Clinical Trial Protocol Amendment GEN-2

	TMC114				
Department:	Clinical R&D	**Nonproprietary name:**	darunavir		
Version:	3.0	**Date:**	20-June-2019	**Status:**	Approved
Title:	Continued access to darunavir/ritonavir (DRV/rtv) in HIV-1 infected adults, adolescents and children aged 3 years and above.				
Trial No:	TMC114IFD3001	**Clinical phase:**	IIIb		

Summary:

This is a continued access trial for adult and pediatric subjects who have completed treatment with darunavir in combination with low-dose ritonavir (DRV/rtv) in the clinical (parent) trials TMC114-C211, TMC114-C214, TMC114-TiDP31-C229 or in the pediatric (parent) trial TMC114-TiDP29-C232, who continue to benefit from the use of DRV/rtv, and who live in a country where DRV is not accessible.

At the baseline visit, inclusion and exclusion criteria will be checked to confirm eligibility. Once the eligibility criteria are met, subjects will continue treatment as follows:

HIV-1 infected subjects having participated in the TMC114-C211(parent) trial and some HIV-1 infected subjects from the pediatric (parent) trial TMC114-TiDP29-C232 will continue on the DRV/rtv 800/100 mg once daily (q.d.) dosing regimen as administered in the original (parent) trial.

Some HIV-infected subjects from the pediatric (parent) trial TMC114-TiDP29-C232 will continue on the selected b.i.d. DRV/rtv dosing regimen as administered in the original (parent) trial, or on an adjusted dose if necessary due to a change in body weight.

HIV-1 infected subjects having participated in the TMC114-C214 or TMC114-TiDP31-C229 (parent) trial will continue on the DRV/rtv 600/100 mg twice daily (b.i.d.) dosing regimen as administered in the original (parent) trial.

Visits and assessments are performed, according to local generally accepted standard of care, but desirable every 3 months for pediatric subjects and not less frequent than every 6 months for adult subjects. The interval between 2 consecutive visits should not exceed 6 months for pediatric subjects. Adverse events (AEs) considered at least possibly related to DRV/rtv, AEs leading to discontinuation or treatment

	interruption, serious AEs (SAEs), and pregnancies (or all AEs if applicable per local regulation) will be recorded at each visit. **As per Protocol Amendment 2,** the next planned visit will be a Final/Withdrawal Visit, which will be the last visit with data collection. Thereafter, visits and assessments will be performed per local standard of care and documented in the subject's medical records only. Investigators will continue to report SAEs possibly related to DRV/rtv and pregnancies to the sponsor using regular pharmacovigilance reporting. This information will only be entered in the company safety repository. If the subject exits the trial, the last visit will be a local standard of care visit but without dispensation of investigational medication. Treatment will be continued until 1 of the following criteria is met (whichever occurs first): virologic failure; treatment-limiting toxicity; loss to follow-up; withdrawal of consent/assent by the subject, withdrawal of consent by the parent(s)/legal representative(s); pregnancy; termination of the trial by the sponsor; a DRV-based treatment regimen becomes commercially available for the subject and is reimbursed, or can be accessed through another source (e.g., access program, government program) in the region the subject is living in or subjects can be switched to local standard of care, as appropriate.
Investigator:	See local Informed Consent/Assent Form
Site address:	See local Informed Consent/Assent Form
Sponsor:	Janssen Research & Development*
Treatment:	Subjects will either continue on the DRV/rtv dose they received in the original (parent) trial or on an adjusted dose if necessary due to a change in body weight for pediatric subjects until the subjects can be switched to locally available DRV-based treatment regimens (ie, commercially available and reimbursed, or accessible through another source [eg, access program or government program]) or to local standard of care, as appropriate.

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; Janssen Sciences Ireland Unlimited Company (which includes former Tibotec Pharmaceuticals); Janssen Biopharma Inc; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

PROTOCOL HISTORY

Protocol History TMC114IFD3001			
Document Type and *File Name*	**Document Identification**	**Amendment Type**	**Comments**
Initial Clinical Trial Protocol *TMC114IFD3001-CTP*	8 July 2010	-	-
CTP Amendment I *TMC114IFD3001-CTPA-GEN-I*	6 February 2017	Substantial	For details, refer to Amendment GEN-I
CTP Amendment 2 ***TMC114IFD3001-CTPA-GEN-II***	**This document**	**Substantial**	**For details, refer to Amendment GEN-II**

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PROTOCOL AMENDMENTS

Amendment GEN-II (This document)

The overall reason for the amendment: The aim of this roll-over study is to provide continued access to darunavir (DRV) in combination with low dose ritonavir (rtv) for adult and pediatric subjects who continue to benefit from the use of DRV/rtv and who live in a country where DRV is either not commercially available, not reimbursed, or cannot be accessed through another source. As of this amendment, the follow-up in this study will be simplified for the reasons outlined below.

DRV is approved since 2006 in adults and since 2011 in children as of the age of 3 years and has a well-established safety profile. The collection of additional data in Study TMC114IFD3001 is unlikely to provide substantial additional information on DRV or to impact the risk-benefit assessment. The TMC114IFD3001 is a roll-over study that has been ongoing since August 2011 and provides already substantial long-term safety information on DRV. The parent adult trials TMC114-C211 and TMC114-TiDP31-C229 ended respectively in March 2010 and August 2009, after which the subjects entered an extension phase until they could rollover into this study. The parent adult trial TMC114-C214 ended in March 2012 and the parent pediatric trial TMC114-TiDP29-C232 ended in November 2017. Hence, the subjects from Study TMC114IFD3001 have been on DRV for a significant amount of time. Therefore, the long-term safety of DRV has been properly assessed in these subjects, thereby allowing the study follow-up to be simplified for all subjects in this roll-over study.

As of this amendment, DRV will continue to be provided through this study until the subjects can be switched to locally available DRV-based treatment regimens (ie, commercially available and reimbursed, or accessible through another source [eg, access program or government program]) or to local standard of care, as appropriate.

This amendment is considered substantial based on the criteria set forth in Article 10(a) of Directive 2001/202EC of the European Parliament and the Council of the European Union.

The table below gives an overview of the rationale of all changes in the GEN-II amendment and all applicable sections.

Rationale: The long-term safety of DRV has been established in patients aged 3 years or more, and the collection of additional data in this study is unlikely to impact the risk-benefit assessment. Therefore, the study follow-up will be simplified, and study-related data will no longer be collected in the CRF. The information that will continue to be collected consists of serious adverse events (SAEs) possibly related to DRV/rtv and information on pregnancies. These are to be reported to the sponsor using regular pharmacovigilance reporting and will only be entered in the company safety repository. Medical records should be maintained according to the local standard of care and should continue to include details on the use of DRV/rtv.

PART I:2 Flowchart

PART I:4.1 Primary Objective

PART I:5.1.1 Overview of Trial

PART I:5.1.2 Discussion of Trial Design

PART I:5.2.5 Removal of Subjects From Therapy or Assessment

PART I:5.3.3 Dosage(s) and Treatment Overview per Subject

PART I:5.3.11 Adherence

PART I:5.4.1 Timing of Assessments

PART I:5.4.3 Efficacy

PART I:5.4.4 Safety

PART I:5.5 Safety Monitoring and Toxicity Management

PART I:5.6 Toxicity Management for Specific Adverse Events with Concomitant Antiretroviral Agents

PART II:1.3 HIV-Related Events or Outcomes

PART II:1.4 Reporting of Adverse Events and HIV-Related Events

PART II:3.4 Source Data

PART II:3.5 Case Report Forms

PART II:5.1 Reporting

PART II:8 Data Quality Control/Assurance

Rationale: To allow continuation of viral suppression, DRV will continue to be provided through this roll-over study until the subjects can be switched to locally available DRV-based treatment regimens (ie, commercially available and reimbursed, or accessible through another source [eg, access program or government program]) or to local standard of care, as appropriate.

PART I:3 Introduction

PART I:4 Trial Objectives

PART I:5.1.1 Overview of Trial

PART I:5.1.2 Discussion of Trial Design

PART I:5.2.5 Removal of Subjects From Therapy or Assessment

PART II:2 Trial Closure Considerations

Rationale: Instructions have been added for investigators to follow the guidance in the most recent Investigator's Brochure regarding any contraindications, precautions, and other restrictions.

PART I:5.2.4 Prohibitions and Restrictions

Rationale: The list of allowed and disallowed antiretroviral agents was updated to align with the most recent Investigator's Brochure and Summary of Product Characteristic.

PART I:5.3.5 Individually Optimized Background Regimen/Underlying Antiretroviral Therapy

Rationale: In line with the simplified study setting, information on the provision and destruction of study drug supplies was updated.

PART I:5.3.9 Drug Accountability

PART I:5.3.10 Storage

PART II:3.1 Investigational Products

Rationale: Information was added to clarify that the final analysis will be done once all subjects have completed the Final/Withdrawal Visit. After termination of data collection, no data will be collected in the CRF and no additional statistical analysis will be performed. The Clinical Study Report will contain CRF data from all study sites that participated in the study.

PART I:5.7.2 Statistical Analyses

PART II:5.1 Reporting

Rationale: A reference was added in the DAIDS grading table to provide guidance on the charts to be used to assess severity grade of abnormal blood pressure values in pediatric subjects.

PART I:7.2 Addendum 2: DAIDS Grading Table

Rationale: The legal entity Janssen, Inc was replaced by Janssen Pharmaceutica NV, Janssen, Inc and the abbreviation in Janssen Sciences Ireland UC was written in full. Furthermore, the legal entity Janssen Biopharma Inc was added.

Title page: **Sponsor** Footer

Rationale: Minor edits and corrections were made.

Throughout the document

Amendment GEN-I (06 February 2017)

This amendment is considered substantial based on the criteria set forth in Article 10(a) of Directive 2001/202EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The main reason of this amendment is to integrate the clinical trial protocol TMC114-TiDP-C232 into protocol TMC114IFD3001, to allow participation of subjects currently enrolled in the pediatric roll-over trial TMC114-TiDP-C232. In addition, the name of the sponsor of the trial is updated from 'Tibotec Pharmaceuticals' to 'Janssen Research & Development' because of the transition of the Johnson & Johnson Pharmaceutical Research & Development companies to a unified Janssen identity, as of 2 February 2012. Finally, the informed consent section was updated to the most recently available version.

The table below gives an overview of the rationale of all changes in the GEN-I amendment and all applicable sections.

Rationale: The Sponsor amends this adult roll-over trial to allow inclusion of the subjects from the pediatric roll-over trial TMC114-TiDP29-C232. The requirements of the two separate protocols have been kept mainly unchanged in this revised protocol. For a few items, integration of the protocols has led to changes in either the adult or the pediatric safety monitoring. These

are motivated by the standardization across protocols and the absence of safety concerns and are described below:

- Section 2 Flowchart - change for the adults:
The adherence counseling was missing in the flowchart and is now added;

- Section 5.2.5 Must withdraw criteria for glucose levels G3/4 and Section 5.6.1 Toxicity Manangement/ Hyperglycemia - change for the adults:
The must withdraw criteria for adults are now extended to the subjects experiencing a persistent grade 3 or 4 glucose elevation despite appropriate antihyperglycemic treatment (except if the subject has pre-existing diabetes) while previously the subjects with glucose grade 3 elevation or asymptomatic glucose grade 4 elevation did not require per se trial discontinuation;

- Section 5.2.5 Must withdraw criteria and Section 5.5.3 Safety Monitoring/AST and ALT elevations - change for the pediatric subjects:
In the pediatric protocol, language was provided in these sections to require withdrawal of the subjects in following circumstances: "The subject meets Hy's Law criteria for drug-induced liver injury (DILI); i.e., alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 ´ the upper limit of laboratory normal range (ULN) in combination with total bilirubin elevation > 2 ´ ULN or international normalized ratio (INR) > 1.5 without evidence of obstructive disease and no other reason* can be found to explain the combination of aminotransferase and total bilirubin elevation."
* E.g.: viral hepatitis A, B, or C, pre-existing or acute liver disease, or another drug capable of causing the observed injury.
This wording is no longer provided in the current protocol since DILI occurs usually early after treatment start and the the pediatric patients entering in this trial have already been treated with DRV for a long time. Additionally, adequate safety monitoring rules and withdrawal criteria pertaining to the liver enzymes are in place in the same sections, to guarantee the safety of the patients in this trial.

- Section 5.5.1 Safety Monitoring/Cutaneous Reaction/Rash - change for the adults:
The use of anesthesia in case of skin biopsy is offered now as well to the adults. In addition, the local laboratory assessments are no longer systematic and are now left at the discretion of the investigator and after approval of the sponsor. Clarification is also provided that the referral to a dermatologist should preferably occur within 24 hours;

- Section 5.5.3 Safety Monitoring/AST and ALT elevations - change for the adults:
A warning on severe acute exacerbation of hepatitis B infection when discontinuing emtricitabine (FTC) or lamivudine (3TC) is present in the pediatric protocol as some patients might be treated with emtricitabine (FTC) or lamivudine (3TC); as adult patients may also be treated by FTC or 3TC, this warning now also applies to the adult population;

- Section 5.6.2 Toxicity Manangement/ Lipids - change for the adults:
The monitoring of low-density lipoprotein (LDL) cholesterol levels, performed for the pediatric patients, has now been added for the adult patients as well;

PART I:2 Flowchart

PART I:5.2.5 Removal of Subjects From Therapy or Assessment

PART I:5.6.1 Hyperglycemia

PART I:5.5.1 Cutaneous Reaction/Rash

PART I:5.5.3 AST and ALT Elevations

PART I:5.6.2 Hypertriglyceridemia, Hypercholesterolemia and LDL Cholesterol increase

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Rationale: The Sponsor amends this adult roll-over trial to allow inclusion of the subjects from the pediatric roll-over trial TMC114-TiDP29-C232. Therefore in most sections, specific wording applying to the pediatric patients was added. The most important additions and adjustments are:

- **Section 5.3.3 Body weight:** For pediatric subjects, body weight will be recorded at the baseline visit and at every visit during the treatment period. Tables for dosage regimens per body weight were added: PART I:5.3.3 Dosage(s) and Treatment Overview per Subject;

- Section 5.3.11 Adherence: Adherence counseling of the pediatric patients, the parents or legal representative is added as well as the requirement to have that documented in the source documents/charts: PART I:5.2.4 Prohibitions and Restrictions, PART I:5.3.11 Adherence;

- **Section 5.5.6 Nausea (With or Without Vomiting):** Grade 1 and grade 2 nausea were updated: PART I:5.5.6 Nausea (With or Without Vomiting);

- **Section 5.5.7 Diarrhea:** Grade 1 and grade 2 diarrhea were updated: PART I:5.5.7 Diarrhea;

- **Section 5.6.4 Fat redistribution:** Assessment of fat redistribution in HIV-infected children and adolescents is complicated by the normal, dynamic alterations in body composition that occur during childhood and adolescence: PART I:5.6.4 Lipodystrophy/Fat Redistribution/Body Changes;

- **Section 6.4 Informed consent/assent process:** The special vulnerability of children and adolescents requires specific measures in the informed consent/assent process in order to safeguard their best interests and to protect them from harm: PART II:6.4 Subject Information and Informed Consent/Assent;

- **Section 5.3.5 Allowed and Disallowed Antiretroviral Agents After Baseline:** The allowed and disallowed ARV agents were added for pediatric subjects: PART I:5.3.5 Individually Optimized Background Regimen/Underlying Antiretroviral Therapy.

Rationale: The Sponsor amends this adult roll-over trial to allow inclusion of the subjects from the pediatric roll-over trial TMC114-TiDP29-C232. Specific wording applying to the pediatric patients and some further clarifications, for consistency reasons, were added to the following sections:

Title Page: Title

Title Page: Treatment

PART I:3 Introduction

PART I:4.1 Primary Objective

PART I:5.1.1 Overview of Trial

PART I:5.1.2 Discussion of Trial Design

PART I:5.1.3 Selection of Dose(s) in the Trial

PART I:5.2.1 Sample Size

PART I:5.2.2 Inclusion Criteria

PART I:5.2.4 Prohibitions and Restrictions

PART I:5.3.1 Identity of Investigational Product

PART I:5.3.2 Other Medication Administered in the Trial

PART I:5.3.4 Timing of Dosing

PART I:5.3.5 Individually Optimized Background Regimen/Underlying Antiretroviral Therapy

PART I:5.3.6 Packaging and Labeling

PART I:5.4.1 Timing of Assessments

PART I:5.4.4.1 Adverse Events/HIV-Related Events

PART I:5.4.4.2 Clinical Laboratory Tests

PART I:5.6.2 Hypertriglyceridemia, Hypercholesterolemia and LDL Cholesterol increase

PART I:5.6.3 Lactic Acidosis

PART I:5.7.1 Sample Size Calculation

PART I:6 References

PART I:7.3 Addendum 3: Visit Schedule for Cutaneous Reaction/Rash Follow-up for pediatric subjects

PART I:7.5 Addendum 5: Lipid Abnormalities (Dyslipidemia)

PART II:1.4 Reporting of Adverse Events and HIV-Related Events

PART II:3.2 Trial Documents

PART II:3.4 Source Data

PART II:3.7 Archiving

PART II:6.2 Independent Ethics Committee/Institutional Review Board

PART II:6.4 Subject Information and Informed Consent/Assent

PART II:7.3 Insurance

Rationale: Allowed and Disallowed Antiretroviral Agents After Baseline - changes for the adults: Dolutegravir is no longer an investigational but an approved integrase inhibitor;

PART I:5.3.5 Individually Optimized Background Regimen/Underlying Antiretroviral Therapy

Rationale: The section on informed consent/assent was updated to reflect the latest language in the Janssen protocol template, taking into account that both adult and pediatric subjects will be included in this study.

PART II:6.4 Subject Information and Informed Consent/Assent

Rationale: A list of clinical trials with specific populations for which darunavir (DRV) is approved is added. For detailed and updated information on the clinical trial data, reference is made to the most recent Investigator's Brochure (IB) of DRV[2].

PART I:3 Introduction

Rationale: Replacement of the Annual Safety Report by the Development Safety Update Report.

PART II:5.1 Reporting

Rationale: Minor editorial changes for clarity and consistency.

List of Abbreviations

Signature Page

Rationale: The name of the sponsor of the trial is updated from 'Tibotec Pharmaceuticals' to 'Janssen Research & Development' because of the transition of the Johnson & Johnson Pharmaceutical Research & Development companies to a unified Janssen identity, as of 2 February 2012.

Title Page: Sponsor

PART I:3 Introduction

PART I:4.1 Primary Objective

PART I:5.1.1 Overview of Trial

PART I:5.1.2 Discussion of Trial Design

PART I:5.2.1 Sample Size

PART I:5.3.1 Identity of Investigational Product

PART I:5.3.2 Other Medication Administered in the Trial

PART I:5.3.6 Packaging and Labeling

PART I:5.3.10 Storage

PART I:5.4.1 Timing of Assessments

PART I:5.5 Safety Monitoring and Toxicity Management

PART I:5.5.1 Cutaneous Reaction/Rash

PART I:5.6 Toxicity Management for Specific Adverse Events with Concomitant Antiretroviral Agents

PART I:5.7.1 Sample Size Calculation

PART I:7.2 Addendum 2: DAIDS Grading Table

PART I:7.5 Addendum 5: Lipid Abnormalities (Dyslipidemia)

PART II:1.4 Reporting of Adverse Events and HIV-Related Events

PART II:5.1 Reporting

Signature Page

Rationale: The sponsor has decided to harmonize the procedures for emergency medical questions and product complaints. Therefore, the telephone number mentioned on the title page has been removed. Appropriate information about who should be contacted regarding safety issues or questions regarding the clinical trial is provided **on the contact information page**.

Title Page: Summary

PART I: CLINICAL TRIAL PROTOCOL

1 LIST OF ABBREVIATIONS

3TC	lamivudine
ABC	abacavir
ACTG	Adult AIDS Clinical Trial Group
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARV	antiretroviral
ASR	Annual Safety Report
AST	aspartate aminotransferase
BRAT	bananas, rice, applesauce and toast
b.i.d.	twice daily (*bis in die*)
CDC	U.S. Centers for Disease Control and Prevention
CRF	Case Report Form
DAIDS	Division of AIDS
DCF	Data Correction Form
DILI	Drug-induced liver injury
ddI	didanosine
DRV	darunavir (formerly known as TMC114)
FTC	emtricitabine
GCP	Good Clinical Practice
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
IB	investigator's brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IUD	intra-uterine device
LDL	low-density lipoprotein
NCEP	National Cholesterol Education Program
NCR	non-carbon required
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
OBR	optimized background regimen
PI	protease inhibitor
QA	Quality Assurance
QC	Quality Control
q.d.	once daily (*quaque die*)
RAM	resistance-associated mutation
RBC	red blood cell
rtv	low-dose ritonavir
SAE	serious adverse event

SJS	Stevens-Johnson syndrome
TDF	tenofovir disoproxil fumarate
TEN	toxic epidermal necrolysis
TMC114	darunavir
TMC125	etravirine
ULN	upper limit of laboratory normal range
WBC	white blood cell

2 FLOWCHART

2.1 Flowchart 1: Trial Follow-up

Up to and including Protocol Amendment 1:

Type of Visit	Baseline	Treatment Period		Post-treatment Period
Time of Visit	Day 1[a]	Visits and assessments are performed, according to Local Standard of Care, but desirable every 3 months for pediatric subjects and not Less Frequent Than Every 6 Months for adult subjects. The interval between 2 consecutive visits should not exceed 6 months for pediatric subjects.	Final / Withdrawal Visit[g]	Follow-up Contact Week 4[b]
Informed consent/assent	X		X[h]	
Inclusion/exclusion criteria	X			
Demographic data	X			
Pregnancy test, if applicable[c]	X	X	X	
Weight[f]	X	X		
Dispensation of investigational medication	X	X	X[h]	
Drug accountability		X	X	
Adherence Counseling	X	X	X[h]	
Collection of the following AEs[d]: - AEs considered to be at least possibly related to DRV/rtv; - AEs leading to discontinuation or treatment interruption; - SAEs and pregnancies.	X	X	X	X
Treatments related to (S)AEs[e]		X	X	X

[a] Subjects will rollover from another (parent) trial. The baseline visit will coincide with the last visit of the previous (parent) trial. Assessments and results from the last visit of the previous (parent) trial will be used for the baseline visit of this trial; overlapping assessments only need to be conducted once. Demographic information will be copied from the previous (parent) trial, if needed.

[b] The Week 4 follow-up contact is only needed for subjects with an ongoing AE as specified in this flowchart.

[c] Urine pregnancy test for the females of childbearing potential only.

[d] Other AEs will only be collected if required per local regulations.

[e] Collection of data on treatments related to (S)AEs for which information is collected.

[f] Only applicable for pediatric subjects.

[g] The next planned visit will be a Final/Withdrawal Visit for all subjects when discontinuing the trial or switching to simplified data collection as per Protocol Amendment 2. For subjects continuing the trial under Protocol Amendment 2, all subsequent visits and assessments will be performed per local standard of care and documented in the subject's medical records only, as described in Flowchart 2: Simplified Trial Follow-up.

[h] Only applicable for subjects continuing the trial under Protocol Amendment 2.

2.2 Flowchart 2: Simplified Trial Follow-up

As of Protocol Amendment 2:

Type of Visit	Local Standard of Care Visit[a]
Informed consent/assent	Refer to the Final/Withdrawal Visit in Flowchart 1: Trial Follow-up
Dispensation of investigational medication	X[d]
Collection of SAEs possibly related to DRV/rtv and pregnancies[b]	X
Study termination[c]	X
Note: Assessments are to be performed per local standard of care and documented in the subject's medical records only.	

[a] The next planned visit before switching to simplified data collection as per Protocol Amendment 2 will be a Final/Withdrawal Visit. During this Final/Withdrawal Visit, the informed consent will be signed, final assessments will be carried out and recorded in the CRF, and the study medication will be dispensed as described in Flowchart 1: Trial Follow-up.
[b] Investigators will continue to report SAEs possibly related to DRV/rtv and pregnancies to the sponsor using regular pharmacovigilance reporting.
[c] Study termination will be documented in the subject's medical records and recorded on a separate, paper termination disposition form to be shared with the sponsor.
[d] If the subject exits the trial, the last visit will be a local standard of care visit but without dispensation of investigational medication.

The next planned visit after approval of Protocol Amendment 2 will be a Final/Withdrawal Visit. During this Final/Withdrawal Visit, the informed consent will be signed, final assessments will be carried out and recorded in the CRF, and the study medication will be dispensed as described in Flowchart 1: Trial Follow-up. All subsequent visits and assessments will be performed per local standard of care and documented in the subject's medical records only. Investigators will continue to report SAEs possibly related to DRV/rtv and pregnancies to the sponsor using regular pharmacovigilance reporting. This information will only be entered in the company safety repository.

If the subject exits the trial, the last visit will be a local standard of care visit but without dispensation of investigational medication.

3 INTRODUCTION

Inhibitors of human immunodeficiency virus (HIV) protease have become cornerstones in the treatment of HIV disease, particularly in HIV-1 infected subjects with a long history of antiretroviral (ARV) therapy. Current options for the treatment of HIV-1 infected adult subjects consist of nucleoside/nucleotide reverse transcriptase inhibitor (NRTIs), non-nucleoside reverse transcriptase inhibitor (NNRTIs), protease inhibitors (PIs), entry inhibitors, and an integrase inhibitor. A triple regimen is considered standard of care[1] and when effective, results in suppression of the virus below the detection limits of the current tests, thereby strongly reducing the emergence of resistance.

Darunavir (DRV, formerly known as TMC114) is an HIV PI with potent in vitro activity against wild-type HIV-1, and, as a result of the drug-screening program aimed at activity against resistant strains of HIV-1, also active against a large panel of viruses resistant to currently licensed PIs.

DRV, co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adult and pediatric patients from the age of 3 years. DRV was first registered in the United States (June 2006) and has obtained marketing authorization in Europe in February 2007. The approved indications and registered tablet strengths for DRV vary per country where registered.

DRV has been approved based on the below mentioned clinical trials in the following populations:

ADULT HIV-Infected subjects:

In ARV-experienced: Studies TMC114-C202, TMC114-C213, TMC114-C215, TMC114-C214
In ARV-experienced without DRV resistance-associated mutations (RAMs): Trial TMC114-TiDP31-C229
In ARV-naive subjects: Trial TMC114-C211

The adult patients could roll-over to trial TMC114IFD3001 for access to DRV if not yet accessible by other means in their country.

PEDIATRIC HIV-Infected subjects:

In ARV-experienced adolescents: Trial TMC114-C212
In ARV-naive adolescents: Trial TMC114-C230
In ARV-experienced subjects aged 3 years to 6 years: Trial TMC114-C228

The pediatric patients could roll-over to trial TMC114-TiDP29-C232 for access to DRV if not yet accessible by other means in their country.

For detailed and updated information on the clinical trial data, refer to the most recent Investigator's Brochure (IB) of DRV.[2]

The aim of the present amended trial TMC114IFD3001 is to provide continued access to DRV/rtv for adult and pediatric subjects who previously received DRV/rtv in the above-mentioned clinical (parent) trials, who continue to benefit from treatment with DRV and cannot have access to DRV in their country by other means.

4 TRIAL OBJECTIVES

4.1 Primary Objective

The primary objective of this trial is to continue the provision of DRV/rtv for adult and pediatric subjects who previously received DRV/rtv in the clinical (parent) trials TMC114-C211, TMC114-C214, TMC114-TiDP31-C229 or in the pediatric (parent) trial TMC114-TiDP29-C232, who continue to benefit from the use of DRV/rtv, in countries where DRV is not commercially available for the subject, is not reimbursed, or cannot be accessed through another source (e.g., access program, governmental program).

In addition, the long-term safety and tolerability of DRV/rtv in combination with other ARVs will be assessed.

Protocol Amendment 2 Objective:

As of Protocol Amendment 2, the objective of the trial is to provide DRV through this trial until the subjects can be switched to locally available DRV-based treatment regimens (ie, commercially available and reimbursed, or accessible through another source [eg, access program or government program]) or to local standard of care, as appropriate.

5 METHODS

5.1 Trial Design

5.1.1 OVERVIEW OF TRIAL

This is a continued access trial for adult and pediatric subjects who have completed treatment with DRV/rtv in the adult clinical (parent) trials TMC114-C211, TMC114-C214, TMC114-TiDP31-C229 or in the pediatric (parent) trial TMC114-TiDP29-C232, who continue to benefit from the use of DRV/rtv, and who live in a country where DRV is not accessible.

At the baseline visit, inclusion and exclusion criteria will be checked to confirm eligibility. Once the eligibility criteria are met, subjects will continue treatment as follows:

- HIV-1 infected subjects participating in the TMC114-C211(parent) trial or in the pediatric (parent) trial TMC114-TiDP29-C232, after original participation in TMC114-TiDP29-C230 trial will continue on the DRV/rtv 800/100 mg q.d. dosing regimen as administered in the original (parent) trial.
- HIV-1 infected subjects participating in the pediatric (parent) trial TMC114-TiDP29-C232, after original participation in TMC114-C212 or TMC114-TiDP29-C228 trial will continue on the selected b.i.d. DRV/rtv dosing regimen as administered in the original (parent) trial, or on an adjusted dose if necessary due to a change in body weight.

HIV-1 infected subjects participating in the TMC114-C214 or TMC114-TiDP31-C229 (parent) trials will continue on the DRV/rtv 600/100 mg b.i.d. dosing regimen as administered in the original (parent) trial.

Visits and assessments are performed, according to local generally accepted standard of care, but desirable every 3 months for pediatric subjects and not less frequent than every 6 months for adult subjects. The interval between 2 consecutive visits should not exceed 6 months for pediatric subjects. Adverse events (AEs) considered at least possibly related to DRV/rtv, AEs leading to discontinuation or treatment interruption, serious AEs (SAEs), and pregnancies (or all AEs if applicable per local regulation) will be recorded at each visit. Subjects will be instructed to report any AEs to the investigator, who reports SAEs within 24 hours to the sponsor (see Part II, Section 1.4 'Reporting of Adverse Events and HIV-Related Events').

Details on the timing of treatment and assessments are provided in the flowchart in Section 2. In addition to the assessments in this flowchart, the following assessments are recommended to be performed locally every 3 months or according to local generally accepted standard of care:

- Efficacy assessments (immunology and plasma viral load); and
- Laboratory safety assessments (hematology and biochemistry, including pancreatic amylase [if available] or lipase and lipid analyses).

As per Protocol Amendment 2, the next planned visit will be a Final/Withdrawal Visit, which will be the last visit with data collection. Thereafter, visits and assessments will be performed per local standard of care and documented in the subject's medical records only. Investigators will continue to report SAEs possibly related to DRV/rtv and pregnancies to the sponsor using regular pharmacovigilance reporting. This information will only be entered in the company safety repository.

If the subject exits the trial, the last visit will be a local standard of care visit but without dispensation of investigational medication.

Treatment will be continued until one of the following criteria is met (whichever occurs first):

- Virologic failure;
- Treatment-limiting toxicity;
- Loss to follow-up;
- Withdrawal of consent/assent by the subject or withdrawal of consent by the parent(s)/legal representative(s);
- Pregnancy;
- Termination of the trial by the sponsor;
- A DRV-based treatment regimen becomes commercially available for the subject and is reimbursed, or can be accessed through another source (e.g., access program, government program) in the region the subject is living in or subjects can be switched to local standard of care, as appropriate.

A post-treatment follow-up contact is to be performed 4 weeks after the last dose of trial medication for subjects with an ongoing adverse event, that discontinue the trial under Protocol Amendment 1, as specified in the flowchart in Section 2.

5.1.2 DISCUSSION OF TRIAL DESIGN

The primary objective of this trial is to continue the provision of DRV/rtv to subjects who have completed treatment with DRV/rtv in the adult clinical (parent) trials TMC114-C211, TMC114-C214, TMC114-TiDP31-C229 or in the pediatric (parent) trial TMC114-TiDP29-C232, who continue to benefit from the use of DRV/rtv, and who live in a country where DRV is not commercially available, is not reimbursed, or cannot be accessed through another source (e.g., access program, government program).

Selected safety data are to be collected during DRV/rtv treatment (see Section 5.4.4). Additional assessments not included in this protocol can be done locally as per local standard of care.

As per Protocol Amendment 2, the next planned visit will be a Final/Withdrawal Visit, which will be the last visit with data collection. Thereafter, visits and assessments will be performed per local standard of care and documented in the subject's medical records only. SAEs possibly related to DRV/rtv and information on pregnancies will continue to be reported to the sponsor using regular pharmacovigilance reporting. This information will only be entered in the company safety repository.

If the subject exits the trial, the last visit will be a local standard of care visit but without dispensation of investigational medication.

5.1.3 SELECTION OF DOSE(S) IN THE TRIAL

Subjects will continue on the DRV/rtv dosing regimen as administered in the original (parent) trial i.e., DRV/rtv 800/100 mg q.d. for HIV-infected subjects from the TMC114-C211 (parent) trial or from the pediatric (parent) trial TMC114-TiDP29-C232; the selected b.i.d. DRV/rtv dosing regimen for HIV-infected subjects from the pediatric (parent) trial TMC114-TiDP29-C232 with weight-based dose adjustment if necessary (see Section 5.3.3); and DRV/rtv 600/100 mg b.i.d. for HIV-infected subjects from the TMC114-C214 or TMC114-TiDP31-C229 (parent) trial.

5.2 Trial Population

5.2.1 SAMPLE SIZE

Not applicable.

Subjects who previously received treatment with DRV/rtv in the clinical (parent) trials TMC114-C211, TMC114-C214, TMC114-TiDP31-C229 or in the pediatric (parent) trial TMC114-TiDP29-C232, who continue to benefit from the use of DRV/rtv, and who live in a country where DRV is not accessible may be eligible to continue treatment with DRV/rtv via this trial.

5.2.2 INCLUSION CRITERIA

Subjects who meet all of the following criteria are eligible for this trial:

1. "Criterion modified per Amendment 1"

1.1 Male or female subjects, aged 3 years and above.

2. "Criterion modified per Amendment 1"

2.1 Subjects treated with DRV/rtv who have successfully completed the TMC114-C211, TMC114-C214, TMC114-TiDP31-C229 (parent) trial or the pediatric (parent) trial TMC114-TiDP29-C232 and in the opinion of the investigator continue to receive benefit from using DRV/rtv.

3. DRV is not commercially available for the subjects, is not reimbursed, or cannot be accessed through another source (e.g. access program, government program) in the region the subject is living in.

4. "Criterion modified per Amendment 1"

4.1 Subject (where appropriate, depending on age) and the parent(s) or legal representative(s) have signed the Informed Consent/Assent Form voluntarily. Children will be informed about the program and asked to give assent (where appropriate, depending on age).

5.2.3 EXCLUSION CRITERIA

Subjects meeting 1 or more of the following criteria cannot be selected:

1. Any condition (including but not limited to alcohol and drug use) which, in the opinion of the investigator, could compromise the subject's safety or adherence to treatment with DRV/rtv.
2. Any active clinically significant disease (e.g., pancreatitis, cardiac dysfunction) or findings of medical history, laboratory or physical examination that, in the investigator's opinion, would compromise the subject's safety during treatment with DRV/rtv.
3. Previously demonstrated clinically significant allergy or hypersensitivity to any of the excipients of the investigational medication (DRV) or ritonavir.
4. Pregnant or breastfeeding female subjects.
5. Female subject of childbearing potential without use of effective non-hormonal birth control methods or not willing to continue practicing these birth control methods for at least 30 days after the end of the treatment period.

   Note: Estrogen hormonal based contraception may not be reliable when taking DRV/rtv, therefore to be eligible for this trial female subjects of childbearing potential should either:

   a. Use a double-barrier method to prevent pregnancy (i.e., use a male condom with either diaphragm or cervical cap)*; or
   b. Use non-estrogen hormonal based contraceptives in combination with a barrier contraceptive (i.e., male condom, diaphragm or cervical cap, or female condom); or
   c. Use an intra-uterine device (IUD) in combination with a barrier contraceptive (i.e., male condom, diaphragm or cervical cap, or female condom); or
   d. Be non-heterosexually active, practice heterosexual abstinence, or have a vasectomized partner (confirmed sterile).

   * A male and female condom should not be used together due to the risk of breakage or damage caused by latex friction.

   Women who are postmenopausal for at least 2 years, women with total hysterectomy, and women with tubal ligation are considered of non-childbearing potential.

6. Heterosexually active male subject not using effective birth control methods or not willing to continue practicing these birth control methods during the trial and until 30 days after the end of the trial (or after last intake of investigational medication).

5.2.4 PROHIBITIONS AND RESTRICTIONS

It is the investigator's responsibility to provide appropriate counseling to HIV-1 infected subjects about taking the necessary precautions to reduce the risk of transmitting HIV.

Since the effects of DRV/rtv on gestation are unknown, heterosexually, non-vasectomized male subjects, who are sexually active and/or female subjects of child-bearing potential having heterosexual intercourse should receive counseling about birth control methods[7] and be advised to use one of the following birth control methods as outlined above in the exclusion criteria (Section 5.2.3). Girls having their first menses during the trial should receive counseling as well.

Female subjects should not breastfeed when taking DRV/rtv, since the effects to the newborn child are unknown. Female subjects who have a newborn child should talk to their physician about the best way to feed their child. They should be aware that HIV could be transmitted through breastfeeding.

The above precautions and restrictions apply from baseline onwards, until at least 30 days after the last intake of investigational medication.

Investigators should follow the guidance in the most recent Investigator's Brochure[2] regarding any contraindications, precautions for use, and other restrictions.

For detailed and updated information on the clinical trial data with regard to the reproductive toxicity of DRV, refer to the most recent Investigator's Brochure (IB) of DRV[2].

5.2.5 REMOVAL OF SUBJECTS FROM THERAPY OR ASSESSMENT

A subject **may** be withdrawn from the trial if:

1. An SAE occurs.
2. The subject fails to comply with the protocol requirements or to cooperate with the investigator.
3. The subject starts disallowed treatment (see Section 5.3.12). The sponsor should be contacted to evaluate the need for withdrawal.
4. The subject demonstrates lack or loss of treatment response during the trial.

A subject **must** be withdrawn from the trial if:

1. The parent(s) or legal representative(s) withdraw(s) consent, or the subject withdraws consent or assent.
2. The investigator considers it, for safety reasons, in the best interest of the subject that he or she be withdrawn.
3. Pregnancy has been determined.
4. The subject is diagnosed with acute hepatitis A, B, or C infection after baseline. For details on monitoring and management of hepatitis, see Section 5.5.4.

5. The subject experiences a grade 3 or 4 cutaneous reaction/rash (according to the DAIDS scale; see Section 7.2, Addendum 2: DAIDS Grading Table). For details on monitoring and management of cutaneous reaction/rash, see Section 5.5.1.
6. The subject experiences a grade 4 AE considered at least possibly related to DRV/rtv or a confirmed grade 4 laboratory abnormality (according to the Division of AIDS [DAIDS] scale; see Section 7.2, Addendum 2: DAIDS Grading Table) considered at least possibly related to DRV/rtv. Exceptions are, unless clinical assessment foresees an immediate health risk to the subject:
7. Subjects with asymptomatic triglyceride grade 4 elevations (see Section 5.6.2).The subject experiences a persistent grade 3 or 4 glucose elevation despite appropriate anti-hyperglycemic treatment (except if the subject has pre-existing diabetes; see Section 5.6.1)
8. The subject experiences a confirmed grade 4 pancreatic amylase elevation or a confirmed grade 3 or grade 4 lipase elevation, which persists after 14 days after the interruption of the trial medication, or if the toxicity recurs more than twice (see also Section 5.6.5.2).The subject experiences, after trial medication interruption because of a confirmed grade 3 increase in alanine aminotransferase (ALT) or aspartate aminotransferase (AST), a confirmed recurrence of grade 3 or 4 increase in ALT or AST. For subjects with hepatitis B or C coinfection present at baseline, refer to Section 5.5.3 for toxicity management plans.
9. The subject experiences a grade 3 or 4 acute systemic allergic reaction (according to the DAIDS scale; see Section 7.2, Addendum 2: DAIDS Grading Table). For details on monitoring and management of acute systemic allergic reactions, refer to Section 5.5.2.
10. A DRV-based treatment regimen becomes commercially available for the subject and is reimbursed, or can be accessed through another source (e.g., access program, government program) in the region the subject is living in or subjects can be switched to local standard of care, as appropriate.

The date and reason for discontinuation must be noted on the Case Report Form (CRF). Unless the parent(s)/legal representative(s) or subject withdraw(s) consent/assent, each subject prematurely discontinuing the trial must be seen for a final evaluation (withdrawal visit). A post-treatment follow-up contact is to be performed 4 weeks after the last dose of trial medication for subjects with an ongoing adverse event, that discontinue the trial under Protocol Amendment 1, as specified in the flowchart in Section 2. After the last visit, the Trial Termination page and Investigator's Signature page of the CRF is to be completed.

As per Protocol Amendment 2, study termination will be documented in the subject's medical records and recorded on a separate, paper termination disposition form to be shared with the sponsor.

5.3 Treatment

5.3.1 Identity of Investigational Product

The investigational medication DRV will be manufactured under the responsibility of the sponsor and will be formulated as follows:

- Formulation F029: oral tablet composed of DRV ethanolate eq. 75 mg, microcrystalline cellulose, colloidal silicon dioxide, crospovidone, magnesium stearate, and OPADRY® white.
- Formulation F050: oral tablet composed of DRV ethanolate eq. 150 mg, microcrystalline cellulose, colloidal silicon dioxide, crospovidone, magnesium stearate, and OPADRY® white.
- Formulation F030: oral tablet composed of DRV ethanolate eq. 400 mg, microcrystalline cellulose, colloidal silicon dioxide, crospovidone, magnesium stearate, and OPADRY® light orange.
- Formulation F032: oral tablet composed of DRV ethanolate eq. 600 mg, microcrystalline cellulose, colloidal silicon dioxide, crospovidone, magnesium stearate, and OPADRY® orange.
- Formulation F052: oral suspension composed of DRV ethanolate eq. 100 mg per ml, hydroxypropylcellulose, microcrystalline cellulose and sodium carboxymethylcellulose, sodium methyl parahydroxybenzoate, citric acid monohydrate, sucralose, masking flavor, strawberry cream flavor, concentrated hydrochloric acid and purified water.

Note: The oral tablets should not be crushed but be swallowed as whole tablets. The oral suspension should be shaken immediately before administration.

5.3.2 OTHER MEDICATION ADMINISTERED IN THE TRIAL

The sponsor provides commercial ritonavir (Norvir®) which is formulated as a capsule or tablet, depending on availability, containing 100 mg ritonavir, as a sachet of 100 mg ritonavir powder for oral suspension (at a ritonavir concentration of 10 mg/mL), or as a liquid solution containing 80 mg/mL ritonavir. Refer to Section 5.3.6 and the current package inserts for further details.

The sponsor will not provide the medication of the optimized background regimen (OBR). The subject will receive the investigator-selected OBR medications according to the locally applicable procedures. Refer to the current package inserts for further details.

5.3.3 DOSAGE(S) AND TREATMENT OVERVIEW PER SUBJECT

Adult Patients

Once eligibility criteria are met, subjects will continue on the DRV/rtv dose they received in the original (parent) trial.

HIV-1 infected subjects participating in the **TMC114-C211** (parent) trial continue on DRV/rtv 800/100 mg q.d (i.e., 2 tablets of 400 mg DRV and 100 mg ritonavir q.d.).HIV-1 infected subjects participating in the **TMC114-C214** or **TMC114-TiDP31-C229** (parent) trial continue on DRV/rtv 600/100 mg b.i.d. (i.e., 1 tablet of 600 mg DRV and 100 mg ritonavir b.i.d.).

Pediatric Patients

The dosing regimen for subjects participating in the pediatric (parent) trial TMC114-TiDP29-C232 is identical to the dosing regimen in the trials that subjects originated from before rolling over into TMC114-TiDP29-C232 (adjusted for weight if applicable).

Table 1 and Table 2 provide an overview of the exact volume of trial medication to be administered per body weight and per intake.

Table 1: Exact volume of trial medication (DRV [oral suspension] and ritonavir [oral solution, 80 mg/mL]) to be administered per body weight and per intake.

Body Weight, kg	DRV dose, mg b.i.d.	DRV volume, mL b.i.d.	Ritonavir dose, mg b.i.d.	Ritonavir volume, mL b.i.d.
10 – 10.9	200	2.0	32	0.4
11 – 11.9	220	2.2	32	0.4
12 – 12.9	240	2.4	40	0.5
13 – 13.9	260	2.6	40	0.5
14 – 14.9	280	2.8	48	0.6
≥ 15 – 29.9	375	3.8	50	0.6
≥ 30 – 39.9	450	4.6	60	0.7
≥ 40*	600	6.0	100	1.25

* It is expected that these subjects are able to swallow the tablets. Therefore, most subjects will be taking the solid formulation only.

Table 2: Exact volume of trial medication (DRV [oral suspension] and ritonavir [powder for oral suspension (prepared as 100 mg/10 mL)*]) to be administered per body weight and per intake.

Body Weight, kg	DRV dose, mg b.i.d.	DRV volume, mL b.i.d.	Ritonavir dose, mg b.i.d.	Ritonavir volume, mL b.i.d.*
10 – 10.9	200	2.0	32	3.2
11 – 11.9	220	2.2	32	3.2
12 – 12.9	240	2.4	40	4.0
13 – 13.9	260	2.6	40	4.0
14 – 14.9	280	2.8	48	4.8
≥ 15 – 29.9	375	3.8	50	5.0
≥ 30 – 39.9	450	4.6	60	6.0
≥ 40**	600	6.0	100	10.0

* When mixed with 9.4 mL of liquid (water, chocolate milk, or infant formula) the concentration of the suspension is 10 mg/mL.
** It is expected that these subjects are able to swallow the tablets. Therefore, most subjects will be taking the solid formulation only.

As the dose recommendations for pediatric subjects changed during the trial, it is recommended to check the subject's viral load after dose adjustment based on the new dosing.

Note: This approach is consistent with the standard practice, whenever a change in ARV therapy is made.

Note: Subjects who experience tolerability issues with the ritonavir liquid or powder (for oral suspension) formulation and/or are at risk of discontinuing DRV/rtv based on investigator assessment will be allowed to switch to one 100-mg capsule or tablet ritonavir b.i.d..

For pediatric subjects, body weight is recorded at the baseline visit and at every visit during the treatment period (Up until the Final/Withdrawal Visit as of Protocol Amendment 2). Subjects will be weighed in underwear, wearing no shoes. The same calibrated weighing scale should be used at each visit.

In case the subject has a relevant change in body weight, the dose of DRV/rtv should be adapted accordingly:

- Increase of weight: no confirmation of the weight required;
- Decrease of weight: confirmed weight is required at the next consecutive visit or at an additional visit, at the investigator's discretion, in case of intended dose decrease.

5.3.4 TIMING OF DOSING

Subjects will be required to take the trial medication (DRV/rtv) **orally within 30 minutes after completion of a meal**, approximately every 12 hours (in case of b.i.d. dosing) or every 24 hours (in case of q.d. dosing). The bitter taste for ritonavir solution may be lessened if mixed with another fluid as suggested in the product information (do not dilute with water). The bitter aftertaste of Norvir® powder for oral suspension may be lessened if peanut butter, hazelnut chocolate spread, or black currant syrup are taken immediately after dose administration.

The type of meal does not need to be considered.

For subjects who miss a dose of DRV/rtv:

If a caregiver (parent or legal representative) or a subject notices that he/she has missed the combined dose, or simply one of its components (DRV or ritonavir) and it is still within 6 hours (in case of b.i.d. dosing) or 12 hours (in case of q.d. dosing) of the time it is usually taken, the subject should always take the combined dose of DRV and ritonavir as soon as possible with food (i.e., when DRV or ritonavir are not taken, both compounds [DRV **and** ritonavir] should be taken if still within the 6 or 12 hours, respectively). The subject may then continue his/her usual dosing schedule.

If a caregiver (parent or legal representative) or subject notices that he/she has missed the dose more than 6 hours (in case of b.i.d. dosing) or 12 hours (in case of q.d. dosing) after the time it is usually taken, the subject must be instructed not to take it, but simply to resume the usual dosing schedule. Subjects should not double the dose to make up for a missed dose.

If a subject vomits immediately after intake of the trial medication, the correct dose of DRV/rtv may be re-taken. Re-dosing is not allowed if the subject vomits more than 15 minutes after intake of the trial medication.

5.3.5 INDIVIDUALLY OPTIMIZED BACKGROUND REGIMEN/UNDERLYING ANTIRETROVIRAL THERAPY

The OBR will be composed at the discretion of the investigator, according to the local standard of care and based on experience with previous therapies. It is strongly recommended that the OBR consists of at least 2 active ARV agents. If abacavir (ABC) is selected as an NRTI in the OBR, documentation should be available showing that a HLA-B*5701 test has been performed with a negative result.

Allowed and disallowed ARV agents after baseline for adult and pediatric subjects are summarized below in Table 3 and Table 4 respectively. All subjects can have their OBR changed or optimized at any time if medically considered, including at trial entry.

Table 3: Allowed and Disallowed Antiretroviral Agents After Baseline for adults

Class	Allowed	Disallowed [a]
PIs	DRV/rtv	All other PIs
NRTIs	All approved NRTIs	Investigational NRTIs
NNRTIs	Efavirenz Etravirine (TMC125) Nevirapine Rilpivirine	Delavirdine Investigational NNRTI
Fusion Inhibitors	Enfuvirtide	-
Entry inhibitors	Maraviroc [b]	-
Integrase inhibitors	Raltegravir (MK-0518) Dolutegravir	Elvitegravir Investigational integrase inhibitors

[a] Note: Investigational ARVs in general are disallowed.
[b] Refer to local product information of maraviroc for dose adjustment when combined with DRV/rtv.

Table 4: Allowed and Disallowed Antiretroviral Agents After Baseline for pediatric subjects

Class	Allowed	Disallowed
PIs	DRV/rtv	All other HIV PIs
NRTIs	All NRTIs with dose recommendations for pediatric use	All NRTIs without approved dose recommendations for pediatric use
NNRTIs	Nevirapine Efavirenz	Investigational NNRTI; Etravirine [a] Delavirdine Rilpivirine [a]
Fusion Inhibitors	-	Enfuvirtide [a]
Entry inhibitors	-	Maraviroc [a]
Integrase inhibitors	-	Elvitegravir Raltegravir (MK-0518) [a]

[a] This agent can only be used as part of the OBR if in the country of the patient there is an approved dose recommendation for the age category of the patient.

Special considerations may be warranted for the discontinuation of certain antiretroviral agents[1, 14]:

- Discontinuation of emtricitabine, lamivudine, or tenofovir in patients with hepatitis B coinfection:

  Subjects with hepatitis B coinfection (hepatitis B surface antigen and/or HBe antigen positive) and receiving one or a combination of the above NRTIs may experience an exacerbation of their hepatitis upon discontinuation of these drugs. If any of the above agents is to be discontinued, the subjects should be closely monitored for exacerbation of hepatitis or hepatic flare.

5.3.6 PACKAGING AND LABELING

DRV tablets will be provided by the sponsor and will be packaged under the responsibility of the sponsor. The tablets will be labeled with a trial-specific label according to the local regulatory requirements.

Ritonavir capsules, tablets, and powder will be provided by the sponsor as the commercially available package to which a trial-specific label according to the local regulatory requirements

will be added. Local sourcing of ritonavir oral solution is recommended. The sponsor will provide the oral solution only if local sourcing is not possible.

For medication provided by the sponsor, the labels will contain the protocol number, batch number, storage caution statements, dispensing instructions and 'Keep out of reach of children'.

For the DRV oral suspension and ritonavir liquid or powder (for oral suspension) formulation, a syringe with a 2 mL graduation will be provided to ensure accurate dosing.

5.3.7 RANDOMIZATION

Randomization is not applicable.

5.3.8 BLINDING AND UNBLINDING

Since this is an open-label trial, blinding procedures are not applicable.

5.3.9 DRUG ACCOUNTABILITY

The investigator, his/her designee, or the hospital pharmacist must maintain an adequate record of the receipt of the trial medication. Dispensation and return, or destruction (if applicable) of the trial medication must be documented on an individual patient level by using the appropriate forms. All these records must be available for inspection at any time. Drug accountability will be performed at each visit (see Part II, Section 3.1 'Investigational Products').

After termination of data collection, compliance check on unused and used trial medication returned by the subject will still be performed by the investigator or designee and will not be verified by the sponsor, however, drug accountability will be reviewed during the on-site monitoring visits.

5.3.10 STORAGE

All trial medication must be strictly handled in accordance with the protocol and the container labels. Storage and dispensing instructions and an expiry date are supplied with the trial material on delivery. Access to the trial medication should be restricted to designated trial personnel.

All storage conditions and specific administration instructions for DRV and ritonavir will be provided to the investigator prior to drug delivery at the investigational site. Storage conditions will be mentioned on the label.

The trial medication must be stored in a limited access area or in a locked cabinet under appropriate environmental conditions. All supplies of trial medication must be stored as specified on the label. Supplies should be stored in the original, childproof container delivered under the responsibility of the sponsor.

The ARVs for the background regimen must be stored according to locally applicable procedures and conditions as stipulated on the package insert.

Temperature logging at the investigational site should be performed. Should a deviation in storage conditions occur, the site must not further dispense the affected drug and must provide the monitor immediately with the following information:

- Date and duration of the deviation;

- Minimum temperature below the range and/or maximum temperature above the range that the product was exposed to.

Deviations in storage conditions will be evaluated by the sponsor. The monitor periodically checks the supplies of trial medication held by the investigator or pharmacist to ensure accountability and appropriate storage conditions of all trial medication used. After termination of data collection, storage conditions will still be checked by the investigator or designee and will not be verified by the sponsor, however, storage conditions will be reviewed during the on-site monitoring visits. At the end of the trial all unused medication will be passed over for destruction on site (conform local regulations), or by an authorized destruction unit after authorization by the sponsor.

5.3.11 ADHERENCE

Medication adherence is critical to successful ARV therapy. In addition to compromising the efficacy of the current treatment regimen, suboptimal adherence has implications for limiting future effective regimens for patients with resistant strains.

Evidence indicates that adherence problems occur frequently in children and adolescents. Studies have reported that fewer than 50% of children and/or their caretakers reported full adherence to ARV regimens[7]. Although a variety of factors have been associated with treatment adherence, no clear predictors of either good or poor adherence have been consistently identified in children.

The investigator should discuss the importance of good compliance to the entire treatment regimen, including DRV taken in combination with low-dose ritonavir and other ARVs. It is highly desirable that the investigator assesses the individual adherence to DRV/rtv, as well as all to the other ARVs used in combination, at each visit. If a subject's medication intake is suggestive of inadequate compliance, the investigator should address the issue and help provide solutions to maximize adherence to the therapy. Adherence counseling of the subject/parent(s)/legal representative(s) by the investigator should be documented in the subject's source document/chart**.**

After termination of data collection, treatment adherence counseling should be performed per local standard of care and documented in the subject's medical records only. Data will no longer be recorded in the CRF.

5.3.12 PRIOR AND CONCOMITANT THERAPY

5.3.12.1 Disallowed Non-Antiretroviral Medication

Refer to the current Investigator's Brochure of DRV for an up-to-date overview of disallowed medications during clinical trials with DRV/rtv.

Please consult the prescribing information/package inserts and the most current Investigator's Brochures for the individual medications as other medications may also not be allowed or cautioned for use given an individual subject's specific situation.

5.3.12.2 Disallowed Antiretroviral Medication

Refer to Section 5.3.5 for an overview of disallowed ARVs during this trial.

Please consult the prescribing information/package inserts of the individual ARVs and most recent DRV Investigator's Brochure for an up-to-date overview of contraindications as other

medications may also not be allowed or cautioned for use given an individual subject's specific situation.

5.4 Assessments

5.4.1 Timing of Assessments

Subjects will rollover after completion of 1 of the following clinical (parent) trials TMC114-C211, TMC114-C214, TMC114-TiDP31-C229 and the pediatric (parent) trial TMC114-TiDP-C232, which was a roll-over trial for the original trials TMC114-C212, TMC114-TiDP-C228 or TMC114-TiDP-C230. The baseline visit will coincide with the last visit of the treatment phase of the previous (parent) trial. Assessments and results from the last visit of the previous (parent) trial will be used for the baseline visit of the present trial; overlapping assessments only need to be conducted once. Additional assessments not included in this protocol can be done locally as per local standard of care.

If a subject is considered eligible after signing informed consent/assent (see Part II, Section 6.4 'Subject Information and Informed Consent/Assent'), completion of the Baseline Form, and evaluation by the sponsor or its designee, the subject receives the trial medication (DRV/rtv) at the baseline visit.

Visits and assessments are performed, according to local generally accepted standard of care, but desirable every 3 months for pediatric subjects and not less frequent than every 6 months for adult subjects. The interval between 2 consecutive visits should not exceed 6 months for pediatric subjects. An additional visit may also be scheduled at the investigator's discretion to follow up on clinically relevant adverse events or laboratory abnormalities and in case of weight decrease for pediatric subjects (see Section 5.3.3). A final/withdrawal visit will be performed.

The exact timing of the assessments is presented in the flowchart in Section 2.

As per Protocol Amendment 2, the next planned visit will be a Final/Withdrawal Visit, which will be the last visit with data collection. Thereafter, visits and assessments will be performed per local standard of care and documented in the subject's medical records only. Investigators will continue to report SAEs possibly related to DRV/rtv and pregnancies to the sponsor using regular pharmacovigilance reporting. This information will only be entered in the company safety repository.

If the subject exits the trial, the last visit will be a local standard of care visit but without dispensation of investigational medication.

5.4.2 Subject and Disease Characteristics

At the baseline visit, information from the previous (parent) trial will be confirmed, including the original subject ID. The overall eligibility of the subject to participate in the trial will be assessed.

5.4.3 Efficacy

In addition to the assessments described in the flowchart in Section 2, it is desirable to perform the following efficacy assessments locally every 3 months or according to the local generally accepted standard of care:

- Immunology; and
- Plasma viral load (HIV-1 RNA copies/mL).

After termination of data collection, efficacy assessments will be performed per local standard of care and documented in the subject's medical records only.

5.4.4 SAFETY

5.4.4.1 Adverse Events/HIV-Related Events

For detailed definitions and reporting procedures of adverse events, refer to Part II, Section 1 'Adverse Events'. For reported HIV-related events, further details will be recorded if these events are AIDS-defining illnesses (U.S. Centers for Disease Control and Prevention [CDC] Category C conditions; see Section 7.4, Addendum 4: Revised WHO Clinical Staging of HIV/AIDS).

For subjects experiencing specific adverse events, toxicity management should be performed as described in Section 5.5 (cutaneous reactions/rash, acute systemic allergic reactions, AST and ALT elevations, clinical hepatitis, renal complications, nausea (with or without vomiting), diarrhea, and other toxicities) and Section 5.6 (hyperglycemia, hypertriglyceridemia and hypercholesterolemia, low-density lipoprotein (LDL) cholesterol increase, lactic acidosis, lipodystrophy/fat distribution/body changes, pancreatitis, and hypersensitivity reactions).

A post-treatment follow-up contact is to be performed 4 weeks after the last dose of trial medication for subjects with an ongoing adverse event, that discontinue the trial under Protocol Amendment 1, as specified in the flowchart in Section 2.

After termination of data collection, safety assessments will be performed per local standard of care and documented in the subject's medical records only. Investigators must continue to report SAEs possibly related to DRV/rtv and pregnancies to the sponsor using regular pharmacovigilance reporting. This information will only be entered in the company safety repository.

5.4.4.2 Clinical Laboratory Tests

Urine pregnancy tests are to be performed at the baseline visit (female subjects of childbearing potential only) and every visit thereafter. The first test for girls having their first menses during the course of the trial can be performed on serum or urine, according to local practice. For girls who have had their first menses, urine tests can be performed at all visits.

In addition to the assessments described in the flowchart in Section 2, it is desirable to perform the following laboratory safety assessments locally every 3 months or according to the local generally accepted standard of care:

- Hematology; and
- Biochemistry, including pancreatic amylase (if available) or lipase and lipid analyses.

After termination of data collection, laboratory safety assessments will be performed per local standard of care and documented in the subject's medical records only.

5.5 Safety Monitoring and Toxicity Management

Toxicity management is at the discretion of the investigator, and is to take into account the protocol-defined procedures defined under 5.5.1, 5.5.2, 5.5.3, 5.5.4, 5.5.5, 5.5.6, 5.5.7, and 5.5.8, and the local standard clinical practice.

After termination of data collection, toxicity management will be performed per local standard of care and documented in the subject's medical records only.

The following guidelines are present in the Clinical Trial Protocols for ongoing HIV-1 trials of DRV. Participating investigators are strongly encouraged to follow these guidelines and to apply the same safety measures for subjects participating in this trial.

Note:For grade 3 or 4 laboratory toxicities, a confirmatory measurement within 48 hours after the laboratory results become available is mandatory. This management scheme is for confirmed laboratory abnormalities and not for isolated events.

The following laboratory abnormalities do not warrant mandatory confirmation within 48 hours:

- Subjects with asymptomatic triglyceride or cholesterol elevations of grade 3 or 4.

All adverse events occurring at any time during the trial will be followed until satisfactory clinical resolution (i.e., value back to baseline value) or stabilization or until final database lock. All grade 3 and grade 4 laboratory abnormalities and laboratory abnormalities resulting in an increase of 2 DAIDS grades from baseline will be followed until return to baseline or within 1 grade from baseline. Certain long-term adverse events of ARV therapy cannot be followed to resolution within the setting of this protocol; in these cases follow-up will be the responsibility of the treating physician, which will be agreed upon with the sponsor.

5.5.1 CUTANEOUS REACTION/RASH

DRV is a sulfonamide. Subjects who previously experienced a sulfonamide allergy will be allowed to enter the trial. To date, no potential for cross sensitivity between drugs in the sulfonamide class and DRV has been identified in subjects participating in Phase II/III adult trials as well as Phase II pediatric trials with HIV-1 infected subjects aged > 6 years.

Management will be at the discretion of the investigator, taking into account the following protocol-defined procedures, and should follow generally accepted medical standards. Cetirizine, levocetirizine, topical corticosteroids, and antipruritic agents will be allowed at the investigator's discretion for all grades of rashes.

Grade 1 and 2 Cutaneous Reaction/Rash

A grade 1 cutaneous reaction/rash is defined as localized macular rash.

A grade 2 cutaneous reaction/rash is defined as diffuse macular, maculopapular or morbilliform rash, or target lesions.

Subjects experiencing a grade 1 or grade 2 rash or cutaneous reaction may continue treatment or have their trial medication interrupted at the investigator's discretion. Local safety sampling at the time of the rash and clinical follow-up for these adverse events will be at the discretion of the investigator, however, close clinical follow-up is recommended to monitor for any progression of the adverse event.

The subject should be advised to contact the investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms worsen, or if mucosal involvement develops.

Grade 3 and 4 Cutaneous Reaction/Rash

A grade 3 cutaneous reaction/rash is defined as:

- Diffuse macular, maculopapular or morbilliform rash with vesicles or limited number of bullae
- Superficial ulcerations of mucous membrane limited to 1 site*
- Cutaneous reaction/rash with at least 1 of the following*:
    1. Elevations of ALT and/or AST > 2 × baseline but at least 5 × ULN;
    2. Fever ≥ 38°C or 100° F;
    3. Serum sickness-like reaction;
    4. Eosinophil count > 1000/mm³.

    * Revised by the sponsor.

A grade 4 cutaneous reaction/rash is defined as:

- Extensive or generalized bullous lesions;
- Stevens-Johnson syndrome (SJS);
- Ulceration of mucous membrane involving 2 or more distinct mucosal sites;
- Toxic epidermal necrolysis (TEN).

A visit schedule for cutaneous reaction/rash follow-up is provided in Table 5 below.

Subjects experiencing a grade 3 or 4 rash or cutaneous event must have their study medication discontinued and be withdrawn from the trial (see Section 5.2.5 and see Section 7.3, Addendum 3: Visit Schedule for Cutaneous Reaction/Rash Follow-up for pediatric subjects). Referral to a dermatologist and biopsy are required for these events. To minimize distress of skin biopsies, the skin should be anesthetized by application of an anesthetic cream and/or an intradermal injection of 1-2% lidocaine. At the discretion of the investigator and after approval of the sponsor, local safety testing of the following parameters is required to determine possible liver or systemic abnormalities: ALT, AST, bilirubin (total, direct and indirect), creatinine and a complete blood cell count (including hemoglobin, hematocrit, red blood cell (RBC) and white blood cell (WBC) count, neutrophils, lymphocytes, monocytes, eosinophils, basophils and platelet count). Close clinical follow-up and appropriate medical intervention should be instituted for these events; daily follow-up is recommended for 5 days from the onset of the event to monitor for progression of the event and weekly afterwards.

Subjects should be advised to contact the investigator immediately if they notice any worsening of the rash.

Table 5: Visit Schedule for Cutaneous Reaction/Rash Follow-up

DAIDS Toxicity Grade	Definitions	Investigator Action
Grade 1	Localized macular rash	May continue trial medication or have their trial medication interrupted at the investigator's discretion.
Grade 2	Diffuse macular, maculopapular or morbilliform rash Target lesions	May continue trial medication or have their trial medication interrupted at the investigator's discretion.
Grade 3	Diffuse macular, maculopapular or morbilliform rash with vesicles or limited number of bullae Superficial ulcerations of mucous membrane limited to 1 site* Cutaneous reaction/rash with at least 1 of the following*: - Elevations in ALT and/or AST (> 2 × baseline but at least 5 × ULN) - Fever ≥ 38°C or 100°F - Serum sickness-like reaction - Eosinophils > 1000/mm³ * Revised by the sponsor	Permanently discontinue trial medication (see Section 5.2.5). Referral to a dermatologist and biopsy are required for these events (preferably within 24 hours). Local laboratory assessments can be performed at the discretion of the investigator and after approval of the sponsor. Daily follow-up visits for the first 5 days and weekly afterwards.
Grade 4	Extensive or generalized bullous lesions Stevens-Johnson syndrome (SJS) Ulceration of mucous membrane involving 2 or more distinct mucosal sites Toxic epidermal necrolysis (TEN)	Permanently discontinue trial medication (see Section 5.2.5). Referral to a dermatologist and biopsy are required for these events (preferably within 24 hours). Local laboratory assessments can be performed at the discretion of the investigator and after approval of the sponsor. Daily follow-up visits for the first 5 days and weekly afterwards.

5.5.2 ACUTE SYSTEMIC ALLERGIC REACTION

A summary of allergic reactions is provided in Table 6 below.

Subjects should be followed until resolution of the AE.

Grade 1 (localized urticaria [wheals] with no medical intervention indicated):

Subjects may continue medication for a grade 1 acute systemic allergic reaction. The subject should be advised to contact the investigator immediately if there is any worsening of the allergic reaction, or if any systemic signs or symptoms develop. Antihistamines or topical corticosteroids or antipruritic agents may be prescribed as long as these are in line with the package inserts of the ARVs (including DRV/rtv and background regimen) and with (dis)allowed medication for DRV indicated in Section 5.3.5.

Grade 2 (localized urticaria with medical intervention indicated or mild angioedema with no medical intervention indicated):

Subjects may continue medication for a grade 2 acute systemic allergic reaction. The subject should be advised to contact the investigator immediately if there is any worsening of the allergic

reaction; the subject should discontinue the trial medication and be withdrawn from the trial. Antihistamines or topical corticosteroids or antipruritic agents may be prescribed as supportive care as long as these are in line with the package inserts of the ARVs (including DRV/rtv and background regimen) and with (dis)allowed medication for DRV indicated in Section 5.3.5.

Grade 3 (generalized urticaria, angioedema with medical intervention indicated, or symptomatic mild bronchospasm):

Subjects will permanently discontinue medication (including DRV/rtv and background regimen) and will be withdrawn from the trial. Subjects will be treated as clinically appropriate. Standard management should be undertaken.

Grade 4 (acute anaphylaxis, life-threatening bronchospasm, or laryngeal edema):

Subjects will permanently discontinue medication (including DRV/rtv and background regimen) and will be withdrawn from the trial. Subjects will be treated as clinically appropriate. Standard management should be undertaken.

Table 6: Summary of Allergic Reaction

DAIDS Toxicity Grade	Definitions	Investigator Action
Grade 1	Localized urticaria (wheals) with no medical intervention indicated	May continue trial medication or have their trial medication interrupted at the investigator's discretion
Grade 2	Localized urticaria with medical intervention indicated, or mild angioedema with no medical intervention indicated	May continue trial medication or have their trial medication interrupted at the investigator's discretion
Grade 3	Generalized urticaria, or angioedema with medical intervention indicated, or symptomatic mild bronchospasm	Permanently discontinue trial medication
Grade 4	Acute anaphylaxis, or life-threatening bronchospasm, or laryngeal edema	Permanently discontinue trial medication

5.5.3 AST AND ALT ELEVATIONS

A summary of AST and ALT elevations is provided in Table 7 below.

Note: For grade 3 or 4 laboratory toxicities, subjects should have a confirmatory measurement within 48 hours after the laboratory results become available. This management scheme is for confirmed laboratory abnormalities and not for isolated events.

Grade 3 AST or ALT elevations (> 5.0 - ≤ 10.0 × ULN):

Subjects are to interrupt all medication (including DRV/rtv and background regimen) except if they are coinfected with hepatitis B or C (see below). Upon resolution of the laboratory abnormality to within 1 grade level (≤ grade 2), the subject may resume all trial medication under the guidance of the investigator and after discussion with a sponsor physician.

If after a grade 3 elevation, the subject has a recurrence of a grade 3 or 4 increase in AST or ALT after restarting trial medications, he/she will permanently discontinue the medication (including DRV/rtv and background regimen) and will be withdrawn from the trial.

Subjects with concomitant hepatitis B and with emtricitabine (FTC) or lamivudine (3TC) as a component of the background regimen:

Warning: Severe acute exacerbations of hepatitis B have been reported in subjects who are co-infected with hepatitis B virus and HIV and have discontinued FTC or 3TC. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in subjects who discontinue FTC or 3TC and are co-infected with hepatitis B virus and HIV. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Subjects with concomitant hepatitis A, B, C, or E:

Subjects with concomitant acute hepatitis A infection diagnosed at or after baseline have to be excluded. If acute viral hepatitis is diagnosed while on trial, the subject must be withdrawn immediately and the necessary follow-up visits performed.

Subjects with chronic hepatitis B or C coinfection are allowed to participate. These subjects will be allowed to continue treatment (including DRV/rtv and background regimen) if they develop a grade 3 elevation in AST or ALT provided alkaline phosphatase (ALP) is not elevated to grade 2 or higher and total bilirubin is not elevated to grade 3 or higher or subjects do not have signs and symptoms of clinically active hepatitis. Signs and symptoms of active hepatitis include, but are not limited to fatigue, malaise, anorexia, nausea, dark urine and clay-colored stools, bilirubinuria, jaundice, and liver tenderness. If signs or symptoms of clinically active hepatitis occur, or if AST or ALT increases to grade 4 elevations, then all treatment (including DRV/rtv and background regimen) will be permanently discontinued and the subject will be withdrawn from the trial.

In regions where hepatitis E is endemic, it is recommended that hepatitis E serologies be tested for the evaluation of unexplained increases of AST or ALT. Subjects diagnosed with acute hepatitis E at or after screening must be withdrawn immediately.

However, if subjects with chronic hepatitis B or C co-infection and with grade 3 elevation in AST or ALT elect to interrupt treatment (including DRV/rtv and background regimen) and have a recurrence of grade 3 increase in AST or ALT they may continue provided ALP is not elevated to grade 2 or higher and total bilirubin is not elevated to grade 3 or greater or subjects do not have signs and symptoms of clinically active hepatitis. If signs or symptoms of clinically active hepatitis occur or if AST or ALT increases to grade 4 elevations, then all treatment (including DRV/rtv and background regimen) will be permanently discontinued and the subject will be withdrawn from the trial.

Grade 4 AST or ALT elevations (> 10.0 × ULN):

Subjects will permanently discontinue treatment (including DRV/rtv and background regimen) and will be withdrawn from the trial.

Table 7: Summary of AST and ALT Elevations

Revised DAIDS Table for Grading Severity	Ranges	Investigator Action	Rechallenge Instructions
Grade 1	≥ 1.25 – ≤ 2.5 × ULN	May continue therapy	Not applicable
Grade 2	> 2.5 – ≤ 5.0 × ULN	May continue therapy	Not applicable
Grade 3	> 5.0 – ≤ 10.0 × ULN	Interrupt HIV therapy until toxicity ≤ grade 2; if coinfected with hepatitis B or C: may continue if ALP is grade 2 or below, bilirubin grade 3 or below, and asymptomatic	Allowed once
Grade 4	> 10.0 × ULN	Discontinue therapy	No

5.5.4 CLINICAL HEPATITIS

Subjects should be followed until resolution of the AE.

5.5.4.1 Non-viral Hepatitis

Subjects should be monitored for the development of signs and symptoms of hepatitis, which include fatigue, malaise, anorexia, nausea, dark urine and clay-colored stools, bilirubinuria, jaundice and liver tenderness, with or without initially abnormal serum transaminase levels.

Subjects with these signs and symptoms should seek medical attention immediately and have liver function tests performed.

5.5.4.2 Viral Hepatitis

If acute viral hepatitis is diagnosed while on trial, the subject should be permanently withdrawn from the trial.

5.5.5 RENAL COMPLICATIONS

Investigators should closely monitor trial subjects for disturbances in serum creatinine, urine electrolytes and for abnormalities in urinalysis (e.g., proteinuria). If renal complications develop, subjects must be treated as clinically appropriate. The trial medication may be continued if the renal complication is considered not related to the treatment (including DRV/rtv and OBR) in the opinion of the investigator.

Renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported in association with the use of Viread® (tenofovir). The majority of these cases occurred in subjects with underlying systemic or renal disease, or in subjects taking nephrotoxic agents, however, some cases occurred in subjects without identified risk factors (please refer to the package insert of tenofovir for details).

5.5.6 NAUSEA (WITH OR WITHOUT VOMITING)

Although common, nausea after the initiation of ARV therapy usually subsides or resolves during the first few weeks of treatment.

Grade 1 nausea (transient [< 24 hours] or intermittent nausea with no or minimal interference with oral intake):

Subjects may continue with the trial medication and may be treated as needed with anti-emetics given orally or by suppository. If vomiting occurs in pediatric subjects, they should wait 15 to 30 minutes and then start hydration in frequently small amounts. Once vomiting has stopped for at least a few hours, solid food can be reintroduced.

Grade 2 nausea (persistent nausea resulting in decreased oral intake for 24-48 hours):

Subjects may continue with the trial medication and may be treated as needed with anti-emetics given orally or by suppository. If vomiting occurs in pediatric subjects, they should wait 15 to 30 minutes and then start hydration in frequently small amounts. Oral rehydration solution should not be used for more than 24 hours, other liquids with salt and sugars should be given. Once vomiting has stopped for at least a few hours, solid food can be reintroduced.

Grade 3 nausea (persistent nausea resulting in minimal oral intake for > 48 hours or aggressive rehydration indicated [e.g., intravenous fluids]):

Subjects developing grade 3 nausea will have all treatment (including DRV/rtv and background regimen) interrupted. The subject will be treated as needed with anti-emetics given orally or by suppository. All medication may be resumed when the nausea resolves to grade ≤ 2.

Grade 4 nausea (life-threatening consequences [e.g., hypotensive shock]):

Subjects developing grade 4 nausea will discontinue treatment (including DRV/rtv and background regimen) and will be withdrawn from the trial.

5.5.7 DIARRHEA

Grade 1 diarrhea (transient or intermittent episodes of unformed stools or increase of ≤ 3 stools over baseline per 24-hour period):

Subjects may continue the trial medication. Loperamide and diphenoxylate can be administered. Pediatric subjects should start with the BRAT (bananas, rice, applesauce and toast) diet.

Grade 2 diarrhea (persistent episodes of unformed to watery stools or increase of 4-6 stools over baseline per 24-hour period):

Subjects may continue the trial medication. Loperamide and diphenoxylate can be administered. Pediatric subjects should start with the BRAT diet and increase the amount of fluids.

Grade 3 diarrhea (bloody diarrhea, increase of ≥ 7 stools per 24-hour period, or intravenous fluid replacement indicated):

Subjects with grade 3 diarrhea will have all treatment (including DRV/rtv and background regimen) interrupted. All medication (including DRV/rtv and background regimen) may be resumed when the diarrhea resolves to grade ≤ 2.

Grade 4 diarrhea (life-threatening consequences [e.g., hypotensive shock]):

Subjects will permanently discontinue treatment (including DRV/rtv and background regimen) and will be withdrawn from the trial.

Note: Rare cases of acute renal insufficiency have been reported in patients receiving DRV/rtv and tenofovir as part of a combination HIV therapy, more specifically in cases where moderate to severe diarrhea resulted in dehydration. Special attention should be given to the appropriate clinical management of diarrhea, dehydration and electrolyte losses, if applicable. In certain cases, temporary interruption of HIV therapy may be appropriate until the condition has improved.

5.5.8 OTHER TOXICITIES

Grade 1

Subjects who develop a grade 1 AE or toxicity may continue intake of the trial medication.

Grade 2

Subjects who develop a grade 2 AE or toxicity may continue intake of the trial medication based on the investigator's clinical judgment.

Note: For grade 3 or 4 laboratory toxicities, subjects should have a confirmatory measurement within 48 hours after the laboratory results become available. This management scheme is for confirmed laboratory abnormalities and not for isolated events.

Grade 3

Subjects who develop a grade 3 AE or toxicity should interrupt all medications (including DRV/rtv and OBR) and may resume all therapy when the AE or laboratory abnormality resolved to within one grade level (≤ grade 2) of the subject's baseline.
The following exceptions apply:

- subjects who experience an asymptomatic glucose elevation of grade 3 (See Section 5.6.1);
- subjects who experience asymptomatic triglyceride or cholesterol elevations of grade 3 (See Section 5.6.2);
- subjects who experience asymptomatic pancreatic amylase elevations of grade 3 with no past or active history of pancreatitis (provided lipase is within normal limits) (See Section 5.6.5);
- subjects who experience an AE that is considered not related or doubtfully related to the study medication.

Grade 4

Subjects experiencing a grade 4 AE or toxicity will permanently discontinue medication (including DRV/rtv and OBR).
The following exceptions apply:

- subjects who experience asymptomatic triglycerides elevations of grade 4 (see also Section 5.2.5);
- subjects who experience an AE that is considered not related or doubtfully related to the trial medication.

5.6 Toxicity Management for Specific Adverse Events with Concomitant Antiretroviral Agents

Participating investigators are strongly encouraged to follow the guidelines and to apply the same safety measures for subjects participating in this trial.

Toxicity management is at the discretion of the investigator, and is to take into account the protocol-defined procedures defined under 5.6.1, 5.6.2, 5.6.3, 5.6.4, 5.6.5, and 5.6.6, and the local standard clinical practice.

After termination of data collection, toxicity management will be performed per local standard of care and documented in the subject's medical records only.

The information below does not imply that the respective adverse events are only related to the concomitant ARV therapy, since a contribution of DRV cannot be excluded.

5.6.1 HYPERGLYCEMIA

Grade 3: 13.89-27.75 mmol/L (251-500 mg/dL);
Grade 4: > 27.75 mmol/L (> 500 mg/dL).

Management decisions should be based on fasted results. Subjects with persistent grade 3 or 4 glucose elevations despite appropriate anti-hyperglycemic treatment should be permanently discontinued with the exception of subjects with pre-existing diabetes. Appropriate clinical management of hyperglycemia must be started in a timely fashion, if applicable.

5.6.2 HYPERTRIGLYCERIDEMIA, HYPERCHOLESTEROLEMIA AND LDL CHOLESTEROL INCREASE

Hypertriglyceridemia **grade 3: 8.49-13.56 mmol/L (751-1200 mg/dL);**
grade 4: > 13.56 mmol/L (> 1200 mg/dL).

Hypercholesterolemia **grade 3: > 7.77 mmol/L (> 300 mg/dL);**
grade 4: not applicable.

LDL cholesterol increase **grade 3: ≥ 4.91 mmol/L (≥ 190 mg/dL);**
grade 4: not applicable.

Management decisions should be based on fasted results. Subjects who experience grade 3 or 4 asymptomatic triglyceride or cholesterol elevations may continue to receive the trial medication unless clinical assessment foresees an immediate health risk to the subject.

Hypertriglyceridemia, hypercholesterolemia and LDL cholesterol increase should be treated according to the specific guidelines for treating HIV-positive subjects (see Section 7.5Addendum 5: Lipid Abnormalities)[13]. Current treatment guidelines (eg, The National Cholesterol Education Program [NCEP] guidelines) specify different lipid thresholds for intervention for different degrees of cardiovascular risk. The presence or absence of other significant cardiovascular risk factors, which include smoking, age, family history of premature cardiovascular disease, diabetes, hypertension, low high density lipoprotein (HDL) cholesterol, and prior history of cardiovascular disease should be taken into account. Appropriate clinical management of hyperlipidemia in the setting of HIV disease should be started in a timely fashion, if applicable.

For the OBR, the respective package inserts should be consulted for contraindicated medications or medications that are not recommended for concomitant use.

For an overview of allowed and disallowed medication, please refer to Section 5.3.5, and the respective sections in the IB of DRV.

5.6.3 LACTIC ACIDOSIS

The relevance of asymptomatic lactic acid elevations is unclear, and lactates are not part of the routine safety evaluations for this trial. Routine lactate monitoring is not currently recommended. However, lactate monitoring should be performed if there is a clinical suspicion of lactic acidosis (see description below).

A sometimes-fatal syndrome of lactic acidosis, often associated with evidence of hepatic steatosis, is a recognized but rare complication of NRTI therapy. This syndrome is felt to be secondary to mitochondrial toxicity induced by the inhibitory effect of NRTIs on DNA polymerase gamma, a key enzyme needed for mitochondrial DNA synthesis. Current knowledge regarding this syndrome is incomplete. Obesity and prolonged NRTI exposure may be risk factors. Females are also at increased risk. Symptoms of lactic acidosis are frequently non-specific (e.g., fatigue, weakness, hyperventilation and fever), but in the majority of cases also involve symptoms suggestive of hepatic dysfunction such as nausea, vomiting, abdominal or epigastric discomfort, abdominal distension, hepatomegaly, and new-onset elevated liver enzymes. A high index of suspicion may be required to diagnose this condition. Alternatively, it is possible that unwarranted concern may be raised by over-interpretation of lactic acid levels. NRTI toxicity is only one cause of lactic acidosis. Type “B” lactic acid elevations or those without clinically apparent tissue hypoxia are also seen in the context of diabetes, uremia, liver disease, infections, malignancies, alkaloses, and drug and toxin ingestion of substances such as ethanol, methanol, ethylene glycol, and salicylates.

The following case definition of lactic acidosis will be used in this protocol:

Symptomatic Hyperlactatemia

New, otherwise unexplained, and persistent (≥ 2 weeks) occurrence of 1 or more of the following symptoms:

- Nausea and vomiting
- Abdominal pain or gastric discomfort
- Abdominal distention
- Increased liver function tests
- Unexplained fatigue
- Dyspnea

and

- Lactate level > 2 × ULN, confirmed by repeat lactate level analysis

Note: All lactates > 2 × ULN should be repeated as soon as possible, generally within 1 week. Lactate levels should not be assessed following physical exertion as this causes elevated lactate levels and may confound assessment of the clinical significance of these findings. If the second result confirms hyperlactatemia (> 2 × ULN) in subjects with symptoms as described above, the subjects should immediately discontinue their medication (DRV/rtv

and background regimen). Standard management should be initiated with follow-up to resolution. If causality is related to the background regimen only and **not** to DRV/rtv, the NRTIs must be changed (see Section 5.3.5) and subjects should continue DRV/rtv if treatment is re-initiated. If causality is (also) related to DRV/rtv, subjects must be withdrawn.

Processing of the lactate needs to be done according to strict guidelines both in the preparation of the patient (ideally, fasting and with no recent exercise) and in the blood drawing/processing procedure (ideally, blood drawn without a tourniquet, no hand clenching, blood drawn into a chilled tube and processed immediately) to minimize false elevations of lactates.

5.6.4 LIPODYSTROPHY/FAT REDISTRIBUTION/BODY CHANGES

Investigators should avoid using the term "lipodystrophy acquired" to describe and report fat redistribution abnormalities associated with ARV therapy as this term is not very descriptive. The different symptoms and gradings are listed in the DAIDS scale under 'Endocrine/Metabolic' (see Section 7.2, Addendum 2: DAIDS Grading Table). The relevant terms include: abnormal fat accumulation, lipoatrophy and gynecomastia.

Although metabolic abnormalities such as hyperlipidemia or hyperglycemia are often associated with body changes, these events should be reported separately for the purpose of AE reporting.

Assessment of fat redistribution in HIV-infected children and adolescents is complicated by the normal, dynamic alterations in body composition that occur during childhood and adolescence.

Children and adolescents can be considered to have abnormal fat accumulation if they have 1 or more of the following signs:

- Trunk with increased abdominal girth
- Dorso-cervix with fat accumulation 'buffalo hump'
- Breast enlargement

Children and adolescents can be considered to have lipoatrophy if they have 1 or more of the following signs:

- Face with sunken cheeks, sunken eyes with prominent zygomatic arch
- Skinny arms with prominent veins; muscularity and bones
- Skinny legs with prominent veins; muscularity and bones
- Buttocks with loose of skin folds, prominent muscles, loss of contour and fat

5.6.5 PANCREATITIS

Pancreatitis must be considered whenever a subject develops abdominal pain, nausea, vomiting, and/or elevated amylase or lipase. Temporary treatment interruption is allowed (including DRV/rtv and background regimen) in case of clinical suspicion and until the diagnosis of pancreatitis can be excluded.

It is not recommended to co-administer tenofovir disoproxil fumarate (TDF) and didanosine (ddI) in the OBR (if applicable) due to an increased risk of pancreatitis[14].

5.6.5.1 Clinical Pancreatitis

Grade 1: not applicable.

Grade 2: symptomatic and hospitalization not indicated (other than emergency room visit).

Grade 3: symptomatic and hospitalization indicated (other than emergency room visit).

Grade 4: life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis).

5.6.5.2 Laboratory Abnormalities

For asymptomatic grade 1 and grade 2 pancreatic amylase and/or lipase elevations, and confirmed asymptomatic grade 3 pancreatic amylase elevations with no past or active history of pancreatitis, subjects should be carefully evaluated and followed closely.

For confirmed grade 4 elevations of pancreatic amylase and/or confirmed grade 3 or 4 elevations of lipase, subjects should interrupt therapy (including DRV/rtv and background regimen) until amylase returns to grade ≤ 2, at which time therapy could be reintroduced. The NRTI(s) most likely related to the elevated lipase will be switched to another NRTI (see Section 5.3.5). If grade 4 elevations of pancreatic amylase and/or grade 3 or 4 lipase levels persist ≥ 14 days following interruption of therapy, or if the toxicity recurs more than twice, therapy (including DRV/rtv and background regimen) should be discontinued.

5.6.6 HYPERSENSITIVITY REACTIONS

In clinical studies approximately 5% of subjects receiving an ABC-containing product developed a hypersensitivity reaction, which in rare cases has been proven fatal[11].

At baseline, it is recommended to test subjects without prior documented HLA-B*5701 negative results in whom the investigator considers ABC/3TC as background regimen to avoid hypersensitivity reactions. In those subjects where HLA-B*5701 is tested positive, ABC should not be administered[12]. In this case, the investigator must select another background regimen (without ABC) consisting of at least 2 NRTIs (see Section 5.3.5 for more details about the background regimen).

It should also be noted that HLA screening and exclusion of HLA-B*5701 positive subjects does not completely eliminate the risk of hypersensitivity reactions.

5.6.6.1 Description of the Hypersensitivity Reaction

The ABC hypersensitivity reaction is characterized by the appearance of symptoms indicating multi-organ involvement. The majority of subjects have fever and/or rash as part of the syndrome, however reactions have occurred without rash or fever.

Other signs and symptoms may include respiratory signs and symptoms such as dyspnea, sore throat, cough and abnormal chest x-ray findings (predominantly infiltrates, which can be localized), gastrointestinal symptoms, such as nausea, vomiting, diarrhea, or abdominal pain, and may lead to misdiagnosis of hypersensitivity as respiratory disease (pneumonia, bronchitis, pharyngitis), or gastroenteritis. Other frequently observed signs or symptoms of the hypersensitivity reaction may include lethargy or malaise and musculoskeletal symptoms (myalgia, rarely myolysis, arthralgia).

The symptoms related to this hypersensitivity reaction worsen with continued therapy and can be life-threatening. These symptoms usually resolve upon discontinuation of ABC.

5.6.6.2 Management of Hypersensitivity Reactions

Subjects developing signs or symptoms of hypersensitivity must contact their doctor immediately for advice.

If a hypersensitivity reaction is diagnosed, the subject must discontinue ABC treatment immediately. The background regimen will be replaced by an alternative background regimen (see Section 5.3.5).

The subject should be asked to return all unused supplies of the ABC-containing product for disposal to prevent an accidental re-challenge.

An ABC-containing medicinal product (Ziagen®, Trizivir®, or Epzicom®/Kivexa®) must never be administered following a hypersensitivity reaction, as more severe symptoms will recur within hours and may include life-threatening hypotension and death.

To avoid a delay in diagnosis and minimize the risk of a life-threatening hypersensitivity reaction, the ABC-containing product should be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (respiratory diseases, flu-like illness, gastroenteritis, or reactions to other medications).

Symptomatic support for ABC hypersensitivity may be indicated. This should include, for example, administration of intravenous fluids to subjects who develop hypotension. Antihistamines or corticosteroids have been used in cases of ABC hypersensitivity, however, there are no clinical data demonstrating the benefit of these in the management of the reaction.

Laboratory and other investigations which may be useful in the evaluation and treatment of ABC hypersensitivity include, but may not be limited to, measurement of ALT, AST, creatine phosphokinase, serum creatinine, and WBC differential count and chest x-ray, if respiratory symptoms are present.

5.6.6.3 Special Considerations Following an Interruption of ABC Therapy

If therapy with ABC has been discontinued and restarting therapy is under consideration, the reason for discontinuation should be evaluated to ensure that the subject did not have symptoms of a hypersensitivity reaction. If a hypersensitivity reaction cannot be ruled out, no medicinal product containing ABC should be restarted.

There have been infrequent reports of hypersensitivity reaction following reintroduction of an ABC-containing product where the interruption was preceded by a single key symptom of hypersensitivity (rash, fever, malaise/fatigue, gastrointestinal symptoms, or a respiratory symptom). If a decision is made to restart any ABC-containing product in these subjects, this should be done only under direct medical supervision.

On very rare occasions hypersensitivity reactions have been reported in subjects who have restarted therapy, and who had no preceding symptoms of a hypersensitivity reaction. If a decision is made to restart an ABC-containing product, this must be done only if the subject or others can access medical care readily.

5.6.6.4 Essential Subject Information

An Alert Card is available in the commercial medication pack containing ABC to remind the subject and the medical staff about ABC hypersensitivity. This card should be removed and kept with the subject at all times.

Investigators must ensure that subjects are fully informed regarding the following information on the hypersensitivity reaction:

- Subjects must be made aware of the possibility of a hypersensitivity reaction to ABC that may result in a life-threatening reaction or death.
- All subjects without prior documented HLA-B*5701 negative results in whom the investigator considers ABC/3TC as background regimen should be tested for HLA-B*5701 (refer to ABC prescribing information/package inserts). In those subjects where HLA-B*5701 is tested positive, ABC should not be administered[12].
- Subjects developing signs or symptoms possibly linked with a hypersensitivity reaction must contact their doctor immediately.
- Subjects who are hypersensitive to ABC should be reminded that they must never take any ABC-containing medicinal product (Ziagen®, Trizivir®, or Epzicom®/Kivexa®) again.
- In order to avoid restarting the ABC-containing product, subjects who have experienced a hypersensitivity reaction should be asked to return the remaining tablets to the site.
- Subjects who have stopped taking an ABC-containing product for any reason, and particularly due to possible adverse events or illness, must be advised to contact their doctor before restarting.

5.6.6.5 Reporting of Hypersensitivity Reaction

All cases of potential ABC hypersensitivity should be reported as a serious adverse event (see Part II, Section 1.4 ‘Reporting of Adverse Events and HIV-Related Events’).

5.7 Statistical Methods Planned and Determination of the Sample Size

5.7.1 Sample Size Calculation

Since the objective of the trial is only to provide continued access to DRV/rtv for HIV-1 infected adult or pediatric subjects who previously received DRV/rtv in a clinical (parent) trial, who continue to benefit from using it, and who live in a country where DRV is not commercially available for the subject, is not reimbursed, or is not accessible through another source (e.g., access program, government program), and since the trial is not set up to show a specific statistical hypothesis, a sample size calculation is not applicable.

Data from this trial may be included in safety updates.

5.7.2 Statistical Analyses

Final analysis will be done once all subjects have completed the Final/Withdrawal Visit. After termination of data collection in the CRF, no additional statistical analysis will be performed.

5.7.2.1 Initial Subject and Disease Characteristics

The demographic and baseline disease characteristics of the subjects included in this trial, such as gender and race, will be tabulated when deemed necessary for submissions or safety updates.

5.7.2.2 Efficacy

There will be no formal efficacy analysis.

5.7.2.3 Safety

The safety and tolerability of DRV/rtv in combination with other ARVs will be summarized in terms of:

- Mortality;
- All serious adverse events;
- Adverse events leading to discontinuation;
- Adverse events considered at least possibly related to DRV/rtv treatment.

The number and causes of deaths will be summarized.

The number of subjects who terminate treatment will be tabulated, and the reasons for drug discontinuation will be summarized.

5.8 Data Quality Assurance

See Data Quality Control/Assurance (Part II, Section 8).

6 REFERENCES

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7 ADDENDA

7.1 Addendum 1: Trial Contact Persons

An up-to-date version of the contact details of sponsor and third parties is available in the investigator site file.

7.2 Addendum 2: DAIDS Grading Table

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS - PUBLISH DATE: DECEMBER 2004

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS grading table") is a descriptive terminology to be utilized for adverse event reporting in this trial. A grading (severity) scale is provided for each adverse event term.

General Instructions

Estimating Severity Grade

If the need arises to grade a clinical adverse event that is not identified in the DAIDS grading table, use the category "Estimating Severity Grade" located at the top of the table on the following page.

Grading Adult and Pediatric Adverse Events

The DAIDS grading table includes parameters for grading both adult and pediatric adverse events. When a single set of parameters is not appropriate for grading specific types of adverse events for both adult and pediatric populations, separate sets of parameters for adult and/or pediatric populations (with specified respective age ranges) are provided. If there is no distinction in the table between adult and pediatric values for a type of adverse event, then the single set of parameters listed is to be used for grading the severity of both adult and pediatric events of that type.

Determining Severity Grade

If the severity of an adverse event could fall under either one of 2 grades (e.g., the severity of an adverse event could be either grade 2 or grade 3), select the higher of the 2 grades for the adverse event.

Note: The laboratory normal ranges should be taken into consideration to assign gradings to a laboratory value.

Definitions

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).
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 (social interactions, play activities, learning tasks, etc.).
Medical intervention	Use of pharmacologic or biologic agent(s) for treatment of an adverse event.
Operative intervention	Surgical OR other invasive mechanical procedures.

CLINICAL				
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 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 (non-axillary)	37.7°C – 38.6°C	38.7°C – 39.3°C	39.4°C – 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.).

CLINICAL				
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 5 x 5 cm – 9 x 9 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.).

CLINICAL				
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 Cutaneous reaction/rash with superficial ulcerations of mucous membrane limited to 1 site[a] OR Cutaneous reaction/rash with at least 1 of the following[a]: elevation of AST and/or ALT > 2 x baseline but at least > 5 x ULN[a]; fever (> 38°C or 100°F) [a]; eosinophils > 1000/mm^3[a]; serum sickness-like reaction[a]	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome (SJS) OR Ulceration of mucous membrane involving 2 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

[a] Revised by the sponsor.

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.).

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Cardiac ischemia/ infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial Infarction
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[a]				
Adult > 17 years (with repeat testing at same visit)	> 140 to < 160 mmHg systolic OR > 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
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, i.v. 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 s	PR interval > 0.25 s	Type II 2nd degree AV block OR Ventricular pause > 3.0 s	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

[a] Revised by the sponsor.
Use as a reference: Blood pressure norms for children < 18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Pediatrics 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009-2107C.

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.).

CLINICAL				
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 s OR Increase in interval < 0.03 s above baseline	Asymptomatic, QTc interval 0.48 – 0.49 s OR Increase in interval 0.03 – 0.05 s above baseline	Asymptomatic, QTc interval ≥ 0.50 s OR Increase in interval ≥ 0.06 s 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 s	Asymptomatic, QTc interval 0.465 – 0.479 s	Asymptomatic, QTc interval ≥ 0.480 s	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])
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (e.g., diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences

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.)

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)
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 i.v. 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 Genito-urinary 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., i.v. fluids)	Life-threatening consequences (e.g., hypotensive shock)

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.)

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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)
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., i.v. 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

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.)

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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
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

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.)

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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
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 (nonrepetitive) without change in seizure character OR Infrequent breakthrough 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

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.)

CLINICAL					
PARAMETER		**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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
	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

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.)

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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
GENITO-URINARY				
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
Intermenstrual 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

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.)

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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
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

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

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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 nonketotic 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)
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/mm³ *300 – 400/µL*	200 – 299/mm³ *200 – 299/µL*	100 – 199/mm³ *100 – 199/µL*	< 100/mm³ *< 100/µL*
Absolute lymphocyte count **Adult and Pediatric > 13 years** (HIV negative only)	600 – 650/mm³ *0.600 x 10^9 – 0.650 x 10^9/L*	500 – 599/mm³ *0.500 x 10^9 – 0.599 x 10^9/L*	350 – 499/mm³ *0.350 x 10^9 – 0.499 x 10^9/L*	< 350/mm³ *< 0.350 x 10^9/L*
Absolute neutrophil count (ANC)				
Adult and Pediatric > 7 days	1,000 – 1,300/mm³ *1.000 x 10^9 – 1.300 x 10^9/L*	750 – 999/mm³ *0.750 x 10^9 – 0.999 x 10^9/L*	500 – 749/mm³ *0.500 x 10^9 – 0.749 x 10^9/L*	< 500/mm³ *< 0.500 x 10^9/L*
Infant[a,b] **2 – ≤ 7 days**	1,250 – 1,500/mm³ *1.250 x 10^9 – 1.500 x 10^9/L*	1,000 – 1,249/mm³ *1.000 x 10^9 – 1.249 x 10^9/L*	750 – 999/mm³ *0.750 x 10^9 – 0.999 x 10^9/L*	< 750/mm³ *< 0.750 x 10^9/L*
Infant[a,b] **1 day**	4,000 – 5,000/mm³ *4.000 x 10^9 – 5.000 x 10^9/L*	3,000 – 3,999/mm³ *3.000 x 10^9 – 3.999 x10^9/L*	1,500 – 2,999/mm³ *1.500 x 10^9 – 2.999 x 10^9/L*	< 1,500/mm³ *< 1.500 x 10^9/L*
Fibrinogen, decreased[c]	100 – 200 mg/dL *1.00 – 2.00 g/L* OR ≥ 0.75 to < 1.00 x LLN	75 – 99 mg/dL *0.75 – 0.99 g/L* OR ≥ 0.50 to < 0.75 x LLN	50 – 74 mg/dL *0.50 – 0.74 g/L* OR ≥ 0.25 to < 0.50 x LLN	< 50 mg/dL *< 0.50 g/L* OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin (Hgb)[d]				
Adult and Pediatric ≥ 57 days (HIV positive only)	8.5 – 10.0 g/dL *5.2 – 6.1 mmol/L*	7.5 – 8.4 g/dL *4.6 – 5.1 mmol/L*	6.5 – 7.4 g/dL *3.9 – 4.5 mmol/L*	< 6.5 g/dL *< 3.9 mmol/L*
Adult and Pediatric ≥ 57 days (HIV negative only)	10.0 – 10.9 g/dL *6.1 – 6.6 mmol/L* OR Any decrease 2.5 – 3.4 g/dL *1.5 – 2.0 mmol/L*	9.0 – 9.9 g/dL *5.5 – 6.0 mmol/L* OR Any decrease 3.5 – 4.4 g/dL *2.1 – 2.6 mmol/L*	7.0 – 8.9 g/dL *4.2 – 5.4 mmol/L* OR Any decrease ≥ 4.5 g/dL *≥ 2.7 mmol/L*	< 7.0 g/dL *< 4.2 mmol/L*
Infant[a,b] **36 – 56 days** (HIV positive or negative)	8.5 – 9.4 g/dL *5.2 – 5.7 mmol/L*	7.0 – 8.4 g/dL *4.2 – 5.1 mmol/L*	6.0 – 6.9 g/dL *3.6 – 4.1 mmol/L*	< 6.0 g/dL *< 3.6 mmol/L*

[a] Values are for term infants.
[b] Use age and sex appropriate values (e.g., bilirubin), including preterm infants.
[c] Revised by the sponsor.
Revised by the sponsor; monomer conversion factor used for conversion from g/dL to mmol/L

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Infant[a,b] **22 – 35 days** (HIV positive or negative)	9.5 – 10.5 g/dL *5.8 – 6.4 mmol/L*	8.0 – 9.4 g/dL *4.8 – 5.7 mmol/L*	7.0 – 7.9 g/dL *4.2 – 4.7 mmol/L*	< 7.00 g/dL *< 4.2 mmol/L*
Infant[a,b] **1 – 21 days** (HIV positive or negative)	12.0 – 13.0 g/dL *7.3 – 7.9 mmol/L*	10.0 – 11.9 g/dL *6.1 – 7.2 mmol/L*	9.0 – 9.9 g/dL *5.5 – 6.0 mmol/L*	< 9.0 g/dL *< 5.5 mmol/L*
International normalized ratio of prothrombin time (INR)[c]	≥ 1.1 to ≤ 1.5 x ULN	> 1.5 to ≤ 2.0 x ULN	> 2.0 to ≤ 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) [d, c]	≥ 1.1 to ≤ 1.25 x ULN	> 1.25 to ≤ 1.50 x ULN	> 1.50 to ≤ 3.00 x ULN	> 3.00 x ULN
Partial thromboplastin time (PTT)[d]	≥ 1.1 to ≤ 1.66 x ULN	> 1.66 to ≤ 2.33 x ULN	> 2.33 to ≤ 3.00 x ULN	> 3.00 x ULN
Platelets, decreased	100,000 – 124,999/mm³ *100.000 x 10^9 – 124.999 x 10^9/L*	50,000 – 99,999/mm³ *50.000 x 10^9– 99.999 x 10^9/L*	25,000 – 49,999/mm³ *25.000 x 10^9– 49.999 x 10^9/L*	< 25,000/mm³ *< 25.000 x 10^9/L*
WBC, decreased	2,000 – 2,500/mm³ *2.000 x 10^9 – 2.500 x 10^9/L*	1,500 – 1,999/mm³ *1.500 x 10^9– 1.999 x 10^9/L*	1,000 – 1,499/mm³ *1.000 x 10^9– 1.499 x 10^9/L*	< 1,000/mm³ *< 1.000 x 10^9/L*
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[c]	≥ 1.25 to ≤ 2.5 x ULN[b]	> 2.5 to ≤ 5.0 x ULN[b]	> 5.0 to ≤ 10.0 x ULN[b]	> 10.0 x ULN[b]
Alkalosis	NA	pH > normal, but ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT (SGPT) [c]	≥ 1.25 to ≤ 2.5 x ULN	> 2.5 to ≤ 5.0 x ULN	> 5.0 to ≤ 10.0 x ULN	> 10.0 x ULN
AST (SGOT) [c]	≥ 1.25 to ≤ 2.5 x ULN	> 2.5 to ≤ 5.0 x ULN	> 5.0 to ≤ 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*

[a] Values are for term infants.
[b] Use age- and sex-appropriate values (e.g., bilirubin), including preterm infants.
[c] Revised by the sponsor.
[d] If the local laboratory is reporting PT as percentage, only INR value will be considered for reporting PT related abnormalities and adverse events.

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Bilirubin (Total) [a]				
Adult and Pediatric >14 days	≥ 1.1 to ≤ 1.5 x ULN	> 1.5 to ≤ 2.5 x ULN	> 2.5 to ≤ 5.0 x ULN	> 5.0 x ULN
Infant[b,c] ≤ 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[b,c] ≤ 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 (corrected for albumin)				
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[b,c] < 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 *3.24 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Calcium, serum, low (corrected for albumin)				
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[b, c] < 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 – 1.49 mmol/L*	< 5.50 mg/dL *< 1.38 mmol/L*
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[a]	≥ 3.0 to ≤ 5.9 x ULN[c]	> 5.9 to ≤ 9.9 x ULN[c]	> 9.9 to ≤ 19.9 x ULN[c]	> 19.9 x ULN[c]
Creatinine[a]	≥ 1.1 to ≤ 1.3 x ULN[c]	> 1.3 to ≤ 1.8 x ULN[c]	> 1.8 to ≤ 3.4 x ULN[c]	> 3.4 x ULN[c]
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*

[a] Revised by the sponsor.
[b] Values are for term infants.
[c] Use age- and sex-appropriate values (e.g., bilirubin), including preterm infants.

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Glucose, serum, low				
Adult and Pediatric ≥ 1 month	55 – 64 mg/dL *3.05 – 3.55 mmol/L*	40 – 54 mg/dL *2.22 – 3.00 mmol/L*	30 – 39 mg/dL *1.67 – 2.21 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
Infant[a,b] < 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	< 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
LDL cholesterol increase (fasting)				
Adult ≥ 18 years	130 – 159 mg/dL *3.37 – 4.12 mmol/L*	160 – 190 mg/dL *4.13 – 4.90 mmol/L*	≥ 191 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[c]	≥ 1.1 to ≤ 1.5 x ULN	> 1.5 to ≤ 3.0 x ULN	> 3.0 to ≤ 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[c]	≥ 1.1 to ≤ 1.5 x ULN	> 1.5 to ≤ 2.0 x ULN	> 2.0 to ≤ 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 – 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*
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*

[a] Values are for term infants.
[b] Use age- and sex-appropriate values (e.g., bilirubin), including preterm infants.
[c] Revised by the sponsor.

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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 months – < 10 years	201 – 499 mg/m2/24 h *0.201 – 0.499 g/d*	500 – 799 mg/m2/24 h *0.500 – 0.799 g/d*	800 – 1,000 mg/m2/24 h *0.800 – 1.000 g/d*	> 1,000 mg/ m2/24 h *> 1.000 sg/d*

7.3 Addendum 3: Visit Schedule for Cutaneous Reaction/Rash Follow-up for pediatric subjects

This visit schedule summarizes the visits and assessments to be performed in case of Cutaneous Reaction/Rash. At the investigator's discretion, additional visits and assessments can be performed.

	Grade 1	**Grade 2**	**Grade 3 or 4**
Day 0[a]	Unscheduled trial visit for initial cutaneous reaction/rash evaluation and local lab assessment. Referral to dermatologist. Biopsy. Trial medication may be continued.	Unscheduled trial visit for initial cutaneous reaction/rash evaluation and local lab assessment. Referral to dermatologist, preferably within 24 hours. Biopsy. Trial medication MAY be continued at the investigator's discretion.	Unscheduled trial visit for initial rash evaluation and local lab assessment. Referral to dermatologist and biopsy, preferably within 24 hours. Trial medication MUST be discontinued.
Day 1	Follow-up visit, including local lab assessment.	Follow-up visit, including local lab assessment.	Follow-up visit, including local lab assessment.
Day 2	No cutaneous reaction/rash follow-up visit required[b].	No cutaneous reaction/rash follow-up visit required[b].	Follow-up visit. Local lab AST/ALT assessment only if AST/ALT on Days 0 and 1 are ≥ 2 x baseline value and/or ≥ 5 x ULN, and/or in case of cutaneous reaction/rash progression.
Day 3	No cutaneous reaction/rash follow-up visit required[b].	No cutaneous reaction/rash follow-up visit required[b].	Follow-up visit. Local lab AST/ALT assessment only if AST/ALT on Days 0 and 1 are ≥ 2 x baseline value and/or ≥ 5 x ULN, and/or in case of cutaneous reaction/rash progression.

[a] Note that Day 0 of the cutaneous reaction/rash follow-up is the first day of investigator assessment and not the first day of cutaneous reaction/rash as reported by the subject.

[b] In case cutaneous reaction/rash progresses to grade 3 or 4, start follow-up schedule for grade 3 or 4 cutaneous reaction/rash as of Day 1 and conduct biopsy/refer to dermatologist as appropriate. (Even if the subject was already referred to dermatologist in scope of grade 1 or 2 cutaneous reaction/rash.)

	Grade 1	Grade 2	Grade 3 or 4
Day 4	No cutaneous reaction/rash follow-up visit required[c].	No cutaneous reaction/rash follow-up visit required[c].	Follow-up visit. Local lab AST/ALT assessment only if AST/ALT on Days 0 and 1 are ≥ 2 x baseline value and/or ≥ 5 x ULN, and/or in case of cutaneous reaction/rash
Day 5	No cutaneous reaction/rash follow-up visit required[c].	No cutaneous reaction/rash follow-up visit required[c].	Follow-up visit, including local lab assessment.
Day 7	Follow-up visit, including local lab assessment[c].	Follow-up visit, including local lab assessment[c].	No cutaneous reaction/rash follow-up visit required.
Further Visits	If cutaneous reaction/rash unresolved after second follow-up visit, further visits (including local lab assessments) at investigator's discretion.	If cutaneous reaction/rash unresolved after second follow-up visit: - without AST/ALT increase: further visits (including local lab assessments) at investigator's discretion[c]; - with AST/ALT increase < 2 x baseline: weekly visits (including local lab assessments)[c]. - with AST/ALT increase ≥ 2 x baseline but not reaching the criteria for grade 3 rash: weekly visits (including local lab assessments)[a].	Weekly visits until resolution/stabilization of cutaneous reaction and AST/ALT elevation, or more frequently at investigator's discretion. Local lab assessments if AST/ALT on Day 5 are ≥ 2 x baseline value and ≥ 5 x ULN.
Upon Rash Resolution/Stabilization[d]	Complete Final Cutaneous Reaction/Rash Evaluation form.	Complete Final Cutaneous Reaction/Rash Evaluation form.	Complete Final Cutaneous Reaction/Rash Evaluation form.

[c] In case cutaneous reaction/rash progresses to grade 3 or 4, start follow-up schedule for grade 3 or 4 cutaneous reaction/rash as of Day 1 and conduct biopsy/referral to dermatologist as appropriate. (Even if the subject was already referred to dermatologist in scope of grade 1 or 2 cutaneous reaction/rash.)

[d] Stabilization: to be agreed upon in collaboration with the sponsor.

7.4 Addendum 4: Revised WHO Clinical Staging of HIV/AIDS

7.4.1 REVISED WHO CLINICAL STAGING OF HIV/AIDS

7.4.1.1 The clinical stages of HIV infection for adults and adolescents are defined as follows (refer to the 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 1992; 41 (RR-17): 1-19; and WHO 2007, Table 3 of: WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children, available at http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf).

Clinical Stage 1

Clinical Stage 1 consists of 1 or more of the conditions listed below in an adolescent or adult (≥ 13 years) with documented HIV infection. Conditions listed in Clinical Stages 2, 3 or 4 must not have occurred.

- Asymptomatic HIV infection;
- Persistent generalized lymphadenopathy.

7.4.1.2 Clinical Stage 2

Clinical Stage 2 consists of symptomatic conditions in an HIV-infected adolescent or adult that are not included among conditions listed in Clinical Stage 3, and that meet at least 1 of the following criteria: a) the conditions are attributed to HIV infection or are indicative of a defect in cell-mediated immunity; or b) the conditions are considered by physicians to have a clinical course or to require management that is complicated by HIV infection. Examples of conditions in Clinical Stage 2 include, but are not limited to the following.

- Moderate unexplained weight loss (< 10% of presumed or measured body weight);
- Recurrent respiratory tract infections sinusitis, tonsillitis, otitis media and pharyngitis);
- Herpes zoster;
- Angular cheilitis;
- Recurrent oral ulceration;
- Papular pruritic eruptions;
- Seborrhoeic dermatitis;
- Fungal nail infections.

7.4.1.3 Clinical Stage 3

Clinical Stage 3 includes the clinical conditions listed in the AIDS surveillance case definition. For classification purposes, once a Clinical Stage 3 condition has occurred, the person will remain in Clinical Stage 3. Conditions in Clinical Stage 3 include the following.

- Unexplained[§] severe weight loss (> 10% of presumed or measured body weight);
- Unexplained chronic diarrhoea for longer than one month;

[§] Unexplained refers to where the condition is not explained by other causes.

- Unexplained persistent fever (above 37.6°C intermittent or constant, for longer than one month);
- Persistent oral candidiasis;
- Oral hairy leukoplakia;
- Pulmonary tuberculosis (current);
- Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis or bacteraemia);
- Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis;
- Unexplained anaemia (< 8 g/dl), neutropaenia (< 0.5×10^9 per litre) or chronic thrombocytopaenia (< 50×10^9 per litre).

7.4.1.4 Clinical Stage 4‡

HIV wasting syndrome;

- Pneumocystis pneumonia;
- Recurrent severe bacterial pneumonia;
- Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site);
- Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs);
- Extrapulmonary tuberculosis;
- Kaposi's sarcoma;
- Cytomegalovirus infection (retinitis or infection of other organs);
- Central nervous system toxoplasmosis;
- HIV encephalopathy;
- Extrapulmonary cryptococcosis including meningitis;
- Disseminated non-tuberculous mycobacterial infection;
- Progressive multifocal leukoencephalopathy;
- Chronic cryptosporidiosis (with diarrhoed);
- Chronic isosporiasis;
- Disseminated mycosis (coccidiomycosis or histoplasmosis);
- Recurrent non-typhoidal Salmonella bacteraemia;
- Lymphoma (cerebral or B-cell non-Hodgkin) or other solid HIV-associated tumours;
- Invasive cervical carcinoma;
- Atypical disseminated leishmaniasis;
- Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy.

‡ Some additional specific conditions can also be included in regional classifications (such as reactivation of American trypanosomiasis [meningoencephalitis and/or myocarditis]) in the WHO Region of the Americas and disseminated penicilliosis in Asia).

7.5 Addendum 5: Lipid Abnormalities (Dyslipidemia)[a]

(Adapted by the sponsor)

Background

Dyslipidemia is only one part of the array of factors that increase cardiovascular risk. At present, there are only limited data linking HIV- and treatment-induced alterations in lipid levels with an increase in cardiovascular disease events. Nonetheless, these abnormalities are reason for serious concern among subjects with improved life expectancy as a result of potent ARV therapy.

Cardiovascular disease risk assessment and intervention must include evaluation of not only lipids, but also other modifiable risk factors such as cigarette smoking, hypertension, diabetes, obesity, and physical inactivity.

Definitions

Increases of triglycerides and LDL cholesterol and decreases in high-density lipoprotein (HDL)-cholesterol have been observed in subjects with HIV infection receiving HIV therapy. A variety of lipid disturbances have been reported due to HIV and its therapies. Briefly, both HIV infection (low HDL-cholesterol, elevation in triglycerides) and PIs (elevation in total and LDL cholesterol and additional elevation in triglycerides) are important underlying causes of dyslipidemia in HIV infected subjects. With NNRTIs, increases in total cholesterol and LDL cholesterol also occur, but these may be offset by increases in HDL-cholesterol. Subjects with fat redistribution (central obesity, loss of peripheral fat) are at increased risk of lipid abnormalities; however, a causal relationship has not been established.

ADULT SUBJECTS:

Recommendations

Clinicians should monitor patients receiving ARV therapy for dyslipidemia by obtaining a fasting lipid profile before and after starting ARV therapy. Frequent monitoring may be indicated by the presence of persistent lipid elevation, cardiovascular risk factors, or cardiovascular symptoms.

Clinicians should recommend lifestyle modifications, such as increased exercise, weight loss, nutrition therapy, smoking cessation, and drug addiction treatment.

Pharmacologic treatment of dyslipidemia should be guided by currently available clinical guidelines.

When a statin is indicated, clinicians should avoid using simvastatin and lovastatin in patients who are receiving PI based regimens.

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[a]Taylor P, Worrell C, Steinberg SM, et al. Natural history of lipid abnormalities and fat redistribution among human immunodeficiency virus-infected children receiving long-term, protease inhibitor-containing, highly active antiretroviral therapy regimens. Pediatrics 2004; 114: e235-e242.

Lipid abnormalities in HIV-infected patients, specifically hypocholesterolemia and hypertriglyceridemia, were described before the advent of ARV therapy; however, the number of patients with lipid abnormalities appears to be increasing in the HAART era. Patients often develop lipid abnormalities within 3 months of initiation of ARV therapy. The full clinical significance of these laboratory abnormalities is not yet clear, although the abnormalities may be associated with premature coronary artery disease in some patients, especially those with other risk factors for coronary heart disease or the metabolic syndrome previously referred to as syndrome X.

Table 8: Major Risk Factors (Exclusive of LDL Cholesterol increase) that Modify LDL Goals*

cigarette smoking;
hypertension (blood pressure ≥140/90 mmHg or on antihypertensive medication);
low HDL cholesterol (<40 mg/dL)†;
family history of premature CHD (coronary heart disease [CHD] in male first-degree relative <55 years; CHD in female first-degree relative <65 years)
age (men ≥45 years; women ≥55 years)

* All the risk factors listed above are captured in the CRF

† HDL cholesterol ≥60 mg/dL counts as a "negative" risk factor; its presence removes one risk factor from the total count

Hypertriglyceridemia, low HDL-cholesterol levels, and elevated low-density lipoprotein (LDL)-cholesterol levels have been described in patients receiving ARV therapy, especially PIs. NNRTI use has been associated with hypercholesterolemia. The mechanism by which PIs cause dyslipidemia is unclear. Hypertriglyceridemia seems to be most significant in patients with regimens that include low-dose ritonavir. Significant hypertriglyceridemia (>500 mg/dL) is associated with an increased risk of pancreatitis, particularly in patients with other risk factors for pancreatitis (e.g., alcohol or didanosine use).

Lipid abnormalities in HIV-infected patients receiving ARV therapy may occur in conjunction with body fat changes. Secondary causes of dyslipidemia, including diabetes, hypothyroidism, liver disease, chronic renal failure, and other medications, such as progestins, anabolic steroids, and corticosteroids, should be considered in patients with new onset dyslipidemia.

A fasting lipid profile (total cholesterol, LDL, HDL, triglycerides) should be obtained prior to starting ARV treatment (ideally at baseline visit). A fasting lipid profile should be obtained 3 to 6 months after starting or changing ARV therapy (ideally at each visit of the study protocol).

Alternatively, if collection of a fasting sample is not feasible, a non-fasting total cholesterol and HDL may be obtained. The clinician should proceed with a fasting lipoprotein profile when the non-fasting TC is >200 mg/dL or the HDL is <40 mg/dL.

The management of lipid disorders in HIV-infected patients parallels management in non-HIV infected patients (see Table 8 to Table 10). Individual risk assessments for an acute coronary event and management of lipid disorders can be accomplished by following current guidelines for assessment and management, such as those published by the National Cholesterol Education Program (NCEP) and the Adult AIDS Clinical Trial Group (ACTG) Cardiovascular Disease

Focus Group (see Table 8 to Table 10). Treatment of dyslipidemia should include lifestyle and risk modification with or without pharmacological therapies.

For patients without known coronary artery disease (CAD), therapeutic lifestyle changes should be the first intervention for the treatment of lipid disorders. These changes include increased physical exercise, weight reduction when indicated, smoking cessation and dietary changes. Consultation with a registered dietitian may be helpful in achieving dietary goals [restriction of total fat to 25%-30% of total caloric intake, and dietary cholesterol to <200 mg/day; use of plant sterols (2 gm/d) found in commercial margarines (e.g., Benecol or Basikol), and increased soluble fiber (10-25 g/d)].

Lipid-lowering agents should be considered for hyperlipidemias that do not respond to changes in ARV therapy or therapeutic lifestyle changes, or for patients in whom such modifications are not appropriate. The first-line pharmacological treatment for patients with isolated elevation of LDL is statin therapy. Pravastatin is the safest drug for treating hyperlipidemia during concurrent therapy with currently FDA approved PIs. Atorvastatin can be used cautiously at lower doses (5-10 mg) with careful titration. Rosuvastatin will not likely interact with PIs and NNRTIs. Use of other statins, particularly lovastatin and simvastatin, is contraindicated.

Fibric acid derivatives, such as gemfibrozil and fenofibrate, are the first-line treatment for isolated elevation of fasting triglyceride levels. The threshold suggested for intervention is 500 mg/dL.

Gemfibrozil and fenofibrate are not metabolized via the cytochrome P450 system and are generally safe to use in patients receiving ARV therapy. For patients with high triglycerides in whom LDL cholesterol increases cannot be measured, the non-HDL cholesterol level may be calculated to guide initiation of therapy (total cholesterol – HDL).

Patients with persistent high-grade hypertriglyceridemia (>1000 mg/dL) may benefit from a very low-fat diet, even if they are not overweight.

Table 9: LDL and non-HDL Cholesterol Goals and Thresholds for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)	Non-HDL Goal (mg/dL)*
CHD or CHD risk equivalents: diabetes mellitus, atherosclerotic disease (CAD or stroke), or multiple risk factors (10-year risk >20%)	<100	≥100	<130 (100-129: drug optional)†	≥130
2+ risk factors: HDL <40, strong family history, age >45	<130	≥130	10-year risk 10%-20%: ≥130 10-year risk	<160

years, and smoking (10-year risk >20%)			<10%: ≥160	
0-1 risk factor‡	<160	≥160	≥190 (160-189: LDL-lowering drug optional)	<190

* Non-HDL cholesterol = (total cholesterol – HDL). When LDL cannot be measured because the triglyceride level is >200 mg/dL, non-HDL cholesterol may be used as a secondary goal. The non-HDL cholesterol goal is 30 mg/dL higher than the LDL cholesterol goal.

† Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes (dietary and exercise intervention). Others prefer use of drugs that primarily modify triglycerides and HDL (e.g., nicotine acid or fibrate). Clinical judgment also may suggest deferring drug therapy in this subcategory.

‡ Almost all people with 0 or 1 risk factors have a 10-year risk <10%; thus, 10-year risk assessment in people with 0 or 1 risk factors is not necessary.

For those with both elevated serum LDL and triglyceride levels, combination therapy with a statin and fibrate may be needed but should be used with extreme caution because of overlapping toxicity (rhabdomyolysis) profiles. Therapy should begin first with a statin, followed by the addition of the fibric acid derivative if response to the maximal statin dose is suboptimal after 3 to 4 months of treatment. Routine monitoring for hepatic and muscle toxicity should be performed in these situations.

The use of additional drugs, such as nicotinic acid or bile sequestrants, may be necessary to manage dyslipidemia. Nicotinic acid may cause hepatotoxicity and elevated serum glucose levels. Therefore, low-dose therapy with incremental dose increases is advisable for those patients who require this drug. Bile acid sequestrants (e.g., colesevelam 3 tablets b.i.d. or ezetimibe 10 mg q.d.) may also be used but may interfere with absorption of oral medications; therefore, proper timing of the dosing of this drug is important when used in conjunction with ARV medications (i.e., 1 hour before or 4 hours after).

Table 10: Choice of Drug Therapy for Dyslipidemia in HIV-infected Individuals Receiving HAART

Lipid Abnormality	First Choice	Second Choice (or if additional treatment is needed)	Comments
Isolated high LDL	Statin*	Fibrate	Start with low doses of statins and titrate upward. Patients receiving PIs may be at increased risk of statin-induced myopathy.

Combined hyperlipidemia (high cholesterol and high triglycerides)	Fibrate or statin*	– If starting with fibrate, add statin* – If starting with statin*, add fibrate	Combining statin and a fibrate may increase risk for myopathy
Isolated hypertriglyceridemia	Fibrate	Statin*	Combining statin and a fibrate may increase risk for myopathy.

Adapted from the Preliminary guidelines for the evaluation and management of dyslipidemia in adults infected with human immunodeficiency virus and receiving antiretroviral therapy: Recommendations of the Adult AIDS Clinical Trial Group Cardiovascular Disease Focus Group.

* Statins should be dosed at bedtime. Simvastatin and lovastatin are not allowed in patients receiving DRV/rtv (the only allowed PI in this trial).

PEDIATRIC SUBJECTS:

Identifying Dyslipidemia in Children and Youth

The National Cholesterol Education Program (NCEP) and the American Heart Association (AHA) recommend an individualized/high-risk approach to identifying dyslipidemia in children and youth as describe below[a]:

Primary Prevention in Children and Youth

Dietary modification

Limit foods with

- Saturated fats to less than 10% calories per day
- Cholesterol below 300 mg/day
- *Trans* fatty acids

Physical activity

- Increase moderate to rigorous more than 60 minutes per day
- Limit sedentary activities less than 2 hours per day

Identification of dyslipidemia

Selective screening

- Family history of coronary heart disease
- One parent with blood cholesterol greater than 240 mg/dL
- No parental history, but coronary heart disease risk factors present
- More than 1 of the following risk factors present: high blood pressure, smoking, sedentary lifestyle, obesity, alcohol intake, use of drugs or diseases associated with dyslipidemia

[a] Fletcher B, Berra K, Ades P, et al. AHA Scientific Statement. Managing abnormal blood lipids. A collaborative approach. Circulation 2005; 112: 3184-3209.

A fasting lipid profile allows for a comprehensive assessment that includes measurement of elevations in total cholesterol and LDL cholesterol, triglycerides and HDL-cholesterol. The AHA recommends the averaged results of 3 fasting lipid profiles as the baseline for guiding treatment modalities.

The AHA endorses the guidelines established by the NCEP in setting the following definitions for acceptable, borderline, and high total cholesterol and LDL- cholesterol levels in children and adolescents between 2 and 19 years of age.

Cholesterol Levels for 2- to 19-Year-Olds

Levels	Total cholesterol, mg/dL	LDL cholesterol, mg/dL
Acceptable	< 170< 110	
Borderline	170–199	110–129
High	>200	> 130

Although these cut off points are recommended to guide treatment decisions, it is important to emphasize that no long-term longitudinal studies have been conducted to determine the absolute levels in childhood and adolescence that accelerate atherosclerotic processes and predict cardiovascular heart disease in adult life.

Lifestyle modification with an emphasis on normalization of body weight and heart-healthy patterns of dietary intake and physical activity is the cornerstone of treatment for children and youth who are identified as having dyslipidemia.

This approach should be supported through education as well as through community-based activities. In the pediatric clinics, the management of dyslipidemia is best accomplished via a multidisciplinary collaborative team approach. Nurses, nurse practitioners, and dietitians experienced in the treatment of dyslipidemia in children and youth are well positioned within these settings to facilitate lifestyle modification with children and families.

The AHA recommends an “adequate” trial (i.e., 6-12 months) of therapeutic lifestyle change before consideration of lipid-lowering medication. Three general classes of lipid-lowering agents are available and have been used in the treatment of dyslipidemia in children and adolescents. These include the bile acid sequestrants, niacin, and statins (refer to the current Investigator’s Brochure of DRV[2] for the allowed and disallowed concomitant medication during clinical trials with DRV).

PART II: PROCEDURES

1 ADVERSE EVENTS

1.1 Definitions

ADVERSE EVENT (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (International Conference on Harmonisation - ICH E6; 1.2).

SERIOUS ADVERSE EVENT (SAE)

Any untoward medical occurrence that at any dose:

- results in death;
- is life threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;

or

- is a congenital anomaly/birth defect (ICH E6; 1.50).

Additionally, any report containing an untoward medical occurrence considered medically significant which includes any suspected transmission of any infectious agent via a medicinal product is a serious adverse event.

Note

- Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above.
- Hospitalizations that were planned prior to the signing of informed consent/assent, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.
- For convenience the investigator may choose to hospitalize the subject for the duration of the treatment period; this will not be considered as a serious adverse event.

UNLISTED (UNEXPECTED) ADVERSE EVENT

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

LIFE THREATENING

Any 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.

ASSOCIATED WITH THE USE OF THE DRUG

An adverse event is considered associated with the use of the drug if the attribution is possible, probable or very likely.

1.2 Attribution Definitions

NOT RELATED

An adverse event, which is not related to the use of the drug.

DOUBTFUL

An adverse event for which an alternative explanation is more likely, e.g., concomitant drug(s) or concomitant disease(s), and/or the relationship in time suggests that a causal relationship is unlikely.

POSSIBLE

An adverse event, which might be due to the use of the drug. An alternative explanation, e.g., concomitant drug(s) or concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be excluded.

PROBABLE

An adverse event, which might be due to the use of the drug. The relationship in time is suggestive, e.g., confirmed by dechallenge. An alternative explanation is less likely, e.g., concomitant drug(s) or concomitant disease(s).

VERY LIKELY

An adverse event, which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s) or concomitant disease(s). The relationship in time is very suggestive (e.g., it is confirmed by dechallenge and rechallenge).

1.3 HIV-Related Events or Outcomes

The events or outcomes listed in the classification list (see PART I:7.4, Addendum 4: Revised WHO Clinical Staging of HIV/AIDS) are to be recorded as HIV-related events on the CRF. These events or outcomes, as well as any sign, symptom, diagnosis, illness, and/or clinical laboratory abnormalities that can be linked to any of these events or outcomes, are not to be reported as an adverse event.

After termination of data collection, safety will continue to be assessed per local standard of care and documented in the subject's medical records only. Data will no longer be recorded in the CRF. Investigators will continue to report SAEs possibly related to DRV/rtv and pregnancies to the sponsor using regular pharmacovigilance reporting. This information will only be entered in the company safety repository.

1.4 Reporting of Adverse Events and HIV-Related Events

Any new adverse event, serious adverse event, or worsening of a condition will be reported to the originating (parent) trial until the Week 4 follow-up contact in the originating protocol.

After the Week 4 follow-up of the originating (parent) trial, adverse events leading to discontinuation or treatment interruption, adverse events considered at least possibly related to treatment with DRV/rtv, serious adverse events, and pregnancies are to be reported in the CRF of trial TMC114IFD3001. All other adverse events that do not meet criteria for seriousness are only to be collected if required per local regulations.

Occurrence of adverse events and HIV-related events are to be reported in the Adverse Event and HIV-Related Events sections of the CRF, respectively.

All reportable adverse events still ongoing at the end of the treatment are to be followed until satisfactory resolution (i.e., value back to baseline value) or stabilization (to be agreed upon in collaboration with the sponsor) at the investigator's discretion, according to the local standard of care, or until final database lock.

New adverse events leading to discontinuation or treatment interruption, new adverse events considered at least possibly related to treatment with DRV/rtv, and new serious adverse events reported during the follow-up period of the trial are to be followed as agreed between the sponsor and investigator.

Certain long-term adverse events of antiretroviral therapy cannot be followed until resolution within the setting of this protocol; in these cases follow-up is the responsibility of the treating physician. However, this has to be agreed upon with the sponsor.

Serious adverse events occurring within the trial (between the signing of informed consent/assent and last follow-up visit) are to be reported. Any serious adverse events with at least a possible relationship to the study medication occurring after the end of the trial must be reported, and are to be handled by the sponsor.

The start date of the serious adverse event documented on the Serious Adverse Event Form must be the same as the start date of the corresponding adverse event documented on the CRF. If a change in severity is noted for the existing adverse event, it must be recorded as a new adverse event. If a worsened adverse event meets the criteria for a serious adverse event, the start date of the serious adverse event must be the same as the start date of the worsened adverse event.

The cause of death of a subject in a clinical trial, whether the event is expected or associated with the investigational agent, is a serious adverse event.

All serious adverse events and pregnancies occurring during clinical trials must be reported to the Drug Safety Officer as specified on the Serious Adverse Event Form immediately (i.e., within 24 hours) after the investigator becoming aware of the event.

For the names and phone numbers of the contact person(s) refer to Part I, Section 7.1, Addendum 1: Trial Contact Persons.

The first report of a serious adverse event may be made by telephone or facsimile (FAX). The investigator must provide the minimal information, i.e., trial number, subject's initials and date of birth, medication code number, period of intake, nature of the adverse event, and investigator's attribution.

This report of a serious adverse event by telephone must always be confirmed by a written, more detailed report. For this purpose, the monitor provides the investigator with a Serious Adverse Event Form, to be completed and signed by the latter. If initial reporting was done by telephone, the person answering the phone can complete the Serious Adverse Event Form according to the information provided by the investigator. This form needs to be reviewed, completed if applicable, signed, and dated for approval by the investigator.

Pregnancies occurring during clinical trials are considered immediately reportable events. They must be reported as soon as possible using the same Serious Adverse Event Form. The outcome of the pregnancy must also be reported to the Drug Safety Officer.

The sponsor or its representatives assumes responsibility for appropriate reporting of adverse events to Regulatory Authorities. Adverse Events reporting, including suspected unexpected serious adverse reactions, is to be carried out in accordance with applicable local regulations. For reported deaths, the investigator should supply the sponsor and the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) with any additional requested information (e.g., autopsy reports and terminal medical reports).

After termination of the clinical trial (last subject last visit in the trial), any unexpected safety issue that changes the risks benefit analysis and is likely to have an impact on the subjects who have participated in it, should be reported as soon as possible to the competent authority(ies) concerned together with proposed actions.

After termination of data collection, safety will continue to be assessed per local standard of care and documented in the subject's medical records only. Data will no longer be recorded in the CRF. Investigators will continue to report SAEs possibly related to DRV/rtv and pregnancies to the sponsor using regular pharmacovigilance reporting. This information will only be entered in the company safety repository.

2 TRIAL CLOSURE CONSIDERATIONS

The sponsor reserves the right to close an investigational site or terminate the trial at any time for any reason. In case of an early termination of the trial or temporary halt by the sponsor, the IEC/IRB should be notified within 15 calendar days, including a detailed written explanation of the reasons for the termination/halt.

When the trial ends in a particular country, the sponsor will submit an end of trial declaration, to both the IEC/IRB and regulatory authority for that particular country by using the "Declaration of the end of trial form" (EU member states only). The declaration will be submitted within 90 days of the end of the trial.

The end of trial declaration will be submitted a second time to the regulatory authorities and IEC/IRB after the complete trial has ended in all participating centers, in all countries. This notification will also be submitted within 90 days of the end of the trial.

Reasons for the closure of an investigational site or termination of a trial by the sponsor may include but are not limited to:

- discontinuation of the trial at the center;
- failure of the investigator to comply with the protocol, ICH-Good Clinical Practice (GCP) guidelines or local requirements;
- safety concerns;
- switch of all subjects enrolled at the site to locally available DRV-based treatment regimens (ie, commercially available and reimbursed, or accessible through another source [eg, access program or government program]) or to local standard of care, as appropriate.

3 TRIAL MATERIALS

3.1 Investigational Products

The investigator acknowledges that the drug supplies are investigational and as such must be handled strictly in accordance with the protocol and the container label. Supplies must be retained in a limited access area and under the appropriate environmental conditions as specified on delivery. Supplies should be dispensed under the supervision of the investigator or subinvestigator, or by a hospital pharmacist. Local regulations should be adhered to.

It is the investigator's responsibility to ensure that subjects or those held to be responsible for subjects, return their medication (including empty packages, e.g., empty blisters). Returned supplies must not be dispensed again, even not to the same subject. Each time medication is dispensed to or returned by the subject, this must be documented on the Drug Accountability Form. Unused medication and medication returned by the subject must be available for verification by the monitor.

After termination of data collection, compliance check on unused and used trial medication returned by the subject will still be performed by the investigator or designee and will not be verified by the sponsor, however, drug accountability will be reviewed during the on-site monitoring visits.

All used and unused trial medication will be passed over for destruction on site (conform local regulations), or by an authorized destruction unit after authorization by the sponsor. This will be documented on the Drug Return Form, and a destruction certificate, if applicable.

3.2 Trial Documents

The following documents must be provided to the sponsor or representatives before shipment of trial medication to the trial center.

- A signed and dated protocol and amendment(s), if any.
- A copy of the signed and dated written IEC/IRB approval specifying the documents being approved: the protocol, amendments, Informed Consent/Assent Forms, any other written information provided to the subject, and subject recruitment materials. This approval must clearly identify the trial by protocol title and trial number.
- Regulatory authority approval or notification, if required.

- Documentation on which the assessment of the principal investigator's qualifications was based (e.g., curriculum vitae).
- The FDA Form 1572, if applicable, and the FDA Waiver Letter provided to non-US investigators.
- Completed Investigator Financial Disclosure Form from the principal investigator.
- Signed and dated Clinical Trial Agreement, if applicable.
- Signed and dated financial agreement.
- Import License, if required.

The following documents must be provided to the sponsor or representatives prior to enrollment of the first subject.

- Current list of the IEC/IRB members, their function and affiliation or equivalent, officially authorized assurance on the IEC/IRB composition.
- Statement or equivalent documentation* that the IEC/IRB operation is in compliance with ICH-GCP, and local regulatory requirements.

  * Equivalent documentation applies to countries where the IEC/IRB is certified through the Local Health Authorities.
- Current license to prescribe and distribute controlled substances, if applicable.
- Completed Investigator Financial Disclosure Form from all participating subinvestigators.
- Documentation on which the assessment of the subinvestigators' qualifications was based (e.g., curriculum vitae).
- Signed and dated agreement between the investigator and Local Health Authority, if applicable.

3.3 Participation Cards

If the subjects are not under 24-hour supervision of the investigator or his/her staff (out-subjects), they must be provided with a Subject Participation Card indicating the name of the investigational product, the trial number, the investigator's name and a 24-hour emergency contact number. The subject should be advised to keep the participation card in his/her wallet at all times.

3.4 Source Data

The nature and location of all source documents is to be identified in the Source Document Identification Form to ensure that all sources of original data required to complete the CRF are known and are accessible for verification by the monitor. If electronic records are maintained, the method of verification must be discussed and agreed upon between the investigational staff and the monitor.

The required source data are listed in the Source Data Verification Plan, and should include sequential notes containing at least the following information for each subject:

- subject identification (name, date of birth, gender);
- documentation that subject meets eligibility criteria, i.e., history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- participation in trial (including trial number);
- trial discussed and date of informed consent/assent;
- dates of all visits;
- documentation that protocol specific procedures were performed;
- start and end date (including dose regimen) of trial medication (preferably drug dispensing and return should be documented as well);
- record of all reportable adverse events (see Section 1.4 of Part II) and other safety parameters (start and end date, and preferably including causality and intensity);
- concomitant medication;
- date of trial completion and reason for early discontinuation, if applicable.

It is recommended that the author of an entry in the source documents is identifiable. Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded on the CRF are consistent with the original source data.

After termination of data collection, visits and assessments will be performed per local standard of care and documented in the subject's medical records only. Data will no longer be recorded in the CRF.

3.5 Case Report Forms

CRFs are provided for each subject. All forms must be filled out legibly in durable black ballpoint pen.

Data Management may make changes to the entries made by the site (self-evident corrections or global rulings such as correction of obvious spelling errors). If global rulings (self-evident corrections) are applied to the clinical database by data management during the trial, the rules are to be documented in a global rulings document and provided to the site for review and sign-off prior to applying the global rulings. If required, an investigator may request a detailed list of corrections applied to the data from his/her site through the trial monitor.

All data must be entered in English.

All data relating to the trial must be recorded on CRFs prepared by the sponsor. These CRFs should always reflect the latest observations on the subjects participating in the trial. Therefore, CRFs are to be completed as soon as possible after (or during) the subject's visit. The investigator must verify that all data entries on the CRFs are accurate and correct. If some assessments are not done, or if certain information is not available, not applicable, or unknown, the investigator must enter "ND", "NAV", "NAP", or "UN/UNK", respectively, in the appropriate space.

Monitoring in this trial is to be done by means of telephone contacts and monitoring visits as per monitoring guidelines. During monitoring visits, the monitor reviews the CRFs and evaluate them for completeness, legibility and consistency. The CRF is to be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections,

and alterations are to be made by the responsible investigator or his/her designee. The monitor cannot write on the CRF pages, except for obvious data modifications. Corrections must be made in such a way that the original entry is not obscured. Correction fluid must NOT be used. The correct data must be inserted, dated, and initialed by the person making the correction. The persons entering data on the CRFs must be identified on the Signature Sheet. The investigational staff must not write on non-carbon required (NCR) copies of CRFs left at the site once the original is transmitted to the sponsor or representative.

A CRF must be completed and the original must be returned to the sponsor or representative. A copy must be archived by the investigator as specified in Section 3.7 (of Part II).

In case corrections to a CRF are needed after removal of the original CRF copy from the site, a Data Correction Form (DCF) is to be used. All DCFs sent to the investigator are to be answered by the appropriate investigational staff and signed and dated for approval.

After termination of data collection, visits and assessments will be performed per local standard of care and documented in the subject's medical records only. Data will no longer be recorded in the CRF. Investigators will continue to report SAEs possibly related to DRV/rtv and pregnancies to the sponsor using regular pharmacovigilance reporting. This information will only be entered in the company safety repository.

3.6 Subject Identification Code List & Subject Screening and Enrollment Log

In order to permit easy identification of the individual subject during and after the trial, the investigator is responsible for keeping an updated Subject Identification Code List. The monitor will review this document for completeness. However, in order to ensure subject confidentiality, this document will remain at the center and no copy will be made.

A Subject Screening and Enrollment Log that report on all subjects who were seen to determine eligibility for inclusion in the trial have to be completed by the investigator also.

3.7 Archiving

The investigator shall maintain the trial documents as specified in "Essential Documents for the Conduct of a Clinical Trial" (ICH E6; 8.2 - 8.4) and as required by the applicable regulatory requirement(s). The investigator should take measures to prevent accidental or premature destruction of these documents.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however, if required by the applicable regulatory requirements.

It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

Under no circumstance shall the investigator relocate or dispose of any trial documents before having obtained a written approval of the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this trial, the investigator must permit access to such reports. The subject is granting access to his/her source data by signing the informed consent/assent.

Any difficulty in storing original documents must be discussed with the monitor prior to the initiation of the trial.

4 CONFIDENTIALITY

All information concerning the product and the sponsor's operations (such as patent applications, formulae, manufacturing processes, basic scientific data, or formulation information supplied to the investigator by the sponsor and not previously published) is considered confidential by the sponsor and should not be disclosed by the investigator to any third party without the sponsor's prior written approval. The investigator agrees to use this information only in accomplishing the trial and will not use it for other purposes.

5 REPORTING AND PUBLICATION

5.1 Reporting

The sponsor will create an Annual Safety Report (ASR) and Line Listings in accordance with the EU Clinical Trials Directive with a data-lock date of 23 June. This study TMC114IFD3001 will be included in the first ASR produced after approval of this protocol, which may be less than 1-year's time from this particular study approval date, and in all subsequent ASRs, as appropriate, until study closure. From January 2011, in accordance to the ICH guideline E2F, ASRs will be replaced by Development Safety Update Reports (DSURs) (data-lock of 23 December). This trial will be included in the first DSUR, and in all subsequent DSURs, as appropriate, until trial closure.

The results of the trial will be reported in a Clinical Research Report and will contain CRF data from all study sites that participated in the study. A summary of the Clinical Study Report will be provided to the investigators, to the applicable regulatory authorities, and IECs/IRBs, if required by the applicable regulatory requirements, within 6 months after end of trial.

After termination of data collection, only limited safety data (SAEs possibly related to DRV/rtv and pregnancies) will continue to be reported using regular pharmacovigilance reporting and will only be entered in the company safety repository. Appropriate safety reports will continue to be provided to IECs/IRBs and regulatory authorities, as required.

One investigator will be appointed for signing off the final Clinical Research Report. The selection of this investigator will be determined by the recruitment performance and specific expertise related to the nature and the key assessment parameter(s).

5.2 Publication

The sponsor will not unreasonably withhold consent to publish the data generated in this trial. However, it is the policy of the sponsor not to allow the investigators to publish their results or findings prior to the sponsor's publication of the overall trial results. The investigator agrees that before he/she publishes any results of this trial, he/she shall allow at least 45 days for the sponsor to review the prepublication manuscript prior to submission of the manuscript to the publisher, as

specified in the Clinical Trial Agreement between Institution/investigator and sponsor. In accordance with generally recognized principles of scientific collaboration, co-authorship with any company personnel will be discussed and mutually agreed upon before submission of a manuscript to a publisher.

6 AUTHORITIES/ETHICS

6.1 Regulatory Authorities

This trial will be submitted to the local regulatory authority for approval or notification whichever is applicable. The trial will only be undertaken in compliance with the local regulatory requirements.

6.2 Independent Ethics Committee/Institutional Review Board

This trial can only be undertaken after full approval of the protocol, informed consent/assent, any other written information given to subjects, and subject recruitment materials has been obtained from the IEC/IRB. This document must be dated and clearly identify the trial and the documents being approved.

During the trial the following documents will be sent to the IEC/IRB for their review:

- changes to the Investigator's Brochure;
- reports of adverse events that are serious, unlisted and associated with the investigational drug;
- DSUR and Quarterly Line Listings (EU member states only).

Substantial amendments and applicable Informed Consent/Assent Form revisions must promptly be submitted to the IEC/IRB for review and approval prior to implementation of the change(s), except when necessary to eliminate an immediate hazard to the trial subjects.

The IEC/IRB is responsible for continuous review of the trial. At least once a year, the investigator will provide the IEC/IRB with a progress report to allow review of the trial. Additional progress reports should be provided if required by the IEC/IRB.

These requests and (re)approvals, if applicable, should be documented in writing.

6.3 ICH-GCP Guidelines

This trial will be conducted in accordance with the current ICH-GCP Guidelines. GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

6.4 Subject Information and Informed Consent/Assent

Each subject or a legally acceptable representative must give written consent/assent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) and assent form that is/are

used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent/assent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent/assent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject or legally acceptable representative is authorizing such access. It also denotes that the subject agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent/assent for additional safety evaluations and subsequent disease-related treatments, if needed. The physician may also recontact the subject for the purpose of obtaining consent to collect information about his or her survival status.

The subject or legally acceptable representative will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent/assent should be appropriately recorded by means of either the subject's or his or her legally acceptable representative's personally dated signature. After having obtained the consent/assent, a copy of the ICF must be given to the subject.

If the subject or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent/assent of the subject or legally acceptable representative] is obtained.

Children (minors) or subjects who are unable to comprehend the information provided can be enrolled only after obtaining consent/assent of a legally acceptable representative. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically subjects 7 years of age and older, depending on the institutional policies. Written assent should be obtained from subjects who are able to write. A separate assent form written in language the subject can understand should be developed for adolescents. After having obtained the assent, a copy of the assent form must be given to the subject, and to the subject's parent or if applicable legally acceptable representative.

When prior consent/assent of the subject is not possible and the subject's legally acceptable representative is not available, enrollment procedures should be described in the protocol with documented approval/favorable opinion by the IEC/IRB to protect the rights, safety, and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or legally acceptable representative must be informed about the study as soon as possible and give consent/assent to continue.

6.5 Privacy of Personal Data

The processing of personal data in pursuit of this trial will be limited to those data that are reasonably necessary to investigate the efficacy, safety, quality, and utility of the investigational product(s) used in this trial. These data will be processed with adequate precautions to ensure confidentiality.

The sponsor ensures that the personal data are:

- collected for a specified and legitimate purpose;
- processed fairly and lawfully;
- credible.

Explicit consent for the processing of personal data will be obtained from the participating subjects or their legally acceptable representative prior to any processing of personal data.

The sponsor or its representatives whose responsibilities require access to personal data are obliged to keep the identity of trial subjects confidential. This confidentiality will be maintained throughout the complete data processing. Trial subjects will be entitled to request confirmation of the existence of personal data held by the sponsor and will have the right to rectify erroneous or inaccurate data.

7 FINANCING AND INSURANCE

7.1 Financial Disclosure

The disclosed financial interest of the investigator must be collected before enrollment of the first subject. The investigator should promptly update this information if any relevant changes occur up to 1 year following trial completion.

Disclosable financial interests will be recorded on the Investigator Financial Disclosure Form.

Any investigator(s) added as investigational staff must complete the Investigator Financial Disclosure Form at the beginning of their participation in the trial. For any investigator(s) leaving the site prior to trial completion, an Investigator Financial Disclosure Form should be obtained at the end of their participation.

7.2 Indemnification

The sponsor undertakes to indemnify and hold harmless the investigator and his/her medical staff from any claim, demand or cost arising from the activities to be carried out in compliance with the protocol, as further specified in the Clinical Trial Agreement.

7.3 Insurance

The sponsor ensures that appropriate liability insurance is available covering injuries arising from the participation of the trial subject in this trial, as further specified in the Informed Consent/Assent and the Clinical Trial Agreement.

8 DATA QUALITY CONTROL/ASSURANCE

The trial is to be monitored by the sponsor or representatives according to the current Standard Operating Procedure for the monitoring of clinical trials.

Shortly before the trial starts, the monitor meets with the investigator and all staff involved to review the procedures regarding trial conduct and recording the data on the CRF. During the trial, the investigator shall permit the monitor to verify the progress of the trial at the center as frequently as necessary. The investigator shall make the CRFs available, provide missing or corrected data and sign the CRFs. Key data transcribed onto the CRFs, such as the subject's sex, date of birth, assessment dates, test results, etc., is to be reviewed against source documents. Personal information is to be treated as strictly confidential and is not to be made publicly available. Any inconsistency between source data and data recorded on the CRF is to be corrected.

After termination of data collection, visits and assessments will be performed per local standard of care and documented in the subject's medical records only. Data will no longer be recorded in the CRF.

The sponsor will ensure that appropriate Quality Control (QC) steps are included into the different clinical processes to guarantee adequate protection of the trial subjects and quality of the data.

An independent Quality Assurance (QA) department, regulatory authorities and/or IECs/IRBs may review this trial. This implies that auditors/inspectors will have the right to inspect the trial center(s) at any time during and/or after completion of the trial and will have access to source documents, including the subject's file. By participating in this trial, investigators agree to this requirement.

For any data transfer, measures will be undertaken to protect subject data handed over against disclosure to unauthorized third parties and subject confidentiality will be maintained at all times.

SIGNATURE PAGE

Global Medical Leader:

This Clinical Trial Protocol has been reviewed and approved by the sponsor in order to ensure compliance with Good Clinical Practices.

Name: Magda Opsomer, M.D.

Affiliation: Janssen Research & Development

See appended electronic signature page

Investigator:

The trial will be performed in compliance with Good Clinical Practices, including the archiving of essential documents.

Name:

Affiliation:

Signature & Date:

SIGNATURES

Signed by	Date	Justification
Magda Opsomer	21Jun2019, 07:48:07 AM, UTC	Document Approval