Infant, < 1 day" to "Infant, ≤1 day"				
Fibrinogen, decreased	100 – 200 mg/dL *1.00 – 2.00 g/L* OR 0.75 – 0.99 x LLN	75 – 99 mg/dL *0.75 – 0.99 g/L* OR 0.50 – 0.74 x LLN	50 – 74 mg/dL *0.50 – 0.74 g/L* OR 0.25 – 0.49 x LLN	< 50 mg/dL *< 0.50 g/L* OR < 0.25 x LLN OR Associated with gross bleeding

* Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Hemoglobin (Hgb)				
Comment: The Hgb values in mmol/L have changed because the conversion factor used to convert g/dL to mmol/L has been changed from 0.155 to 0.6206 (the most commonly used conversion factor). For grading Hgb results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using the appropriate conversion factor for that lab.				
Adult and Pediatric ≥ 57 days (HIV POSITIVE ONLY)	8.5 – 10.0 g/dL *5.24 – 6.23 mmol/L*	7.5 – 8.4 g/dL *4.62–5.23 mmol/L*	6.50 – 7.4 g/dL *4.03–4.61 mmol/L*	< 6.5 g/dL *< 4.03 mmol/L*
Adult and Pediatric ≥ 57 days (HIV NEGATIVE ONLY)	10.0 – 10.9 g/dL *6.18 – 6.79 mmol/L* OR Any decrease 2.5 – 3.4 g/dL *1.58 – 2.13 mmol/L*	9.0 – 9.9 g/dL *5.55 - 6.17 mmol/L* OR Any decrease 3.5 – 4.4 g/dL *2.14 – 2.78 mmol/L*	7.0 – 8.9 g/dL *4.34 - 5.54 mmol/L* OR Any decrease ≥ 4.5 g/dL *> 2.79 mmol/L*	< 7.0 g/dL *< 4.34 mmol/L*
Comment: The decrease is a decrease from baseline				
Infant*†, 36 – 56 days (HIV POSITIVE OR NEGATIVE)	8.5 – 9.4 g/dL *5.24 – 5.86 mmol/L*	7.0 – 8.4 g/dL *4.31 – 5.23 mmol/L*	6.0 – 6.9 g/dL *3.72 – 4.30 mmol/L*	< 6.00 g/dL *< 3.72 mmol/L*
Infant*†, 22 – 35 days (HIV POSITIVE OR NEGATIVE)	9.5 – 10.5 g/dL *5.87 - 6.54 mmol/L*	8.0 – 9.4 g/dL *4.93 – 5.86 mmol/L*	7.0 – 7.9 g/dL *4.34 – 4.92 mmol/L*	< 7.00 g/dL *< 4.34 mmol/L*
Infant*†, ≤ 21 days (HIV POSITIVE OR NEGATIVE)	12.0 – 13.0 g/dL *7.42 – 8.09 mmol/L*	10.0 – 11.9 g/dL *6.18 – 7.41 mmol/L*	9.0 – 9.9 g/dL *5.59- 6.17 mmol/L*	< 9.0 g/dL *< 5.59 mmol/L*
Correction: Parameter changed from "Infant < 21 days" to "Infant ≤ 21 days"				
International Normalized Ratio of prothrombin time (INR)	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 3.0 x ULN	> 3.0 x ULN
Methemoglobin	5.0 – 10.0%	10.1 – 15.0%	15.1 – 20.0%	> 20.0%
Prothrombin Time (PT)	1.1 – 1.25 x ULN	1.26 – 1.50 x ULN	1.51 – 3.00 x ULN	> 3.00 x ULN
Partial Thromboplastin Time (PTT)	1.1 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3.00 x ULN	> 3.00 x ULN
Platelets, decreased	100,000 – 124,999/mm^3 *100.000 x 10^9 – 124.999 x 10^9/L*	50,000 – 99,999/mm^3 *50.000 x 10^9 – 99.999 x 10^9/L*	25,000 – 49,999/mm^3 *25.000 x 10^9 – 49.999 x 10^9/L*	< 25,000/mm^3 *< 25.000 x 10^9/L*
WBC, decreased	2,000 – 2,500/mm^3 *2.000 x 10^9 – 2.500 x 10^9/L*	1,500 – 1,999/mm^3 *1.500 x 10^9 – 1.999 x 10^9/L*	1,000 – 1,499/mm^3 *1.000 x 10^9 – 1.499 x 10^9/L*	< 1,000/mm^3 *< 1.000 x 10^9/L*

*Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
CHEMISTRIES	***Standard International Units are listed in italics***			
Acidosis	NA	pH < normal, but ≥ 7.3	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, serum, low	3.0 g/dL – < LLN *30 g/L – < LLN*	2.0 – 2.9 g/dL *20 – 29 g/L*	< 2.0 g/dL *< 20 g/L*	NA
Alkaline Phosphatase	1.25 – 2.5 x ULN†	2.6 – 5.0 x ULN†	5.1 – 10.0 x ULN†	> 10.0 x ULN†
Alkalosis	NA	pH > normal, but ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT (SGPT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
AST (SGOT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
Bicarbonate, serum, low	16.0 mEq/L – < LLN *16.0 mmol/L – < LLN*	11.0 – 15.9 mEq/L *11.0 – 15.9 mmol/L*	8.0 – 10.9 mEq/L *8.0 – 10.9 mmol/L*	< 8.0 mEq/L *< 8.0 mmol/L*
Comment: Some laboratories will report this value as Bicarbonate (HCO_3) and others as Total Carbon Dioxide (CO_2). These are the same tests; values should be graded according to the ranges for Bicarbonate as listed above.				
Bilirubin (Total)				
Adult and Pediatric > 14 days	1.1 – 1.5 x ULN	1.6 – 2.5 x ULN	2.6 – 5.0 x ULN	> 5.0 x ULN
Infant*†, ≤ 14 days (non-hemolytic)	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	25.1 – 30.0 mg/dL *429 – 513 µmol/L*	> 30.0 mg/dL *> 513.0 µmol/L*
Infant*†, ≤ 14 days (hemolytic)	NA	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	> 25.0 mg/dL *> 428 µmol/L*
Calcium, serum, high				
Adult and Pediatric ≥ 7 days	10.6 – 11.5 mg/dL *2.65 – 2.88 mmol/L*	11.6 – 12.5 mg/dL *2.89 – 3.13 mmol/L*	12.6 – 13.5 mg/dL *3.14 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Infant*†, < 7 days	11.5 – 12.4 mg/dL *2.88 – 3.10 mmol/L*	12.5 – 12.9 mg/dL *3.11 – 3.23 mmol/L*	13.0 – 13.5 mg/dL *3.245 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Calcium, serum, low				
Adult and Pediatric ≥ 7 days	7.8 – 8.4 mg/dL *1.95 – 2.10 mmol/L*	7.0 – 7.7 mg/dL *1.75 – 1.94 mmol/L*	6.1 – 6.9 mg/dL *1.53 – 1.74 mmol/L*	< 6.1 mg/dL *< 1.53 mmol/L*
Infant*†, < 7 days	6.5 – 7.5 mg/dL *1.63 – 1.88 mmol/L*	6.0 – 6.4 mg/dL *1.50 – 1.62 mmol/L*	5.50 – 5.90 mg/dL *1.38 – 1.51 mmol/L*	< 5.50 mg/dL *< 1.38 mmol/L*
Comment: Do not adjust Calcium, serum, low or Calcium, serum, high for albumin				

*Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Cardiac troponin I (cTnI)	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cardiac troponin T (cTnT)	NA	NA	NA	≥ 0.20 ng/mL OR Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cholesterol (fasting)				
Adult ≥ 18 years	200 – 239 mg/dL *5.18 – 6.19 mmol/L*	240 – 300 mg/dL *6.20 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Pediatric < 18 years	170 – 199 mg/dL *4.40 – 5.15 mmol/L*	200 – 300 mg/dL *5.16 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Creatine Kinase	3.0 – 5.9 x ULN†	6.0 – 9.9 x ULN†	10.0 – 19.9 x ULN†	≥ 20.0 x ULN†
Creatinine	1.1 – 1.3 x ULN†	1.4 – 1.8 x ULN†	1.9 – 3.4 x ULN†	≥ 3.5 x ULN†

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Glucose, serum, high				
Nonfasting	116 – 160 mg/dL *6.44 – 8.88 mmol/L*	161 – 250 mg/dL *8.89 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
Fasting	110 – 125 mg/dL *6.11 – 6.94 mmol/L*	126 – 250 mg/dL *6.95 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
Glucose, serum, low				
Adult and Pediatric ≥ 1 month	55 – 64 mg/dL *3.05 – 3.55 mmol/L*	40 – 54 mg/dL *2.22 – 3.06 mmol/L*	30 – 39 mg/dL *1.67 – 2.23 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
Infant*†, < 1 month	50 – 54 mg/dL *2.78 – 3.00 mmol/L*	40 – 49 mg/dL *2.22 – 2.77 mmol/L*	30 – 39 mg/dL *1.67 – 2.21 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
Lactate	ULN - < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences
Comment: Added ULN to Grade 1 parameter				

*Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

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LDL cholesterol (fasting)				
Adult ≥ 18 years	130 – 159 mg/dL *3.37 – 4.12 mmol/L*	160 – 190 mg/dL *4.13 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
Pediatric > 2 - < 18 years	110 – 129 mg/dL *2.85 – 3.34 mmol/L*	130 – 189 mg/dL *3.35 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
Lipase	1.1 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 5.0 x ULN	> 5.0 x ULN
Magnesium, serum, low	1.2 – 1.4 mEq/L *0.60 – 0.70 mmol/L*	0.9 – 1.1 mEq/L *0.45 – 0.59 mmol/L*	0.6 – 0.8 mEq/L *0.30 – 0.44 mmol/L*	< 0.60 mEq/L *< 0.30 mmol/L*
Pancreatic amylase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN
Phosphate, serum, low				
Adult and Pediatric > 14 years	2.5 mg/dL – < LLN *0.81 mmol/L – < LLN*	2.0 – 2.4 mg/dL *0.65 – 0.80 mmol/L*	1.0 – 1.9 mg/dL *0.32 – 0.64 mmol/L*	< 1.00 mg/dL *< 0.32 mmol/L*
Pediatric 1 year – 14 years	3.0 – 3.5 mg/dL *0.97 – 1.13 mmol/L*	2.5 – 2.9 mg/dL *0.81 – 0.96 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
Pediatric < 1 year	3.5 – 4.5 mg/dL *1.13 – 1.45 mmol/L*	2.5 – 3.4 mg/dL *0.81 – 1.12 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
Potassium, serum, high	5.6 – 6.0 mEq/L *5.6 – 6.0 mmol/L*	6.1 – 6.5 mEq/L *6.1 – 6.5 mmol/L*	6.6 – 7.0 mEq/L *6.6 – 7.0 mmol/L*	> 7.0 mEq/L *> 7.0 mmol/L*
Potassium, serum, low	3.0 – 3.4 mEq/L *3.0 – 3.4 mmol/L*	2.5 – 2.9 mEq/L *2.5 – 2.9 mmol/L*	2.0 – 2.4 mEq/L *2.0 – 2.4 mmol/L*	< 2.0 mEq/L *< 2.0 mmol/L*
Sodium, serum, high	146 – 150 mEq/L *146 – 150 mmol/L*	151 – 154 mEq/L *151 – 154 mmol/L*	155 – 159 mEq/L *155 – 159 mmol/L*	≥ 160 mEq/L *≥ 160 mmol/L*
Sodium, serum, low	130 – 135 mEq/L *130 – 135 mmol/L*	125 – 129 mEq/L *125 – 129 mmol/L*	121 – 124 mEq/L *121 – 124 mmol/L*	≤ 120 mEq/L *≤ 120 mmol/L*
Triglycerides (fasting)	NA	500 – 750 mg/dL *5.65 – 8.48 mmol/L*	751 – 1,200 mg/dL *8.49 – 13.56 mmol/L*	> 1,200 mg/dL *> 13.56 mmol/L*

LABORATORY

*Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Uric acid	7.5 – 10.0 mg/dL *0.45 – 0.59 mmol/L*	10.1 – 12.0 mg/dL *0.60 – 0.71 mmol/L*	12.1 – 15.0 mg/dL *0.72 – 0.89 mmol/L*	> 15.0 mg/dL *> 0.89 mmol/L*
URINALYSIS	***Standard International Units are listed in italics***			
Hematuria (microscopic)	6 – 10 RBC/HPF	> 10 RBC/HPF	Gross, with or without clots OR with RBC casts	Transfusion indicated
Proteinuria, random collection	1 +	2 – 3 +	4 +	NA
Proteinuria, 24 hour collection				
Adult and Pediatric ≥ 10 years	200 – 999 mg/24 h *0.200 – 0.999 g/d*	1,000 – 1,999 mg/24 h *1.000 – 1.999 g/d*	2,000 – 3,500 mg/24 h *2.000 – 3.500 g/d*	> 3,500 mg/24 h *> 3.500 g/d*
Pediatric > 3 mo - < 10 years	201 – 499 mg/m^2/24 h *0.201 – 0.499 g/d*	500 – 799 mg/m^2/24 h *0.500 – 0.799 g/d*	800 – 1,000 mg/m^2/24 h *0.800 – 1.000 g/d*	> 1,000 mg/ m^2/24 h *> 1.000 g/d*

*Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

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APPENDIX 3 AIDS-DEFINING DIAGNOSES

I. PARASITIC INFECTIONS

Pneumocystis carinii (PC)

1011 PC pneumonia histologically proven.

1012 PC pneumonia, clinical diagnosis by the following specifications and confirmed HIV infection:

A history of dyspnea on exertion or non-productive cough of recent onset (within the past 3 months).

AND

Chest X-ray evidence of diffuse bilateral interstitial or gallium scan evidence of diffuse bilateral pulmonary disease;

AND

Arterial blood gas analysis showing an arterial pO2 of < 70 mmHg or a low respiratory diffusing capacity (< 80% of predicted values) or an increase in the alveolar-arterial oxygen tension gradient;

AND

Successful response to appropriate therapy and no evidence of pneumonias of other etiologies.

1013 Pneumocystis carinii, histologically proven, at a site other than lungs.

Toxoplasmosis (in patients > 1 month old)

1021 Toxoplasmosis, clinical diagnosis (of brain only) by the following specifications and confirmed HIV infection:

Recent onset of a neurologic disease consistent with toxoplasmosis;

AND

Brain imaging evidence of a mass lesion (on computed tomography, nuclear magnetic resonance of radiography enhanced by injection of contrast medium);

AND

Serum antibody to toxoplasmosis and successful response to therapy for toxoplasmosis.

1022 Toxoplasmosis, of brain or internal organs other than liver, spleen or lymph nodes. Proven by microscopy.

Isosporiasis

1031 Isosporiasis causing chronic diarrhea of > 1 month. Proven by microscopy.

Cryptosporidiosis

1041 Cryptosporidiosis causing chronic diarrhea of > 1 month. Proven by microscopy.

II. FUNGAL INFECTIONS

Candidiasis

2011 Candidiasis, Esophageal, definitive diagnosis by the following specifications:

Gross inspection by endoscopy or autopsy or by microscopy (histology or cytology) on a specimen obtained directly from the tissues affected (including scrapings from the mucosal surface), not from a culture.

2012 Candidiasis, Esophageal, presumptive diagnosis by the following specifications and confirmed HIV infection:

Recent onset of retrosternal pain on swallowing:

AND

Oral candidiasis diagnosed by the gross appearance of white patches or plaques on an erythematous base OR by the microscopic appearance of fungal mycelial filaments in an uncultured specimen scraped from the oral mucosa;

AND

Response to appropriate therapy.

2013 Candidiasis, Bronchial/Pulmonary, definitive diagnosis by the following specifications; Gross inspection by endoscopy or autopsy or by microscopy (histology or cytology) on a specimen obtained directly from the tissues affected (including scrapings from the mucosal surface), not from a culture.

Cryptococcosis

2022 Cryptococcosis, Extra-pulmonary, proven by microscopy (histology or cytology), culture or detection of antigen in a specimen obtained directly from the tissues affected or a fluid from those tissues.

Histoplasmosis

2031 Histoplasmosis, Disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes), proven by microscopy (histology or cytology), culture or detection of antigen in a specimen obtained directly from the tissues affected or a fluid from those tissues.

Coccidioidomycosis

2041 Coccidioidoidomycosis, Disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes), proven by microscopy (histology or cytology), culture or detection of antigen in a specimen obtained directly from the tissues affected or a fluid from those tissues.

2042 Coccidioidomycosis, clear reactivation of prior infection, proven by microscopy (histology or cytology), culture or detection of antigen in a specimen obtained directly from the tissues affected or a fluid from those tissues.

III. BACTERIAL INFECTIONS

Mycobacterium

3001 Mycobacterium (unidentified species). Presumptive diagnosis, by the following specifications and confirmed HIV infection.

Acid fast bacilli (AFB) positive stain of specimen obtained from endoscopic biopsy or from a normal sterile site other than lungs, skin or cervical or hilar lymph nodes. Species NOT identified by culture.

Mycobacterium tuberculosis

3011 Mycobacterium tuberculosis, Pulmonary, definitive diagnosis proven by culture, without evidence of upper respiratory infection symptoms of Mycobacterium tuberculosis that could account for the positive culture.

3012 Mycobacterium tuberculosis, definitive diagnosis proven by culture, of at least one extra pulmonary site regardless of concurrent pulmonary involvement.

3013 Mycobacterium tuberculosis, Disseminated, definitive diagnosis proven by culture.

Mycobacterium avium intracellulare

3022 MAI in Blood, proven by culture.

3023 MAI Colitis, proven by histology and culture. (This does not include MAI of the stool alone).

3024 MAI, Disseminated, at a site other than or in addition to lungs or cervical or hilar lymph nodes, proven by culture.

Mycobacterium Kansasii, Mycobacterium Scrofulaceum and Other Atypical Mycobacterium

3032 M. Kansasii, in Blood, proven by culture.

3033 M. Kansasii Colitis, proven by histology and culture. (NOT including positive M. Kansasii of stool alone).

3034 M. Kansasii, Disseminated, at a site other than or in addition to lungs, or cervical or hilar lymph nodes, proven by culture.

3035 M. Scrofulaceum or other Atypical Mycobacterium, proven by culture.

Salmonella

3041 Salmonella, recurrent Bacteremia (non-typhoid), proven by culture.

IV. VIRAL INFECTIONS

Cytomegalovirus

4011 CMV, Pneumonitis, pathologically or histologically confirmed. Serum antibody titer and culture alone is not sufficient for the diagnosis.

4012 CMV, Esophagitis, as diagnosed by histology, pathology or culture of an esophageal lesion. Serum antibody titer and culture of other than esophageal tissue is not sufficient for the diagnosis.

4013 CMV, Retinitis as evidenced by a characteristic appearance on serial ophthalmoscopic examinations (eg, discrete patches of retinal whitening with distinct borders, spreading in a centrifugal manner, following blood vessels, progressing over several months, frequently associated with retinal vasculitis, hemorrhage, and necrosis). Resolution of active disease leaves retinal scarring and atrophy with retinal pigment epithelial mottling.

4014 CMV, Colitis, as diagnosed by histology, pathology or culture of a colonic lesion. Serum antibody titer and culture of other than colonic tissue is not sufficient for the diagnosis.

4015 CMV, Encephalitis, as diagnosed by histology, pathology or culture of brain tissue or CSF. Serum antibody titer and culture of other than brain tissue or CSF is not sufficient for the diagnosis.

Herpes Simplex (in patients > 1 month old).

4021 HSV, Disseminated (but not encephalitis alone), proven by microscopy (histology or cytology), culture or detection of antigen in a specimen obtained directly from affected tissues.

4022 HSV, Esophagitis, as diagnosed by microscopy (histology or cytology), culture or detection of antigen in a biopsy specimen obtained directly from affected tissue. Serological measurement and culture from other than the affected tissue is not sufficient for the diagnosis.

4023 HSV, Bronchitis, as diagnosed by microscopy (histology or cytology), culture or detection of antigen in a biopsy specimen obtained directly from affected tissue. Serological measurement and culture from other than the affected tissue is not sufficient for the diagnosis.

4024 HSV, Pneumonitis, as diagnosed by microscopy (histology or cytology), culture or detection of antigen in a biopsy specimen obtained directly from affected tissue. Serological measurement and culture from other than the affected tissue is not sufficient for diagnosis.

4025 HSV, GI, other than mouth, throat, or peri-rectal, as diagnosed by microscopy (histology or cytology), culture or detection of antigen in a biopsy specimen obtained directly from

affected tissue. Serological measurement and culture from other than the affected tissue is not sufficient for diagnosis.

4026 HSV, Mucocutaneous, ulcers persisting for ≥ 1 month despite appropriate therapy, as diagnosed by microscopy (histology or cytology), culture or detection of antigen in a biopsy specimen obtained directly from affected tissue. Serological measurement and culture from other than the affected tissue is not sufficient for the diagnosis.

Progressive Multifocal Leukoencephalopathy

4041 Progressive Multifocal Leukoencephalopathy, proven by microscopy.

VI. NEOPLASTIC DISEASES

Kaposi's Sarcoma

6011 Kaposi's sarcoma, Mucocutaneous, proven by microscopy.

6012 Kaposi's sarcoma. Mucocutaneous, presumptive diagnosis with characteristic gross appearance and confirmed HIV infection.

6013 Kaposi's sarcoma, Visceral.

6014 Kaposi's sarcoma, other than above.

Lymphoma of the Brain

6021 Primary Lymphoma of the brain at any age, proven by microscopy.

Non-Hodgkins Lymphoma

6031 Small Non-cleaved lymphoma (either Burkitt or non-Burkitt type).

6032 Immunoblastic sarcoma, equivalent to any of the following, although not necessarily all in combination: Immunoblastic lymphoma, large-cell lymphoma, diffuse histocytic lymphoma.

Cervical Carcinoma

6041 Histologically proven invasive carcinoma of the cervix.

VII. OTHER CONDITIONS

HIV Dementia/Motor Defects

7011 HIV Dementia, clinical findings of disabling cognitive and/or motor dysfunction interfering with occupation or activities of daily living progressing over weeks to months, in the absence of a concurrent illness or condition other than HIV infection that could explain the findings. Method to rule out such concurrent illnesses and conditions must

include cerebrospinal fluid examination and either brain imaging (computed tomography or magnetic resonance) or autopsy.

Slim Disease or HIV Wasting Syndrome

7021 HIV Wasting Syndrome, findings of profound involuntary weight loss > 10% of baseline body weight plus either chronic diarrhea (at least two loose stools per day for ≥ 30 days) or chronic weakness and documented fever (for ≥ 30 days, intermittent to constant) in the absence of a concurrent illness or condition other than HIV infection that could explain the findings (eg, cancer, tuberculosis, cryptosporidiosis, or other specific enteritis).

7061 Recurrent pneumonia, acute onset within 12 months of most recent episode.

Pediatric patients only:

VII. OTHER CONDITIONS

HIV Dementia/Motor Defects

7012 Loss of Developmental Milestone, loss of behavioral development milestones affecting a child.

7013 Progressive Symmetrical Motor Defects.

Slim Disease or HIV Wasting Syndrome

7022 Failure to Thrive.

Lymphoid Interstitial Pneumonitis

7031 Lymphoid Interstitial Pneumonitis, characterized by diffuse interstitial and peribronchiolar infiltration of lymphocytes and plasma cells and without identifiable pathogens to appropriate antimicrobial therapy.

OR

Chronic Pneumonitis, characterized by bilateral reticulonodular intestinal infiltrates with or without hilar lymphadenopathy unresponsive to therapy.

APPENDIX 4 SPECIFIC RECOMMENDATION FOR MANAGEMENT OF OTHER TOXICITIES

1 CLINICAL PANCREATITIS

If a subject develops nausea, vomiting, or abdominal pain of any grade associated with any elevation of serum fractionated pancreatic amylase or lipase, or develops a clinical syndrome that in the opinion of the subject's clinician is classified as pancreatitis, study medications should be permanently discontinued. Future consideration should be given to avoiding ddI or other drugs potentially affecting the pancreas. Notify BMS medical monitor or designee immediately.

2 HYPERLIPASEMIA

For elevations of lipase in blood, follow this algorithm:

- For Grade 2 hyperlipasemia (> 1.5 ULN), consider holding all study drugs, Notify BMS medical monitor or designee immediately, schedule follow-up visits every two weeks if necessary until toxicity resolves to ≤ Grade 1.
- For any Grade 3 hyperlipasemia (> 2.5 ULN), hold all study drugs until both lipase and amylase are ≤ Grade 1. Notify BMS medical monitor or designee immediately.
- For Grade 4 hyperlipasemia (> 5.0 ULN), all study drugs should be held and may be permanently discontinued. If study drugs are not permanently discontinued, do not restart until both lipase and amylase are ≤ Grade 1. Notify BMS medical monitor or designee immediately to determine course of action. If hyperlipasemia recurs, discontinue all study drugs.

3 HYPERAMYLASEMIA

For Grade 3 or 4 hyperamylasemia, the amylase should be fractionated and the pancreatic fraction should then be used for toxicity management. A lipase should also be obtained and the following algorithm applies:

- If there is an elevation in lipase, hold all study drugs until both amylase and lipase are ≥ Grade 1. Notify BMS medical monitor or designee immediately.
- Pending the results of the fractionated amylase evaluation if the lipase is normal, study medications may be continued. Notify BMS medical monitor or designee.
- Once available, fractionated pancreatic amylase elevations should be managed in consultation to with the BMS Medical Monitor or designee.

4 INCREASE IN VALUES FOR THE LIVER FUNCTION TESTS (LFTS):

The following algorithm for management of this toxicity should be observed:

- For all Grade 2 LFTs, monitor subject every two weeks until values return to Grade 1. Notify BMS medical monitor or designee
- In general all Grade 2 LFTs or higher, should be reported to the team every other week.
- Elevations in LFTs should be managed as per Section 6.7.1 depending on the toxicity grade.

5 CNS SYMPTOMS

For grading CNS symptoms follow Appendix 2 "Division of AIDS (DAIDS) Toxicity Table for Grading Severity of Adult and Pediatric (> 3 months of age) Adverse Experiences [December 2004; clarification August 2009]."

For management of CNS toxicities follow Section 6.7.1. Contact the BMS medical monitor or designee if you have any doubts on how to proceed after observing specific CNS symptoms.

6 CHOLESTEROL AND TRIGLYCERIDES

Initiation of HAART therapy, with and without PIs and/or NNRTIs has been associated with elevations in cholesterol and triglyceride levels. (See Appendix 2 "the Division of AIDS (DAIDS) Table for Grading Severity of Adult and Pediatric (> 3 Months of Age) Adverse Experiences [December 2004; clarification August 2009]").

If triglycerides ≥ 750mg/dL (Grade 2 or greater), obtain fasting triglycerides, as well as amylase and lipase (follow Section 6.7.1 for toxicity management if elevated); if fasting triglycerides < 749mg/dL, continue study drugs; if fasting triglycerides ≥ 750mg/dL (Grade 2), notify BMS medical monitor or designee immediately to determine course of action. After a subject has had a Grade 2 or Grade 3 triglycerides in non-fasting state, all future triglycerides must be obtained in fasting state.

7 HYPERGLYCEMIA/GLYCOSURIA

If non-fasting blood glucose > 200 or urinary dipstick > 2+ positive, obtain fasting blood glucose. If the fasting blood glucose is ≥ 150mg/dL or greater, notify BMS medical monitor or designee immediately. Consult with an endocrinologist regarding possible new onset diabetes, and relay this information to the BMS medical monitor or designee.

8 SKIN RASH

Rashes which meet the criteria for Grade 2 or higher AE (using the Division of AIDS (DAIDS) Toxicity Table for Grading Severity of Adult and Pediatric (> 3 months of age) Adverse Experiences [December 2004; clarification August 2009]), (Appendix 2) must be reported immediately to the BMS medical monitor or designee.

Study drugs may be continued for Grade 2 (A or B) skin rash following consultation with the BMS medical monitor or designee. All study drugs must be permanently discontinued for any Grade 3 or 4 rash.

APPENDIX 5 RECOMMENDATIONS FOR GRADING ACUTE AND SUBACUTE TOXIC EFFECTS (WHO)

ITEM	GRADE 1 TOXICITY	GRADE 2 TOXICITY	GRADE 3 TOXICITY	GRADE 4 TOXICITY
HEMATOLOGY				
HEMATOCRIT	≥ 28.5 to < 31.5%	≥ 24 to < 28.5%	≥ 19.5 to < 24%	< 19.5%
HEMOGLOBIN	9.5 - 11.0 g/dL	8.0 - 9.4 g/dL	6.5 - 7.9 g/dL	< 6.5 g/dL
WHITE BLOOD CELLS	≥ 2500 to < 4000/mm^3	≥ 1000 to < 2500/mm^3	≥ 800 to < 1000/mm^3	< 800/mm^3
ABSOLUTE NEUTROPHIL COUNT	≥ 1000 to < 1500/mm^3	≥ 750 to < 1000/mm^3	≥ 500 to < 750/mm^3	< 500/mm^3
PLATELETS	75,000 - 99,000/mm^3	50,000 - 74,999/mm^3	20,000 - 49,999/mm^3	< 20,000/mm^3 or diffuse petechiae
PT	1.01 - 1.25 X upper normal	1.26 - 1.5 X upper normal	1.51 - 3.0 X upper normal	> 3 X upper normal
PTT	1.01 - 1.66 X upper normal	1.67 - 2.33 X upper normal	2.34 - 3 X upper normal	> 3 X upper normal
FIBRINOGEN	0.99 - 0.75 X lower normal	0.74 - 0.50 X lower normal	0.49 - 0.25 X lower normal	< 0.25 X lower normal
FIBRIN SPLIT PRODUCT	20 - 40 g/mL	41 - 50 g/mL	51 - 60 g/mL	> 60 g/mL
METHEMOGLOBIN	5 - 9.9%	10.0 - 14.9%	15.0 - 19.9%	≥ 20%
CHEMISTRIES				
HYPONATREMIA	130 - 132 meq/L	123 - 129 meq/L	116 - 122 meq/L	115 meq/L and less or mental status changes or seizures
HYPERNATREMIA	148 - 150 meq/L	151 - 157 meq/L	158 - 165 meq/L	> 165 meq/L OR mental status changes/seizures
HYPOKALEMIA	3.0 - 3.4 meq/L	2.5 - 2.9 meq/L or replacement Rx req	2.0 - 2.4 meq/L or intensive replacement Rx Reg or hosp	< 2.0 meq/L or paresis or ileus or life - threatening arrhythmias
HYPERKALEMIA	5.6 - 6.0 meq/L	6.1 - 6.5 meq/L	6.6 - 7.0 meq/L	> 7.0 OR paresis or ileus or life - threatening arrhythmias
HYPOGLYCEMIA	55 - 64 mg/dL	40 - 54 mg/dL	30 - 39 mg/dL	< 30 mg/dL or mental status changes or coma

ITEM	GRADE 1 TOXICITY	GRADE 2 TOXICITY	GRADE 3 TOXICITY	GRADE 4 TOXICITY
HYPERGLYCEMIA	116 - 160 mg/dL	161 - 250 mg/dL	251 - 500 mg/dL	> 500 mg/dL or ketoacidosis or seizures
HYPERTRIGLYCER – IDEMIA	250 - 400 mg/dL	401 - 750 mg/dL	751 - 1250 mg/dL	> 1250 mg/dL
HYPERURICEMIA				
13 - 18 yrs	9.1 - 12.0 mg/dL	12.1 - 14.0 mg/dL	14.1 - 17.0 mg/dL	> 17.0 mg/dL
> 18 yrs	9.6 - 9.9 mg/dL	10.0 - 12.0 mg/dL	12.1 - 15.0 mg/dL	> 15.0 mg/dL
HYPOCALCEMIA corrected for albumin	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/dL or life - threatening arrhythmia or tetany
HYPERCALCEMIA corrected for albumin	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/dL	12.6 - 13.5 mg/dL	> 13.5 mg/dL or coma or cardiac arrhythmias
HYPOMAGNESEMIA	0.8 - 1.0 meq/L	0.5 - 0.7 meq/L or replacement Rx req.	0.3 - 0.4 meq/L or intensive Rx req. hospitalization	< 0.3 meq/L or life - threatening arrhythmias
HYPOPHOSPHATEMIA	2.0 - 2.4 mg/dL	1.5 - 1.9 mg/dL or replacement Rx req.	1.0 - 1.4 mg/dL intensive Rx req. hospitalization	< 1.0 mg/dL life - threatening arrhythmias or CHF
BUN	1.25 - 2.5 X upper normal	2.6 - 5.0 X upper normal	5.1 - 10 X upper normal	> 10 X upper normal
CREATININE	1.1 - 1.5 X upper normal	1.6 - 3.0 X upper normal	3.1 - 6 X upper normal	> 6 X upper normal or requires dialysis
HYPOCARBIA (BICARBONATE)	19 - 21 meq/L	15 - 18 meq/L	10 - 14 meq/L	< 10 meq/L
HYPERCARBIA (BICARBONATE)	33 - 36 meq/L	37 - 40 meq/L	41 - 45 meq/L	> 45 meq/L
HYPOCHLOREMIA	90 - 93 meq/L	85 - 89 meq/L	80 - 84 meq/L	< 80 meq/L
HYPERCHLOREMIA	113 - 116 meq/L	117 - 120 meq/L	121 - 125 meq/L	> 125 meq/L
ENZYMES				
BILIRUBIN	1.1 - 1.5 x upper normal	1.6 - 2.5 X upper normal	2.6 - 5 X upper normal	> 5 X upper normal
AST/SGOT	1.25 - 2.5 X upper normal	2.6 - 5 X upper normal	5.1 - 10 X upper normal	> 10 X upper normal
ALT/SGPT	1.25 - 2.5 X upper normal	2.6 - 5 X upper normal	5.1 - 10 X upper normal	> 10 X upper normal
GGT	1.25 - 2.5 X upper normal	2.6 - 5 X upper normal	5.1 - 10 X upper normal	> 10 X upper normal

ITEM	GRADE 1 TOXICITY	GRADE 2 TOXICITY	GRADE 3 TOXICITY	GRADE 4 TOXICITY
ALKALINE PHOSPHATASE	1.25 - 2.5 X upper normal	2.6 - 5 X upper normal	5.1 - 10 X upper normal	> 10 X upper normal
AMYLASE	1.10 - 1.39 X upper normal	1.40 - 2.09 X upper normal	2.10 - 5.0 X upper normal, mild clinical pancreatitis	> 5.0 X upper normal or severe clinical pancreatitis
LIPASE	1.10 - 1.39 X upper normal	1.40 - 2.09 X upper normal	2.10 - 5 X upper normal or mild clinical pancreatitis	5.0 X upper normal or severe clinical pancreatitis
CPK	2 - 3.0 X upper normal	3.1 - 5.0 X upper normal, mild myalgia	5.1 - 10.0 X upper normal moderate/severe myalgia requiring non - steroidals	> 10 X upper normal severe myalgia requiring narcotics
LDH	1.10 - 1.39 X upper normal	1.40 - 2.09 X upper normal	2.1 - 5.0 X upper normal	> 5 X upper normal
URINALYSIS				
PROTEINURIA	1+ or ≤ 1g loss/day	2 - 3 + or> 1 - 2 g loss/day	4+ or > 2 - 3.5 g loss/day	nephrotic syndrome or > 3.5 g loss/day
HEMATURIA	microscopic only, ≤ 10	gross, no clots, 11 - 100	gross + clots, ≥ 101	obstructive or requires catheterization
CARDIAC				
CARDIAC RHYTHM		asymptomatic, transient signs, no Rx required	recurrent/persistent no Rx required	requires treatment
HYPERTENSION	transient inc. > 20mm, no Rx	recurrent, chronic > 20mm, Rx req.	requires outpt. acute Rx	hospitalization
HYPOTENSION	transient orthostatic hypotension, No Rx	symptoms correctable with oral fluid Rx	requires IV fluids no hosp. required	requires hospitalization
PERICARDITIS	minimal effusion	mild/mod. asymp. effusion no Rx	symptomatic effusion, pain, EKG changes	tamponade; pericardio - centesis or surgery req.
HEMORRHAGE, BLOOD LOSS	microscopic/occult	mild, no transfusion	gross blood loss, 1 - 2 units transfused	massive blood loss, > 3 units transfused
RESPIRATORY				
COUGH	transient - no Rx	local non - narcotic Rx	narcotic Rx required	uncontrolled
SHORTNESS OF BREATH	mild, does not interfere with routine activities	moderate, interferes with routine activities req. intermittent Rx	moderate, debilitating requiring nasal oxygen	severe, requiring ventilatory assistance

ITEM	GRADE 1 TOXICITY	GRADE 2 TOXICITY	GRADE 3 TOXICITY	GRADE 4 TOXICITY
BRONCHOSPASM ACUTE	transient, no Rx, FEV_1, or peak flow of > 70% NL	req. Rx, normalize w/ broncho - dilator; FEV_1, or peak flow 50%	no normalization w/bronchodilator, FEV_1, or peak flow 25 - 50%; retractions	cyanosis; FEV_1, or peak flow < 25%; intubated
GASTROINTESTINAL				
STOMATITIS	mild discomfort, no limits on activity	some limits on eating/talking	eating/talking very limited	unable to drink fluids; req. IV fluids
NAUSEA	mild discomfort, maintains reasonable intake	mod. discomfort, sign. dec of intake, some limit of activity	severe discomfort; no significant food intake activities limited	minimal fluid intake;
VOMITING	transient emesis	occ/moderate vomiting	orthostatic hypotension or IV fluid Rx req.	hypotensive shock hospitalization IV fluid therapy
CONSTIPATION	mild	moderate; Rx required	severe; Rx required; vomiting	distention with vomiting;
DIARRHEA	transient or 3 - 4 loose stools/day	5 - 7 loose stools/day and/or nocturnal loose stools. Rx required	orthostatic hypotension of > 7 loose stools/day or req. IV fluid Rx	hypotensive shock or hospitalization for IV fluid therapy

ITEM	GRADE 1 TOXICITY	GRADE 2 TOXICITY	GRADE 3 TOXICITY	GRADE 4 TOXICITY
NEURO/PSYCHOLOGICAL				
LEVEL OF CONSCIOUSNESS	Mildly inattentive to outside stimuli	Drowsy, but readily responds to verbal or uncomfortable stimuli	Stuporous. Able to be aroused by vigorous stimuli but verbal responses are slow or absent; able to make some effort to avoid painful stimuli	Comatose. Cannot be aroused by vigorous stimuli and makes no purposeful attempt to avoid painful stimuli
CONFUSION	Oriented to person, place and time, but has difficulty performing tasks requiring logic, math or spatial organization	Oriented to person and place, not time. Unable to perform complex tasks requiring logic, math	Oriented to person only. Unable to focus attention or care for bodily needs.	Delirious; not oriented to person, place or time; agitated
NEURO CEREBELLAR	slight incoordination Dysdiadochokinesias	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
MOOD	mild anxiety or depression	mod. anxiety or depression and therapy required	severe anxiety or depression or manic; (needs assistance)	acute psychosis; incapacitated requires hospitalization
NEUROMUSCULAR				
MUSCLE STRENGTH	subjective weakness; no objective symptoms/signs	mild objective weak - ness; no decrease in function	objective weakness; function limited	paralysis
PAINFUL NEUROPATHY	mild discomfort; no therapy required	moderate discomfort persisting for > 72 hrs; analgesia required	severe discomfort, marked antalgic gait. Narcotic analgesia required, with symptomatic improvement	incapacitating, intolerable discomfort. Not improved or unable to walk despite narcotic analgesics
“PINS & NEEDLES”	mild; does not interfere with routine activities	moderate; interferes with some ADL, but responds to symptomatic therapy	severe; significantly impairs ability to perform ADL despite symptomatic therapy; interferes with patient's sleep	Very severe; incapacitates patient

ITEM	GRADE 1 TOXICITY	GRADE 2 TOXICITY	GRADE 3 TOXICITY	GRADE 4 TOXICITY
NUMBNESS	mild decrease in sensation reported by patient, but pinprick and vibration exams are normal; does not interfere with ADL	moderate decrease in sensation reported by patient; reduced pinprick and vibratory sensation on exam; interferes with some ADL, but responds to symptomatic therapy	severely impaired sensation with inability to perceive pinprick or vibration; significantly impairs ability to perform ADL despite symptomatic therapy	Total lack of sensation on examination; incapacitates patient despite symptomatic therapy
MYALGIAS	Mild discomfort; no Rx required	Moderate discomfort persisting for > 72 hrs; analgesia required	severe discomfort; narcotic analgesia required with symptomatic improvement	severe discomfort not relieved by narcotic analgesic
NEUROMUSCULAR (continued)				
MYOSITIS	minimal findings	Patients must have some measures of myositis (positive EMG or muscle biopsy) and one of the following: 1) mild to moderate myalgias, > 4 weeks requiring non - steroidal anti - inflammatory agents. 2) difficulty climbing stairs or rising from a sitting position but able to ambulate without assistance	Patients must have some measures of myositis (positive EMG or muscle biopsy) and one of the following: 1) moderate/severe myalgias or muscle tenderness > 4 weeks requiring non - steroidal anti - inflammatory agents 2) requires some assistance with ambulation or general activities	Patients must have some measures of myositis (positive EMG or muscle biopsy) and one of the following: 1) severe muscle pain (myalgias) not related to exercise, requiring narcotics. 2) muscle weakness resulting in inability to ambulate, requiring special care and assistance with mobilization.

ITEM	GRADE 1 TOXICITY	GRADE 2 TOXICITY	GRADE 3 TOXICITY	GRADE 4 TOXICITY
				3) acute rhabdomyolysis with muscle necrosis and edema, moderate to severe muscle weakness with inability to ambulate or mobilize self without assistance. 4) acute rhabdomyolysis associated with electrolyte imbalance or renal failure.
OTHER PARAMETERS				
FEVER; oral, W/O infection, > 12 hrs.	37.7 - 38.5°C or 100.0 - 101.5°F	38.6 - 39.5°C or 101.6 - 102.9°F	39.6 - 40.5°C or 103 - 105°F	> 40.5°C > 105°F
HEADACHE	mild, no Rx therapy	transient, mod.; Rx req/	severe, responds to initial narcotic therapy	intractable, req. repeated narcotic therapy
FATIGUE	no dec. in daily activities	normal activity dec. 25 - 49%	normal activity dec. 50%, can't work	unable to care for self
ALLERGIC REACTION	pruritus w/o rash	localized urticaria, angioedema	generalized urticaria angioedema	anaphylaxis
LOCAL REACTION	tenderness or erythema	induration < 10cm or phlebitis or inflammation;	induration> 10cm or ulceration	necrosis
MUCOCUTANEOUS	erythema, pruritus	diffuse, mac. pap. rash dry desquamation	vesiculation, moist desquam, ulceration	exfoliative dermatitis, mucous membrane involvement suspected, Stevens Johnson or erythema multiforme, necrosis requiring surgery

FOR TOXICITIES NOT LISTED ABOVE, GRADE AS FOLLOWS:

Intensity Grades: 1 = Mild = does not interfere with routine activity.
2 = Moderate = interferes with performance of some activities of daily living (ADL), but responds to symptomatic therapy or rest.
3 = Severe = significantly limits ability to perform ADL despite symptomatic therapy.
4 = Very severe = incapacitates patient despite symptomatic therapy; hospitalization