Clinical Trial Protocol Amendment III

	TMC125-TiDP35				
Department:	Clinical R&D	**Nonproprietary name:**	etravirine		
Version:	4.0	**Date:**	22 July 2019	**Status:**	Approved
Title:	Continued access to etravirine in treatment experienced HIV-1 infected subjects.				
Trial No:	TMC125-TiDP35-C239			**Clinical phase:**	N/A

Summary:

This is a continued access trial for subjects who have completed treatment in a clinical (parent) trial with etravirine sponsored by or in collaboration with Janssen Research & Development and who continue to benefit from the use of etravirine.

At the baseline visit, inclusion/exclusion criteria will be checked to confirm eligibility. Once eligibility criteria are met, subjects will either continue on the etravirine dose they have received in the previous etravirine (parent) trial or on an adjusted dose if deemed necessary by the investigator. For pediatric subjects, etravirine dose adjustment will be based on weight using the dosing guidelines provided.

Assessment visits are recommended according to local generally accepted standard of care, but not less frequent than every three and six months for pediatric and adult subjects respectively. Adverse events leading to treatment interruption or discontinuation, adverse events at least possibly related to treatment with etravirine, serious adverse events (SAEs), and pregnancies are to be recorded at each visit. In addition to the assessments described in the flowchart, additional assessments not included in this protocol can be done locally at the investigator's discretion as per local standard of care.

As per Protocol Amendment 3:
For ongoing subjects, the next planned visit will be a Final/Withdrawal Visit, which will be the last visit with data collection. For new subjects that rollover from (parent) trial TMC125-C234 (IMPAACT P1090), the next planned visit will be a

For European Submissions the EudraCT number is: 2009-013126-16

GCP STATEMENT

This trial will be conducted in compliance with this protocol, Good Clinical Practices and applicable regulatory requirements.

	Baseline Visit which will be performed per local standard of care and documented in the subject's medical records only. For all new and ongoing subjects, 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 etravirine and pregnancies to the sponsor using regular pharmacovigilance reporting. This information will only be entered in the company safety repository. For all new and ongoing subjects, 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: the investigator determines that the subject no longer benefits from etravirine treatment (e.g., based on viral load); treatment limiting toxicity; loss to follow-up; patient withdrawal of consent; pregnancy; termination of the program by the sponsor; an etravirine-based treatment regimen becomes commercially available for the subject's indication 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 Form/Assent
Site address:	See local Informed Consent Form/Assent
Sponsor:	Janssen Research & Development[*]
Treatment:	Subjects will continue to receive etravirine until an etravirine-based treatment regimen becomes commercially available for the subject's indication and is reimbursed, or can be accessed from another source (e.g. access program, government program) or subjects can be switched 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; 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[a] TMC125-TiDP35-C239			
Document Type and *File Name*	**Document Identification**	**Amendment Type**	**Comments**
Initial Clinical Trial Protocol *TMC125-TiDP35-C239-CTP*	0313504 07-Jul-2009		
CTP Amendment I *TMC125-TiDP35-C239-CTPA-GEN-I*	18-Aug-2011	Non-Substantial	
First Revised Clinical Trial Protocol *TMC125-TiDP35-C239-CTP-v2*	18-Aug-2011		Integrates the Initial Clinical Trial Protocol and CTP Amendment I
CTP Amendment II *TMC125-TiDP35-C239-CTPA-GEN-II*	28-Oct-2016	Non-Substantial	For details, refer to Amendment GEN-II
CTP Amendment III *TMC125-TiDP35-C239-CTPA-GEN-III*	**This document**	**Substantial**	**For details, refer to Amendment GEN-III**

[a] This overview lists general amendments to the protocol only. Site and country specific amendments to the protocol are not included.

TABLE OF CONTENTS

PROTOCOL AMENDMENTS

Amendment GEN-III (This document)

The overall reason for the amendment: The aim of this roll-over study is to provide continued access to etravirine (ETR) for adult and pediatric subjects who continue to benefit from the use of ETR and who live in a country where ETR 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.

ETR is approved since 2008 in adults and since 2012 in children as of the age of 6 years and has a well-established safety profile. The collection of additional data in Study TMC125-C239 is unlikely to provide substantial additional information on ETR or to impact the risk-benefit assessment. The TMC125-C239 is a roll-over study that has been ongoing since December 2009 and provides already substantial long-term safety information on ETR. The parent trials TMC125-C206 and TMC125-C216 (in adults) ended in August 2008, after which the subjects were able to roll-over in the TMC125-C217 trial and subsequently into this roll-over study. Parent trial TMC125-C213 (in subjects aged 6 to 18 years) ended in August 2011. The parent trial TMC125-C234 (or IMPAACT trial P1090), conducted in subjects aged 1 to 5 years, is still ongoing and subjects still in this trial are expected to roll-over to Study TMC125-C239. By the time of entry in Study TMC215-C239, most of these subjects will have completed 48 weeks of ETR treatment plus an additional few years (up till 5 years) of follow-up in the parent trial. Hence, the subjects from Study TMC125-C239 have been on ETR for a significant amount of time. Therefore, the long-term safety of ETR 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, ETR will continue to be provided through this study until the subject can be switched to locally available ETR-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.

Furthermore, subjects aged 2 years and older are allowed to roll-over from parent trial TMC125-C234 and dosing instructions are added for pediatric subjects receiving another dose than provided in the dosing chart.

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-III amendment and all applicable sections.

Rationale: The long-term safety of ETR has been established in patients aged 6 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 Case Report Form (CRF). The information that will continue to be collected consists of serious adverse events (SAEs) possibly related to etravirine 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 ETR.

PART I:2 Flowchart

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 I:5.3.10 Adherence

PART I:5.4.1 Timing of Assessments

PART I:5.4.3 Safety

PART I:5.5 Safety Management Guidelines for Cutaneous Events

PART I:5.6 Toxicity Management for Specific Adverse Events With Concomitant Antiretrovirals

PART II:1.3 HIV-Related Events or Outcomes

PART II:1.4 Reporting of Adverse 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, ETR will continue to be provided through this roll-over study until the subject can be switched to locally available ETR-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:4 Trial Objectives

PART I:5.1.1 Overview of Trial

PART I:5.2.5 Removal of Subjects From Therapy or Assessment

PART II:2 Trial Closure Considerations

Rationale: Inclusion criterion 2 was modified to allow subjects older than 2 years to participate in this roll-over study. Furthermore, dosing instructions were added for pediatric subjects rolling-over from parent trial TMC125-234 who are receiving another dose than the doses provided in the pediatric dosing chart.

PART I:5.2.2 Inclusion Criteria

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

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

PART I:5.2.4 Prohibitions and Restrictions

PART I:5.3.11 Prior and Concomitant Therapy

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

PART I:5.3.8 Drug Accountability

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. Furthermore, the information on the statistical analysis was adapted based on the definition of pediatric and adult subjects.

PART I:5.7.3 Statistical Analysis

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: Adherence counseling was added to flowchart 1 to align with the information on adherence included in Section 5.3.10.

PART I:2 Flowchart

Rationale: The introduction section was updated and shortened.

PART I:3 Introduction

Rationale: The legal entity Janssen, Inc was replaced by Janssen Pharmaceutica NV, Janssen, Inc and 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-II (28-Oct-2016)

This amendment is considered non-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 name of the sponsor of the trial changed from 'Tibotec Pharmaceuticals' to 'Janssen Research & Development' because of the transition of the Johnson & Johnson Research & Development companies to a unified Janssen identity, as of 2 February 2012.

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

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

Title Page: Sponsor

PART I:3.2 Aim of the Study

PART I:4.1 Primary Objective

PART I:5.1.1 Overview of Trial

PART I:5.2.2 Inclusion Criteria

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 Individually Optimized Background Regimen/Underlying Antiretroviral Therapy

PART I:5.3.5 Packaging and Labeling

PART I:5.3.11.1 Disallowed Non-ARV Medication

PART I:5.3.11.2 Disallowed ARV Medication

PART I:5.4.1 Timing of Assessments

PART I:5.5.1 Rash Management

PART I:5.7.1 Sample Size Calculation

PART I:7.2 Addendum 2: DAIDS Grading Table

PART II:1.4 Reporting of Adverse 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 study is provided on the contact information page.

Title Page: Sponsor Footer

PART I: CLINICAL TRIAL PROTOCOL

1 LIST OF ABBREVIATONS AND DEFINITION OF TERMS

1.1 List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
ART	antiretroviral therapy
ARV	anti-retroviral
AST	aspartate aminotransferase
b.i.d.	bis in die (twice daily)
CCR5	chemokine (C-C motif) receptor 5
CPK	creatine phosphokinase
CRF	Case Report Form
CSR	Clinical Study Report
DAPY	diarylpirimidine
DNA	deoxyribonucleic acid
DRV	darunavir
EFV	efavirenz
ENF	enfuvirtide
ETR	etravirine (formerly known as TMC125)
GCP	Good Clinical Practice
HDL	high densitiy lipoprotein
HIV-1(2)	human immunodeficiency virus – type 1 (type 2)
HPMC	hydroxypropylmethylcellulose
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
ICF	Informed Consent Form
INR	international normalized ratio
IRB	Institutional Review Board
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LPV	lopinavir
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
NVP	nevirapine
OBR	optimized background regimen
PI	protease inhibitor
PK	Pharmacokinetic(s)
QA	Quality Assurance
QC	Quality Control

RAL	raltegravir
RAM	resistance-associated mutation
RBC	red blood cell
RNA	ribonucleic acid
RT	reverse transcriptase
SAE	serious adverse event
SJS	Stevens-Johnson Syndrome
SQV	saquinavir
TEN	toxic epidermal necrolysis
TLOVR	time to loss of virologic response
ULN	upper limit of normal
VL	viral load
WBC	white blood cell
WT	wild type

1.2 Definition of Terms

Pediatric subjects	subjects who are at age < 18 years old at the Baseline Visit in this trial
Adult subjects	subjects who are at age ≥ 18 years old at the Baseline Visit in this trial

2 FLOWCHART

2.1 Flowchart 1: Trial Follow-up

Up to and including Protocol Amendment 2:

Type of Visit	Baseline[a]	Treatment period			Follow-up visit[b]
Time of Visit	**Day 1**	**Every 3 months for pediatric subjects**	**Every 6 months for adult subjects**	**Final / Withdrawal visit[c,i]**	**4 weeks after withdrawal**
Informed Consent/Assent[g]	X			X[j]	
Demographic data[d]	X				
Height[h], Tanner staging[h]	X			X	
Weight	X	X	X		
Urine pregnancy test, if applicable[e]	X	X	X	X	
Inclusion/exclusion criteria	X				
Dispensation of investigational medication	X	X	X	X[j]	
Drug accountability		X	X	X	
Adherence Counseling	X	X	X	X[j]	
Collection of the following AEs[f]: **- AEs considered to be at least possibly related to ETR;** **- AEs leading to discontinuations or treatment interruption;** **- SAEs and pregnancies**	X	X	X	X	X

[a] Subject will rollover from another (parent) trial. 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.
[b] Only for subjects who drop out of the study due to the occurrence of a (S)AE.
[c] Any AE event ongoing at the end of treatment should be followed up until satisfactory clinical resolution or stabilization at the investigator's discretion, according to the local standard of care.
[d] Including Subject ID from parent trial.
[e] Urine pregnancy test for females of childbearing potential only.
[f] Other AEs will only be collected if required per local regulations.
[g] Informed assent only applicable to pediatric subjects.
[h] Only applicable to pediatric subjects.
[i] 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 3. For subjects continuing the trial under Protocol Amendment 3, 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.
[j] Only applicable for subjects continuing the trial under Protocol Amendment 3.

2.2 Flowchart 2: Simplified Trial Follow-up

As of Protocol Amendment 3:

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

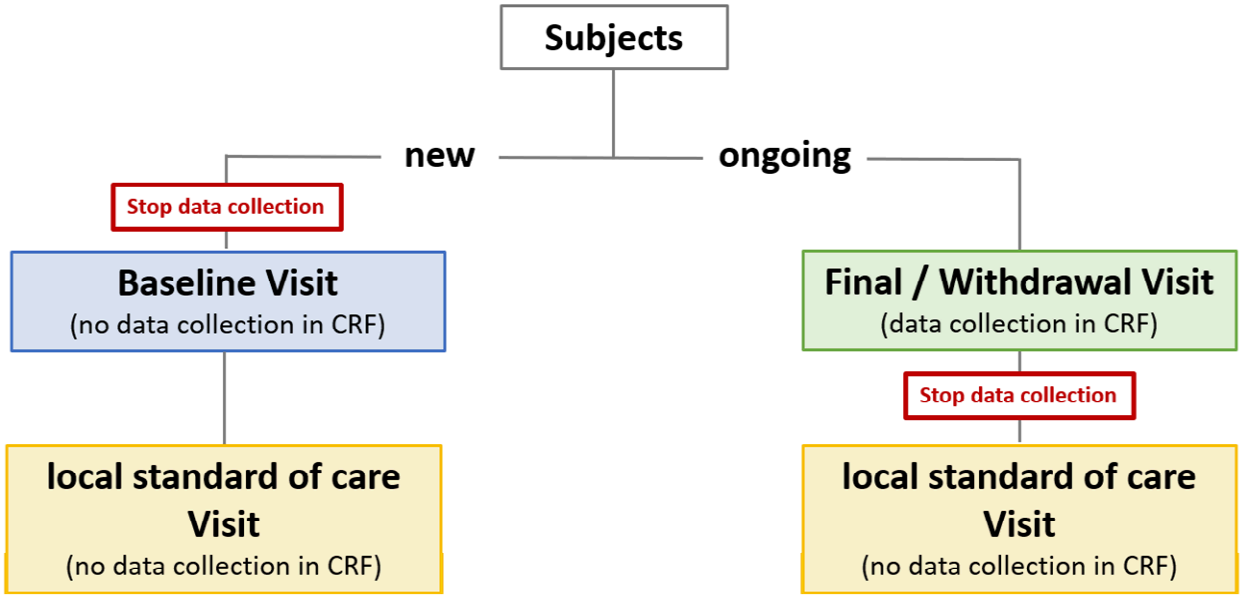
[a] For new subjects that roll-over from (parent) trial TMC125-C234 (IMPAACT P1090). The Baseline Visit will coincide with the last visit of the previous trial.
[b] The next planned visit for ongoing subjects before switching to simplified data collection as per Protocol Amendment 3 will be a Final/Withdrawal 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.
[c] Informed assent only applicable to pediatric subjects coming from (parent) trial TMC125-C234.
[d] Investigators will continue to report SAEs possibly related to ETR and pregnancies to the sponsor using regular pharmacovigilance reporting.
[e] 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.
[f] If the subject exits the trial, the last visit will be a local standard of care visit but without dispensation of investigational medication.

For ongoing subjects, the next planned visit after approval of amendment 3 will be a Final/Withdrawal Visit (Figure 1). 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. For new subjects that roll-over from (parent) trial TMC125-C234 (IMPAACT P1090) after approval of amendment 3, the next planned visit will be a Baseline Visit (Figure 1). During this Baseline Visit, the informed consent will be signed and assessments will be performed per local standard of care and documented in the subject's medical records only.

For all new and ongoing subjects, 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 ETR and pregnancies to the sponsor using regular pharmacovigilance reporting. This information will only be entered in the company safety repository.

For all new and ongoing subjects, if the subject exits the trial, the last visit will be a local standard of care visit but without dispensation of investigational medication.

Figure 1: Study Schematic



3 INTRODUCTION

Over the past decade, drugs for the treatment of human immunodeficiency virus (HIV) disease have been introduced sequentially for use in the clinic. As a consequence, a fraction of the HIV-infected population currently living in North America and Europe has been exposed serially to a variety of anti-HIV drugs and has developed resistance to these drugs. Resistance to antiretroviral (ARV) agents is a major reason for therapy failure. Based on their mechanism of action, six different classes of anti-HIV compounds exist. The following have been approved for the treatment of adult HIV infection so far: nucleo(side)/(tide) reverse transcriptase inhibitors (NRTIs/NtRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), a fusion inhibitor, an integrase strand transfer inhibitor and a chemokine (C-C motif) receptor 5 (CCR5) antagonist.

Etravirine (ETR, also known as TMC125) is a diarylpyrimidine (DAPY) NNRTI, which has high intrinsic activity, not only against wild type (WT) HIV-1, but also against strains harboring NNRTI and other resistance-associated mutations (RAMs). In addition, ETR was shown to have an increased genetic barrier to the development of resistance as compared to first generation NNRTIs.

ETR received accelerated approval in the US in January 2008, and has obtained conditional marketing authorization in Europe in August 2008 for the treatment of HIV-1 infection in ARV treatment-experienced adult patients. At the time of protocol writing, registration procedures are ongoing worldwide, and additional approvals in several regions have been obtained.

Based on the current edition of the IB[1], 64 Phase I trials (58 trials in healthy subjects and 6 trials in HIV-1 infected subjects) have been completed to assess the safety, tolerability, and pharmacokinetics of ETR. A total of 1,281 healthy adults, 145 HIV-1 infected adults and 35 HIV-1 infected children were included in these trials. Three proof-of-principle Phase IIa trials, in which 48 HIV-1 infected subjects received ETR, were conducted and reported.

Seven Phase IIb studies (TMC125-C203, -C209, -C223, -C227, -C211, -C229, and -C238 [TEACH]) were completed, in which a total of 486 HIV-1 infected subjects were treated with ETR. In the 2 completed Phase III studies TMC125-C206 and TMC125-C216 (DUET 1 and 2) 599 HIV-1 infected subjects were treated with ETR. The roll-over Phase III study (TMC125-C217) for subjects from the DUET studies who had failed multiple regimens and had limited treatment options left, has also been completed. In total, 503 subjects were treated with ETR in this roll-over study, including 256 ETR treatment-naïve subjects, who were previously treated with DRV + OBR in the placebo arm of the DUET studies, and 247 ETR treatment-experienced subjects, who were previously treated with ETR + DRV + OBR in the ETR arm of the DUET studies. One Phase 4 study TMC125IFD3002 (VIOLIN) is completed.

One Phase II study TMC125-C213 (PIANO) in children as of 6 years of age and adolescents has been completed, in which 101 subjects were treated with ETR. One Phase I/II study TMC125-C234 (IMPAACT P1090) in 26 HIV-1 infected children aged ≥1 year to <6 years is ongoing.

The Early Access Program, TMC125-C214, aimed to provide access of ETR to HIV-1 infected subjects who had failed multiple ARV regimens and who had limited treatment options. In total, 5,178 subjects have been treated with ETR in this program, which is now completed. For detailed and updated information on the clinical trial data, refer to the most recent Investigator's Brochure (IB) of ETR.[1]

3.1 Aim of the Study

The aim of the study is to provide continuous access to ETR for subjects who have completed a clinical study with ETR sponsored by or in collaboration with Janssen Research & Development.

4 TRIAL OBJECTIVES

4.1 Primary Objective

The primary objective is to continue the provision of ETR for subjects who previously received ETR in a clinical (parent) trial sponsored by or in collaboration with Janssen Research & Development, and who continue to benefit from the use of ETR, in countries where ETR is not commercially available for the subject’s indication, is not reimbursed, and cannot be accessed through another source (e.g. access program or government program), or where the subject is not eligible for ongoing trials/programs with ETR.

Protocol Amendment 3 Objective:

As of Protocol Amendment 3, the objective of the trial is to provide ETR through this trial until the subjects can be switched to locally available ETR-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 subjects who have completed treatment in a clinical (parent) trial with ETR sponsored by or in collaboration with Janssen Research & Development, and who continue to benefit from the use of ETR.

At the baseline visit, inclusion/exclusion criteria will be checked to confirm eligibility. Once eligibility criteria are met, subjects will either continue on the ETR dose they have received in the previous ETR (parent) trial or on an adjusted dose if deemed necessary by the investigator. For pediatric subjects, ETR dose adjustment will be based on weight using the dosing guidelines provided.

Assessment visits are recommended according to local generally accepted standard of care, but not less frequent than every three and six months for pediatric and adult subjects respectively. Adverse events leading to discontinuation or treatment interruption, adverse events at least possibly related to treatment with ETR, serious adverse events, and pregnancies are to be recorded at each visit. In addition to the assessments described in the flowchart, additional assessments not included in this protocol can be done locally at the investigator's discretion as per local standard of care.

As per Protocol Amendment 3:

For ongoing subjects, the next planned visit will be a Final/Withdrawal Visit, which will be the last visit with data collection. For new subjects that roll-over from (parent) trial TMC125-C234 (IMPAACT P1090), the next planned visit will be a Baseline Visit which will be performed per local standard of care and documented in the subject's medical records only.

For all new and ongoing subjects, 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 ETR and pregnancies to the sponsor using regular pharmacovigilance reporting. This information will only be entered in the company safety repository.

For all new and ongoing subjects, 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: the investigator determines that the subject no longer benefits from ETR treatment (e.g., based on viral load); treatment limiting toxicity; loss to follow-up; patient withdrawal of consent; pregnancy; termination of the program by the sponsor; an ETR-based treatment regimen becomes commercially available for the subject's indication 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.

Details on the timing of the treatment and assessments are given in the flowchart (see Section 2).

5.1.2 DISCUSSION OF TRIAL DESIGN

The primary objective of the trial is to continue to provide ETR to subjects who previously received ETR in a clinical (parent) trial and continue to benefit from the use of ETR, in countries where ETR is not commercially available for the subject's indication, is not reimbursed, and cannot be accessed through another source (e.g. access program or government program), or where the subject is not eligible for ongoing trials/programs with ETR.

Selected safety data are to be collected while on treatment with ETR (see Section 5.4.3). Additional assessments not included in this protocol can be done locally at the investigator's discretion as per local standard of care.

As per Protocol Amendment 3:

For ongoing subjects, the next planned visit will be a Final/Withdrawal Visit, which will be the last visit with data collection. For new subjects that roll-over from (parent) trial TMC125-C234 (IMPAACT P1090), the next planned visit will be a Baseline Visit which will be performed per local standard of care and documented in the subject's medical records only.

For all new and ongoing subjects, all subsequent visits and assessments will be performed per local standard of care and documented in the subject's medical records only. Serious Adverse Events (SAEs) possibly related to ETR 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.

For all new and ongoing subjects, 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

The subject will continue on his/her current ETR dosage as received in the previous ETR (parent) trial, with weight-based dose adjustment for pediatric subjects if necessary.

5.2 Trial Population

5.2.1 SAMPLE SIZE

No formal sample size calculation is done.

Subjects who completed treatment in a clinical study with ETR, and continue to benefit from the use of ETR, may be eligible to continue ETR via this trial.

5.2.2 INCLUSION CRITERIA

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

1. Subjects with documented HIV-1 infection.
2. Criterion modified per Amendment 3

2.1. Male or female subjects, aged 2 years and older.

3. Subject has successfully completed a clinical (parent) trial with ETR sponsored by or in collaboration with Janssen Research & Development, and continues to receive benefit from the use of ETR.
4. Adult has voluntarily signed the Informed Consent Form (ICF). Pediatric subject (where appropriate, depending on age) and their parent(s) or legal representative(s) have signed the ICF/Assent voluntarily. Children will be informed about the program and asked to give assent (where appropriate, depending on age).
5. Negative urine pregnancy test for females of childbearing potential.

5.2.3 EXCLUSION CRITERIA

Subjects meeting one 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 ETR.
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 ETR.
3. Previously demonstrated clinically significant allergy or hypersensitivity to ETR or to any of the excipients of ETR.
4. Pregnant or breastfeeding female subject.
5. Non-vasectomized heterosexually active males not using safe and effective birth control methods (see Section 5.2.4), 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 the last intake of the investigational medication).
6. Females, who are sexually active and able to become pregnant, not using safe and effective birth control methods (see Section 5.2.4), 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 the last intake of the investigational medication).

5.2.4 PROHIBITIONS AND RESTRICTIONS

It is the investigator's responsibility to provide appropriate counseling about precautions to avoid the risk of transmitting HIV. All HIV-infected subjects are advised to use a condom during intercourse to reduce the risk of transmitting HIV.

Since the effect of ETR on gestation is unknown, sexually active males, or females who are sexually active and of child-bearing potential, should receive counseling about birth control methods. They must either practice sexual abstinence during the trial, or use a safe and effective birth control method such as a double barrier method of contraception (i.e., using a condom with diaphragm or cervical cap) or hormone-based contraceptives in combination with a barrier contraceptive (i.e., male condom, diaphragm or cervical cap or female condom) during the trial. It is advised not to use a male and female condom together due to risk of breakage or damage as a result of latex friction.

Women should not breastfeed when taking ETR, as the effects to their newborn child are unknown. Women 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.

These precautions apply from Baseline onwards, until 1 month after the last intake of investigational medication.

For details on the existing data with regard to the reproductive toxicity of ETR, please refer to the current IB[1].

Investigators should follow the guidance in the most recent IB[1] regarding any contraindications, precautions for use, and other restrictions.

5.2.5 REMOVAL OF SUBJECTS FROM THERAPY OR ASSESSMENT

Subjects **may** be withdrawn from the trial if:

1. a SAE occurs;
2. they fail to comply with the protocol requirements or to cooperate with the investigator;
3. a grade 3 AE (with the exception of skin events / allergic reaction) occurs according to the DAIDS grading scale. Exceptions (unless clinical assessment foresees an immediate health risk to the subject) are:
   - subjects with pre-existing diabetes who experience a glucose elevation of grade 3;
   - subjects who experience a glucose, triglyceride or cholesterol elevation of grade 3 under non-fasted conditions;
   - subjects who experience asymptomatic glucose, triglyceride or cholesterol elevations of grade 3;
   - subjects who experience asymptomatic pancreatic amylase elevations of grade 3 with no past or active history of pancreatitis;
   - subjects who experience a grade 3 AE that is considered not related or doubtfully related to the study medication;
   - subjects who experience grade 3 absolute neutrophil count or asymptomatic grade 3 platelets.

Subjects **must** be withdrawn from the trial if:

1. the parent(s) or legal representative(s) withdraws consent for a pediatric subject, or the subject withdraws consent or assent;
2. the investigator considers, for safety reasons, it is in the best interest of the subject that he or she is withdrawn;
3. they experience a grade 4 AE or grade 4 laboratory toxicity considered at least possibly related to ETR by the investigator;
4. they experience a grade 3 or higher rash;
5. they experience a grade 3 or higher allergic reaction;

6. they develop clinical hepatitis;
7. pregnancy has been determined.
8. they can be switched to locally available ETR-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.

The date and the reason for discontinuation must be noted on the Case Report Form (CRF). If consent/assent is not withdrawn, all subjects prematurely discontinuing the trial must be seen for a follow-up visit, if they are not continuing treatment with ETR. The Trial Termination Section of the CRF is to be completed.

As per Protocol Amendment 3, 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 will be provided under the responsibility of the sponsor.

ETR is formulated as an oral tablet containing 100 mg (formulation F060) or 25 mg (formulation F066) ETR base, in combination with hypromellose and microcrystalline cellulose, colloidal anhydrous silica, croscarmellose sodium, magnesium stearate, and lactose monohydrate. Adults will only be using the 100-mg tablet.

5.3.2 Other Medication Administered in the Trial

The subjects will receive the investigator-selected OBR medications according to locally applicable procedures. If they are not available commercially, the sponsor will provide ARVs which were provided by the sponsor in the previous (parent) trial until the end of the subject's participation in the TMC125-C239 trial if these drugs are selected in the OBR based on the resistance profile. In regions where these ARVs are approved for the subject's indication, reimbursed, and available via the health care system, or can be accessed through another source (e.g. access program, government program), subjects should use commercial supplies.

5.3.3 Dosage(s) and Treatment Overview per Subject

Subjects will be instructed to take ETR following a meal, twice daily.

Adult subjects will receive a dose of ETR 200 mg b.i.d..

Pediatric subjects will receive ETR, dosed as they have received in the previous ETR (parent) trial, with weight-based dose adjustment if necessary.

A pediatric ETR Dosing Chart is depicted in Table 1 and only provides dosing instructions for pediatric subjects of 6 years and older. Subjects coming from the parent trial TMC125-C234 (IMPAACT P1090) and who received another dose than indicated in Table 1, may continue on the parent trial dose with weight-based dose adjustment as necessary (to be discussed with the sponsor).

Table 1: ETR Dosing Chart (Pediatric subjects only)

Weight	Dose	Tablets
10 to < 20 kg	100 mg b.i.d.	4 tablets 25 mg b.i.d. or 1 tablet 100 mg b.i.d.
20 to < 25 kg	125 mg b.i.d.	5 tablets 25 mg b.i.d. or 1 tablet 100 mg + 1 tablet 25 mg b.i.d.
25 to < 30 kg	150 mg b.i.d.	6 tablets 25 mg b.i.d. or 1 tablet 100 mg + 2 tablets 25 mg b.i.d.
≥ 30 kg	200 mg b.i.d.	8 tablets 25 mg b.i.d. or 2 tablets 100 mg b.i.d.

Tablets should be swallowed whole with a sufficient amount of water, fruit juice (with the exception of grapefruit juice), or milk. Subjects unable to swallow the tablets may disperse the tablets in a glass with a minimum of 5 mL of water. One minute should be allowed for the tablet to be dispersed. Once dispersed, subjects should stir the dispersion well and drink it immediately. The glass should be rinsed with a minimum of 5 mL of water, fruit juice (with the exception of grapefruit juice), milk or infant formula and the rinse completely swallowed to ensure the entire dose is consumed. This step may be repeated as needed. The dispersion should always be used immediately after preparation and the use of warm (>40°C) or carbonated beverages should be avoided. The dispersion should be consumed completely.

If a subject, parent(s) or legal representative(s) notices that the subject missed an investigational medication intake, and this is discovered within 6 hours of the time it is usually taken, the subject is advised to take the missed dose as soon as possible, with food. The subject may then continue his/her usual dosing schedule afterwards.

If a subject, parent(s) or legal representative(s) notices that the subject missed an investigational medication intake, and this is discovered more than 6 hours after the time it is usually taken, the subject is advised not to take the missed dose and simply resume the usual dosing schedule.

Other ARVs in the OBR should be administered according to their individual package inserts for those drugs that are labeled for the subject's indication or by the sponsor-approved dosing and administration for those drugs that are not labeled for the subject's indication.

5.3.4 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. An overview of the allowed and disallowed ARVs for pediatric subjects is provided in Table 2. It is recommended that the regimen consists of at least 2 active ARV drugs (not including low-dose rtv), including a boosted PI (either LPV, DRV, ATV or saquinavir [SQV]) in combination with N(t)RTI(s). Additional use of the fusion inhibitor ENF is optional.

If abacavir 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.

Investigational ARV drugs are not allowed in pediatric subjects, unless appropriate pediatric dosing guidelines are available. For pediatric subjects meeting the aforementioned condition, and for all adults, investigational ARVs are allowed if favorable pharmacokinetic interaction and safety data exist for co-administration with ETR, and the use was discussed with and approved by the sponsor (e.g. Raltegravir [RAL] for those age groups where dosing guidelines have been established[2,3]).

Table 2 Allowed and Disallowed Antiretrovirals From Baseline and Throughout the Trial for Pediatric Subjects

ART Class	Allowed	Disallowed
PIs	LPV/rtv, DRV/rtv[4], ATV/rtv, SQV/rtv[5]	All other PIs
NRTIs	All NRTIs approved for pediatric use Tenofovir[6-7]	Investigational NRTIs or NRTIs approved in adults but not approved for pediatric use, unless dose recommendations for children are available and the use was discussed with, and approved by, the sponsor.
NNRTIs	ETR	NNRTIs other than ETR
FIs	ENF	-
Other Investigational ART Class - Integrase inhibitors - CCR5 inhibitors	Allowed only if appropriate pediatric dosing guidelines are available and if favorable pharmacokinetic interaction and safety data exist for co-administration with ETR and the use was discussed with and approved by the sponsor (e.g. RAL for those age groups where dosing guidelines have been established[2,3]).	All other agents are disallowed

Note: generics are allowed, but should be (tentatively) approved by the FDA

For allowed and disallowed ARVs for adult subjects refer to the IB[1].

5.3.5 PACKAGING AND LABELING

ETR will be packaged under the responsibility of the sponsor.

ETR will be labeled according to the local regulatory requirements. The labels will contain the protocol number, batch number, storage caution statements, dispensing instructions and 'Keep out of reach of children'.

5.3.6 RANDOMIZATION

Randomization is not applicable.

5.3.7 BLINDING AND UNBLINDING

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

5.3.8 DRUG ACCOUNTABILITY

The investigator, his/her designee, or the hospital pharmacist must maintain an adequate record of the receipt of the investigational medication. Dispensation and return, or destruction (if applicable) of the investigational 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.

After termination of data collection (see Figure 1), compliance check - at pill count level - 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 - at kit level - will be reviewed during the on-site monitoring visits.

5.3.9 STORAGE

All storage conditions and specific administration instructions regarding ETR will be provided to the investigator prior to drug delivery at the investigational site. Storage conditions will be mentioned on the label. At the trial site, temperature logging should be performed on a regular basis.

Access to the investigational medication should be restricted to designated trial personnel. The investigator or pharmacist will ensure accountability and appropriate storage conditions of all trial medication used.

At the subject's home, the investigational medication should be stored in the childproof containers and out of reach of younger children and pets.

At the end of the trial, all unused medication will be handled as described in Part II, Section PART II:3.1.

5.3.10 ADHERENCE

Medication adherence is critical to successful antiretroviral therapy. In addition to compromising the efficacy of the current 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[8]. Although a variety of factors have been associated with adherence, no clear predictors of either good or poor adherence have been consistently identified in children.

The investigator will discuss the importance of good compliance to the entire treatment regimen, including ETR whether taken alone or in combination with other ARVs. It is recommended that the investigator regularly assesses the individual adherence to ETR, as well as all the other ARVs used in combination. If a subject's medication intake is suggestive of inadequate adherence, the investigator should address the issues 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 (see Figure 1), 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.

5.3.11 PRIOR AND CONCOMITANT THERAPY

All non-ARVs, and all ARVs, which should not be co-administered with ETR are mentioned in Section PART I:5.3.11.1 and Section PART I:5.3.11.2. This list of disallowed medication is based on established or theoretical interactions with ETR. Investigators should refer to the current IB of ETR[1] for an up-to-date overview of disallowed medications during clinical trials with ETR.

For other ARVs to be used in the combination therapy, please consult prescribing information/package inserts and the most current IBs for those individual ARVs as other medications may also be disallowed or cautioned for use given an individual subject's specific situation.

5.3.11.1 Disallowed Non-ARV Medication

For an up to date overview of prohibited medications during trials with ETR please refer to the most current edition of the IB[1].

The following medications are not allowed from the baseline visit until the end of treatment, or withdrawal visit:

- All investigational medications or investigational vaccines, unless the use was discussed with and approved by the sponsor. An additional requirement for pediatric subjects is the availability of dose recommendations for children;
- Chemotherapeutic agents unless previously allowed by the sponsor;
- All disallowed medication as mentioned in the package insert of ARV drugs included in the OBR.

5.3.11.2 Disallowed ARV Medication

For allowed and disallowed ARVs, please refer to Section 5.3.4.

The following ARV drugs are not allowed from baseline onwards and throughout the trial:

- All investigational ARVs, except for emtricitabine [FTC] where this is not licensed yet in a participating country. Another exception, for pediatric subjects, are ARVs approved in adults but not approved for pediatric use, with the exception of tenofovir. Investigational ARVs will be allowed only if favourable pharmacokinetic interaction and safety data exist for co-administration with ETR and the use was discussed with and approved by the sponsor. An additional requirement for pediatric subjects is the availability of dose recommendations for children (e.g. RAL for those age groups where dosing guidelines have been established[2,3]).
- HIV vaccines;
- NNRTIs (except for ETR);
- PIs other than LPV/rtv, DRV/rtv, ATV/rtv and SQV/rtv for pediatric use. For adults refer to the IB[1].

5.4 Assessments

5.4.1 Timing of Assessments

Subjects will rollover after completion of a previous (parent) trial sponsored by or in collaboration with Janssen Research & Development. 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. Additional assessments not included in this protocol can be done locally at the investigator's discretion as per local standard of care.

As subjects roll over from a clinical (parent) trial, a urine pregnancy test is to be performed at the Baseline visit (females of childbearing potential only) and is repeated every 3 months (pediatric subjects) or every 6 months (adult subjects) thereafter.

If a subject is considered eligible after signing of the ICF/Assent, completion of the Baseline Form, and evaluation by the sponsor or its designee, the subject receives the investigational medication (ETR) at the Baseline visit.

It is recommended that subjects be evaluated every 3 months (pediatric subjects) or every 6 months (adult subjects) after starting ETR. A Final/Withdrawal Visit is to be be performed.

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

As per Protocol Amendment 3:

For ongoing subjects, the next planned visit will be a Final/Withdrawal Visit, which will be the last visit with data collection. For new subjects that roll-over from (parent) trial TMC125-C234 (IMPAACT P1090), the next planned visit will be a Baseline Visit which will be performed per local standard of care and documented in the subject's medical records only.

For all new and ongoing subjects, 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 ETR and pregnancies to the sponsor using regular pharmacovigilance reporting. This information will only be entered in the company safety repository.

For all new and ongoing subjects, if the subject exists 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 will be copied from the previous (parent) trial. **As of Protocol Amendment 3,** this information will be documented in the subject's medical records only for the subjects rolling-over from the TMC125-C234 (IMPAACT P1090) trial.

The overall eligibility of the subject to participate in the trial will be assessed.

5.4.3 Safety

Safety and toxicity monitoring is performed throughout the trial as per local standard of care.

5.4.3.1 Adverse Events/HIV-Related Events

For detailed definitions and reporting procedures of AEs refer to Section 1 in Part II of this protocol. For reported HIV events, further details will be recorded if these events are AIDS-defining illnesses (CDC category C conditions; see 7.3 Addendum 3).

For subjects experiencing specific adverse events, toxicity management should be performed as described in Section 5.5 (Rash Management, and Acute Systemic Allergic Reaction) and Section 5.6 (Hyperglycemia, Hypertriglyceridemia and Hypercholesterolemia, Lactic Acidosis, and Lipodystrophy/Fat Redistribution/Body Changes).

After termination of data collection (see Figure 1), all visits and 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 ETR and pregnancies to the sponsor using regular pharmacovigilance reporting. This information will only be entered in the company safety repository.

5.4.3.1.1 Clinical Laboratory Tests

A urine pregnancy test is to be performed every 3 months (pediatric subjects) or every 6 months (adult subjects) after starting ETR (females of childbearing potential only).

After termination of data collection (see Figure 1), clinical laboratory tests will occur according to the local standard of care and documented in the subject's medical records only.

5.5 Safety Management Guidelines for Cutaneous Events

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

After termination of data collection (see Figure 1), toxicity management will be performed per local standard of care and documented in the subject's medical records only.

Clinical data in adults have shown that ETR is generally safe and well tolerated. As rash is a known class effect with NNRTIs, cutaneous events as described below have been closely monitored in trials with ETR. Rash events with ETR are now well characterized based on the large safety dataset from our double-blind placebo-controlled trials. This section describes the guidelines for management of rash and acute allergic reactions.

In general, all other AEs that are ongoing at the end of the treatment period should be followed up until satisfactory clinical resolution or stabilization at the investigator's discretion as per the local standard clinical practice.

5.5.1 RASH MANAGEMENT

Rash

In case of rash, visits and assessments should be performed as described below and in the "Visit Schedule for Rash Management in Pediatric Patients" (see Section 7.4, Attachment 4) and "Visit Schedule for Rash Management in Adult Patients" (see Section 7.5, Attachment 5). Unscheduled follow-up visits for close follow-up of rash will be performed based on the grade (severity) of the rash. At the investigator's discretion, additional visits and assessments can be performed.

Dermatologist fees for evaluating subjects who experience a rash will be reimbursed by the sponsor.

The following grades are based on the DAIDS grading table (see Section 7.2, Attachment 2), with adaptations made by the sponsor.

Subjects (and/or their legally acceptable representative) should be informed that they should contact their doctor and visit the clinic immediately when they notice any rash.

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 2 rash or cutaneous event 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 AEs will be at the discretion of the investigator, however, close clinical follow-up is recommended to monitor for any progression of the AE.

Grade 3 or 4 Cutaneous Reaction/Rash

A grade 3 cutaneous reaction/rash is defined as:

- Diffuse macular, maculo-papular, or morbilliform rash with vesicles or limited number of bullae
- Superficial ulceration of mucous membrane limited to 1 site
- Cutaneous reaction/rash with at least 1 of the following*:
    1. elevations of ALT/AST > 2 x baseline but at least 5 x ULN*
    2. fever ≥ 38°C or 100 F*
    3. serum sickness-like reaction*
    4. eosinophil count > 1000/mm³*.

** added 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).

Subjects experiencing a grade 3 or 4 rash or cutaneous event must have their trial medication discontinued and be withdrawn from the trial. Referral to a dermatologist is recommended for these events. Local safety sampling to determine determine possible liver or systemic abnormalities is recommended. Close clinical follow-up and appropriate medical intervention is recommended for these events; daily follow-up is recommended for 5 days from the onset of the event to monitor for progression of the event.

5.5.2 ACUTE SYSTEMIC ALLERGIC REACTION

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

Subjects may continue the investigational 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 localized urticaria, 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 or the (dis)allowed medications for ETR as indicated above.

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

Subjects may continue the investigational medication for a grade 2 acute systemic allergic reaction. If there is any worsening of the acute systemic allergic reaction, the subject should be advised to contact the investigator immediately and to discontinue the investigational 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 or the (dis)allowed medications for ETR as indicated above.

Grade 3 (generalized urticaria, or angioedema with medical intervention indicated, or symptomatic mild bronchospasm) and grade 4 (acute anaphylaxis, or life-threatening bronchospasm, or laryngeal edema):

Subjects will permanently discontinue trial medication and be withdrawn from the trial. Rechallenge with ETR is not allowed. Subjects will be treated as clinically appropriate. Standard management should be undertaken.

5.6 Toxicity Management for Specific Adverse Events With Concomitant Antiretrovirals

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 (see Figure 1), 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 following AEs are caused by concomitant ARVs alone, but may also be due to ETR.)

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)

If elevated glucose levels are from a non-fasting blood draw, repeat the draw after a 10-hour fast. Management decisions must be based on fasted results. Subjects who experience asymptomatic glucose elevations of grade 3 or 4 and subjects with pre-existing diabetes may continue trial medication unless clinical assessment foresees an immediate health risk to the subject. 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.

5.6.2 HYPERTRIGLYCERIDEMIA AND HYPERCHOLESTEROLEMIA

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

Management decisions should be based on fasted results. If elevated triglyceride or cholesterol levels are from a non-fasting blood draw, repeat the draw after a 10-hour fast. Subjects who experienced asymptomatic triglyceride elevations of grade 3 or 4 or cholesterol elevations of grade 3 may continue to receive trial medication.

Hypertriglyceridemia and hypercholesterolemia should be treated according to the specific guidelines for treating HIV-infected subjects. Appropriate clinical management of dyslipidemia in the setting of HIV disease should be started in a timely fashion. Investigators may choose to initiate pharmacologic treatment in addition to the usual counseling on diet and exercise. Medications should be introduced with caution. Lovastatin and simvastatin are not allowed as there is the potential for a significant drug interaction with PIs (ATV/rtv).

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 N(t)RTI therapy. This syndrome is felt to be secondary to mitochondrial toxicity induced by the inhibitory effect of N(t)RTIs on DNA polymerase gamma, a key enzyme needed for mitochondrial DNA synthesis. Current knowledge regarding this syndrome is incomplete. Obesity and prolonged N(t)RTI exposure may be risk factors. Women are also at greater risk. Symptoms of lactic acidosis are frequently non-specific such as fatigue, weakness, and fever, but in the majority of cases also include 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. N(t)RTI 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 mellitus, uremia, liver disease, infections, malignancies, alkaloses, and drug and toxin ingestion of such substances as ethanol, methanol, ethylene glycol, and salicylates.

The following case definition of lactic acidosis, defined differently for symptomatic vs asymptomatic individuals, 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 ALT or AST;
- unexplained fatigue;
- dyspnea;

AND

- lactate level > 2 x ULN confirmed by repeat lactate level analysis.

Note: All lactates > 2 x 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 x ULN) in subjects with symptoms as described above, subjects should immediately discontinue their current trial regimen (including ETR and other ARVs) and be withdrawn from the trial. Standard management should be initiated with follow-up to resolution.

Processing of the lactate needs to be done according to strict guidelines both in the preparation of the subject (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

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

Children can be considered to have abnormal fat accumulation if they had one or more of the following signs:

1. Trunk with increased abdominal girth;
2. Dorso-cervix with fat accumulation ‘buffalo hump’;
3. Breast enlargement.

Children can be considered to have lipoatrophy if they had one or more of the following signs:

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

Investigators should avoid using the term "lipodystrophy acquired" to describe and report fat redistribution abnormalities associated with ART as this term is not very descriptive. The different symptoms and gradings are listed in the DAIDS grading table under Endocrine/Metabolic. 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 AE reporting.

5.6.5 PANCREATITIS

Pancreatitis, which has been fatal in some cases, is a major clinical toxicity associated with ddI (with or without concomitant administration of TDF) and/or stavudine (d4T) therapy and has been reported with other ARVs. Pancreatitis must be considered whenever a subject receiving ddI (with or without concomitant administration of TDF) and/or d4T develops abdominal pain and nausea, vomiting, or elevated pancreatic amylase or lipase, and ddI (and/or TDF) and/or d4T use should be suspended until the diagnosis of pancreatitis is excluded.

Laboratory Abnormalities

For asymptomatic grade 1 and 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 confirmed grade 3 or 4 elevations of lipase, subjects should interrupt all trial medications until pancreatic amylase and/or lipase returns to grade ≤ 2, at which time trial medication could be reintroduced. N(t)RTIs such as ddI (with or without TDF) and d4T may be resumed at either reduced or full dose at the investigator's discretion. If grade 4 elevations of pancreatic amylase and/or grade 3 or 4 lipase levels persist ≥ 14 days following interruption of all trial medications, or if the toxicity recurs more than twice, all trial medications should be permanently discontinued.

5.6.6 PERIPHERAL NEUROPATHY

Subjects should be monitored for the development of peripheral neuropathy, which is usually characterized by numbness, tingling and/or pain in the feet or hands. Peripheral neuropathy is a common AE of ddI and d4T.

Treatment of the peripheral neuropathy is according to the physician, but generally begins with non-opioid analgesics, including non-steroidal anti-inflammatory agents and acetaminophen, and the use of tricyclic antidepressants and other agents when more severe symptoms are present.

5.7 Statistical Methods Planned and Determination of the Sample Size

5.7.1 Sample Size Calculation

No formal sample size calculation has been performed. The trial is not set up to show a specific statistical hypothesis but to provide ETR to subjects who previously received ETR in a clinical (parent) trial sponsored by Janssen Research & Development, and continue to benefit from the use of ETR, in countries where ETR is not commercially available to subjects, is not reimbursed, and is not accessible through another source (e.g. access program or government program), or where the subject is not eligible for ongoing trials/programs with ETR. Data from this trial may be included in Safety Updates.

5.7.2 Initial Subject and Disease Characteristics

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

5.7.3 Statistical Analysis

Data of adult and pediatric subjects will be analyzed separately. For the statistical analysis of TMC125-C239, a pediatric and adult subject will be defined as a subject who entered the current trial at age < 18 and ≥ 18 years old respectively. Final analysis will be done once all subjects have completed the Final/Withdrawal Visit. After termination of data collection in the CRF (see Figure 1), no additional statistical analysis will be performed.

5.7.3.1 Safety

The safety of ETR will be summarized in terms of:

- Mortality
- All SAEs
- AEs leading to discontinuation
- AEs possibly related to ETR treatment

The number of and causes of deaths will be summarized.

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

5.7.3.2 (S)AEs

From the collected (S)AE data in TMC125-C239, the following events will be subject to additional analysis:

- Skin
- Cardiac
- Hepatobilliary
- Neuropsychiatric

5.8 Data Quality Assurance

See Data Quality Assurance (PART II:8)

6 REFERENCES

1. TMC125-Etravirine, Investigator's Brochure, Edition 20, November 2018.
2. Nachman S. et al. Raltegravir (RAL) pharmacokinetics (PK) and safety in adolescents: preliminary results from IMPAACT P1066. ICAAC/IDSA 2008; abstract H-4059a.
3. Nachman S et al. Pharmacokinetic (PK), safety and efficacy data on cohort IIA; youth aged 6-11 from IMPAACT P1066: A Phase I/II study to evaluate raltegravir (RAL) in HIV-1 infected youth. CROI 2010; abstract 873.
4. Spinosa-Guzman S, Vangeneugden T, Sekar V, Dierynck I. A Phase II, open-label trial, to investigate pharmacokinetics, safety, tolerability and antiviral activity of TMC114/rtv b.i.d. in treatment-experienced HIV-1 infected children and adolescents - Analysis with cut-off date of 10 April 2008, at which time all subjects had reached Week 48 or discontinued before. Tibotec Pharmaceuticals, Clinical Research Report TMC114-C212, January 2009.
5. Grub S, DeLora P, Lüdin E et al. Pharmacokinetics and pharmacodynamics of saquinavir in pediatric patients with human immunodeficiency virus infection. Clin Pharmacol Ther 2002;71:122-30.
6. Hazra R, Balis FM, Tullio AN, et al. Single-dose and steady-state pharmacokinetics of tenofovir DF in HIV-infected children. Antimicrob Agents Chemother.2004;48(1):124-129.
7. Ramos JT, Gonzalez-Tome MI, Rojo P, Fernandez-Ibieta M, Vargas C, Garcia L. Experience with tenofovir disoproxil fumarate (TDF) in heavily pretreated HIV infected children [poster]. Paper presented at: XV International AIDS Conference; July 11-16, 2004; Bangkok, Thailand.
8. Rimsza ME. Counseling the adolescent about contraception. Pediatrics in Review 2003; 24: 162-170.

7 ADDENDA

7.1 Addendum 1: Trial Contact Persons

An up-to-date version of the contact details of sponsor, central laboratories and other 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 AE could fall under either one of 2 grades (e.g., the severity of an AE 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 (e.g., 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 (nonaxillary)	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 Nonurgent medical intervention indicated	Symptomatic, non-life threatening AND Nonurgent 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 nonurgent 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 postictal 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 (noninjection 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 lifethreatening 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 lifethreatening 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

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**
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.
[d] 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 (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: HIV-Related Events or Outcomes

7.3.1 CLINICAL CATEGORIES[a]

The clinical categories of HIV infection are defined as follows.

7.3.1.1 Category A

Category A consists of 1 or more of the conditions listed below in an adolescent or adult (≥ 13 years) with documented HIV infection. Conditions listed in Categories B and C must not have occurred.

- Asymptomatic HIV infection
- Persistent generalized lymphadenopathy
- Acute (primary) HIV infection with accompanying illness or history of acute HIV infection

7.3.1.2 Category B (Symptomatic Non-AIDS Conditions)

Category B consists of symptomatic conditions in an HIV-infected adolescent or adult that are not included among conditions listed in clinical Category C, 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 category B include, but are not limited to the following.

- Bacillary angiomatosis
- Candidiasis, oropharyngeal (thrush)
- Candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to therapy
- Cervical dysplasia (moderate or severe)/cervical carcinoma in situ
- Constitutional symptoms, such as fever (38.5°C) or diarrhea lasting > 1 month
- Hairy leukoplakia, oral
- Herpes zoster (shingles), involving at least 2 distinct episodes or more than one dermatome;
- Idiopathic thrombocytopenic purpura
- Listeriosis
- Pelvic inflammatory disease, particularly if complicated by tubo-ovarian absces;
- Peripheral neuropathy

For classification purposes, Category B conditions take precedence over those in Category A. For example, someone previously treated for oral or persistent vaginal candidiasis (and who has not developed a Category C disease) but who is now asymptomatic should be classified in clinical Category B.

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[a] 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.

The following list of other non-CDC HIV-associated conditions was compiled, as the CDC notes that Category B is not limited to events listed in the CDC 1993 definition.

- Aspergillosis
- Leishmaniasis
- Microsporidiosis
- Molluscum contagiosum
- Nocardiasis
- Thrombotic microangiopathy (haemolytic uremic syndrome [HUS]/thrombotic thrombocytopenia purpura [TTP])

7.3.1.3 Category C (AIDS Indicator Conditions as Defined by Diagnostic or Presumptive Measures)

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

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, oesophageal
- Cervical cancer, invasive
- Coccidiomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (> 1 month's duration)
- Cytomegalovirus disease (other than liver, spleen or nodes)
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcer(s) (> I month's duration); or bronchitis, pneumonitis, or oesophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (> 1 month's duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, or brain
- Mycobacterium avium complex or M. kansaii, disseminated or extrapulmonary
- Mycobacterium tuberculosis, any site (pulmonary or extrapulmonary)
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis carinii pneumonia
- Pneumonia, recurrent

- Progressive multifocal leukoencephalopathy
- Salmonella septicaemia, recurrent
- Toxoplasmosis of brain
- Wasting syndrome due to HIV

7.4 Addendum 4: Visit Schedule for Rash Management in Pediatric Patients

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

	Grade 1 Rash	Grade 2 Rash	Grade 3 or 4 Rash
Day 0[a]	• Study medication **MAY** be **CONTINUED**. • Unscheduled visit for initial rash evaluation **REQUIRED**. • Referral to dermatologist **ONLY IF** rash diagnosis uncertain (within 24h).	• Study medication **MAY** be **CONTINUED**. • Unscheduled visit for initial rash evaluation **REQUIRED**. • Referral to dermatologist **REQUIRED** (within 24h). • Assessment of safety blood sample by local laboratory **ONLY IF** requested by investigator or dermatologist. • Biopsy **ONLY IF** required by dermatologist.	• Study medication **MUST** be permanently **DISCONTINUED**. Rechallenge is **NOT ALLOWED**. • Unscheduled visit for initial rash evaluation **REQUIRED**. • Referral to dermatologist **REQUIRED** (within 24h). • Assessment of safety blood sample by local laboratory **ONLY IF** requested by investigator or dermatologist. • Biopsy **ONLY IF** required by dermatologist.
Day 1	• Follow-up visit **REQUIRED**. • Digital pictures **REQUIRED.**	• Follow-up visit **REQUIRED**.	• Follow-up visit **REQUIRED**.
Day 2	No Rash follow-up visit required[b]	No Rash follow-up visit required[b]	• Follow-up visit **REQUIRED**. • Assessment of safety blood sample by local laboratory **ONLY IF** requested by investigator or dermatologist.
Day 3	No Rash follow-up visit required[b]	No Rash follow-up visit required[b]	• Follow-up visit **REQUIRED**. • Assessment of safety blood sample by local laboratory **ONLY IF** requested by investigator or dermatologist.

[a] Note that Day 0 of the rash is the first day of investigator assessment and not the first day of rash as reported by the subject.
[b] In case rash progresses from a grade 1 or a grade 2 to a higher grade, start follow-up schedule for grade 2, 3 or 4 rash as appropriate.

	Grade 1 Rash	Grade 2 Rash	Grade 3 or 4 Rash
Day 4	No Rash follow-up visit required[b]	No Rash follow-up visit required[b]	• Follow-up visit **REQUIRED**. • Assessment of safety blood sample by local laboratory **ONLY IF** requested by investigator or dermatologist.
Day 5	No Rash follow-up visit required[b]	No Rash follow-up visit required[b]	• Follow-up visit **REQUIRED**. • Assessment of safety blood sample by local laboratory **ONLY IF** requested by investigator or dermatologist.
Day 6	No Rash follow-up visit required[b]	No Rash follow-up visit required[b]	No Rash follow-up visit required
Day 7	• Follow-up visit **REQUIRED**.[b]	• Follow-up visit **REQUIRED**.[b] • Digital pictures **REQUIRED.**	No Rash follow-up visit required
Further Visits	If rash is unresolved after second follow-up visit, further visits at the investigator's discretion.[b]	If rash is unresolved after second follow-up visit, further visits at the investigator's discretion.[b]	Weekly follow-up visits **REQUIRED** until resolution of grade 3-4 rash to grade ≤ 2 rash (further follow-up visits according to grade 1 or grade 2 rash instructions).

[b] In case rash progresses from a grade 1 or a grade 2 to a higher grade, start follow-up schedule for grade 2, 3 or 4 rash as appropriate.

7.5 Addendum 5: Visit Schedule for Rash Management in Adult Patients

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

	Grade 1 Rash	**Grade 2 Rash**	**Grade 3 or 4 Rash**
Day 0[1]	• Study medication **MAY** be **CONTINUED.** • Unscheduled visit for initial rash evaluation **REQUIRED**.	• Study medication **MAY** be **CONTINUED**. • Unscheduled visit for initial rash evaluation **REQUIRED**. • Assessment of safety blood sample by local laboratory **OPTIONAL**. • Referral to dermatologist **OPTIONAL** (within 24h).	• Study medication **MUST** be permanently **DISCONTINUED**. Rechallenge is **NOT ALLOWED**. • Unscheduled visit for initial rash evaluation **REQUIRED**. • Assessment of safety blood sample by local laboratory **REQUIRED**. • Digital pictures **OPTIONAL** (within 24h). • Referral to dermatologist **REQUIRED** (within 24h). • Biopsy **REQUIRED** for Grade 4 rash (within 24h). Biopsy at the dermatologist's discretion for Grade 3 rash.
Day 1	• Follow-up visit **REQUIRED**.	• Follow-up visit **REQUIRED**. • Assessment of safety blood sample by local laboratory **OPTIONAL**.	• Follow-up visit **REQUIRED**. • Assessment of safety blood sample by local laboratory **REQUIRED**. • Digital pictures **OPTIONAL.**
Day 2	No Rash follow-up visit required[2]	No Rash follow-up visit required[2]	• Follow-up visit **REQUIRED**. • Assessment of safety blood sample by local laboratory **REQUIRED** only if on Days 0 and/or 1 of rash AST/ALT > 2 x baseline value, AND/OR ≥ 5 x ULN, AND/OR in case of rash progression. • Digital pictures **OPTIONAL**

[1] Note that Day 0 of the rash is the first day of investigator assessment and not the first day of rash as reported by the subject.

[2] In case rash progresses from a grade 1 or a grade 2 to a higher grade, start follow-up schedule for grade 2, 3 or 4 rash as appropriate.

Day 3	No Rash follow-up visit required[2]	No Rash follow-up visit required[2]	• Follow-up visit **REQUIRED**. • Assessment of safety blood sample by local laboratory **REQUIRED** only if on Days 0 and/or 1 of rash AST/ALT > 2 x baseline value, AND/OR ≥ 5 x ULN, AND/OR in case of rash progression. • Digital pictures **OPTIONAL**
Day 4	No Rash follow-up visit required[2]	No Rash follow-up visit required[2]	• Follow-up visit **REQUIRED**. • Assessment of safety blood sample by local laboratory **REQUIRED** only if on Days 0 and/or 1 of rash AST/ALT > 2 x baseline value, AND/OR ≥ 5 x ULN, AND/OR in case of rash progression. • Digital pictures **OPTIONAL**
Day 5	No Rash follow-up visit required[2]	No Rash follow-up visit required[2]	• Follow-up visit **REQUIRED**. • Assessment of safety blood sample by local laboratory **REQUIRED**. • Digital pictures **OPTIONAL.**
Day 6	No Rash follow-up visit required[2]	No Rash follow-up visit required[2]	No Rash follow-up visit required
Day 7	• Follow-up visit **REQUIRED**.[2]	• Follow-up visit **REQUIRED**.[2] • Assessment of safety blood sample by local laboratory **OPTIONAL**.	No Rash follow-up visit required
Further Visits	If rash is unresolved after second follow-up visit, further visits at the investigator's discretion.[2]	If rash is unresolved after second follow-up visit, further visits at the investigator's discretion.[2]	• Weekly follow-up visits **REQUIRED** until resolution of grade 3-4 rash to grade ≤ 2 rash (further follow-up visits according to grade 1 or grade 2 rash instructions) • Weekly assessment of safety blood sample by local laboratory **REQUIRED** as long as grade 3 or 4 rash is present but only if on Day 5 of rash AST/ALT > 2 x baseline value, AND/OR ≥ 5 x ULN, AND/OR in case of rash progression, until resolution of AST/ALT abnormalities.

[2] In case rash progresses from a grade 1 or a grade 2 to a higher grade, start follow-up schedule for grade 2, 3 or 4 rash as appropriate.

			• Digital pictures **OPTIONAL**
Upon Rash Resolution/ Stabilization[3]			Take digital pictures (**OPTIONAL**).

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

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 unfavourable 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 Harmonization - 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).

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 1 of the outcomes listed in the definition above.
- Hospitalizations that were planned prior to the signing of C/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, Section 7.3, Addendum 5) 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 (see Figure 1), 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 ETR 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

Adverse events considered to be at least possibly related to ETR treatment, adverse events leading to treatment interruption or discontinuation, serious adverse events and pregnancies are to be collected from the signing of ICF/assent onwards. 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 is to be reported in the Adverse Event section of the CRF.

All reportable adverse events and adverse events leading to treatment interruption or discontinuation still ongoing at the end of the treatment are to be followed by the investigator according to the local standard of care.

New adverse events considered to be at least possibly related to ETR treatment, adverse events leading to treatment interruption or discontinuation, and 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 clinical trial (between signing of C/assent and last follow-up visit) are to be reported. Any SAEs 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) see Part I, Section 7.1, Addendum 1.

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 IEC/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 (see Figure 1), 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 ETR 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". 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:

- successful completion of the trial at the centre;
- failure of the investigator to comply with the protocol, ICH-GCP guidelines or local requirements;
- safety concerns;
- sufficient data suggesting lack of efficacy;
- inadequate recruitment of subjects by the investigator;
- switch of all subjects enrolled at the site to locally available ETR-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 (see Figure 1), compliance check - at pill count level - 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 - at kit level - will be reviewed during the on-site monitoring visits.

All used and unused investigational 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 centre.

- 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, ICF/Assent, 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 investigator's qualifications was based (e.g., curriculum vitae written in English).

The following documents must be provided to the sponsor or representatives prior to enrolment 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, when applicable.
- Completed Investigator Financial Disclosure Forms from the investigator and all subinvestigators.
- Signed and dated FDA Form 1572 received and, when applicable, 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.
- Import License if required
- Signed and dated financial agreement.
- Documentation on which the assessment of the subinvestigators' qualifications was based (e.g., curriculum vitae).
- Current laboratory normal ranges for all tests required by the protocol that will be performed.
- Laboratory documentation demonstrating competence and test reliability (e.g., accreditation/license), if applicable.
- Signed and dated agreement between the investigator and Local Health Authority

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 Verification Plan 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 Document 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, a copy of the C/assent was given to the subject;
- 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), 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 (see Figure 1), all 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 or 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. 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 initialled 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 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 (see Figure 1), all 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 ETR 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

The sponsor will provide the site with a subject identification code list, and screening and enrollment log. Both documents are to be completed for each new screened and enrolled subject to assure subject identification at any point in time during the trial. The subject identification code list will not be transferred to the sponsor to maintain the confidentiality of the subject.

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 C/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 27-MAR.This study TMC125-C239 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.

The results of the trial will be reported in a CSR 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 1 year after end of trial.

After termination of data collection (see Figure 1), only limited safety data (SAEs possibly related to ETR 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 CSR. 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 pre-publication 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, including the subject compensation programs.

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;
- ASR and Quarterly Line Listings.

Substantial amendments and applicable ICF/Assent 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.

Good Clinical Practice (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

General

Prior to entry in the trial, the investigator or a person designated by the investigator must explain to potential subjects or their legally acceptable representative the trial and the implications of participation. Subjects will be informed that their participation is voluntary and that they may withdraw from the trial at any time. They will be informed that choosing not to participate or to withdraw from the trial will not have an impact on the care the subject will receive for the treatment of his/her disease. Subjects will be told that alternative treatments are available if they decide not to take part in this trial. Finally, they will be told that their records may be accessed by the IEC/IRB, regulatory authorities and authorized representatives of the sponsor without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) and/or regulations. By signing the ICF/Assent, the subject is authorizing such access.

In case the subject is unable to read and write, an impartial witness must confirm the informed consent/assent.

The subject will be given sufficient time to read the ICF/Assent, and to ask additional questions. After this explanation and before entry in the trial, consent should be appropriately recorded by means of the subject's personally dated signature or by the signature of an independent witness who certifies the subject's consent in writing. After having obtained the consent, a copy of the signed and dated ICF/Assent must be given to the subject.

Any information relevant to the subject's willingness to participate in the trial will be provided to the subject or his/her legally acceptable representative in a timely manner by means of an updated ICF/Assent. This amended ICF/Assent will be signed and dated by the subject and the investigator to document the willingness of the subject to continue with the trial.

This signed and dated amended version will be filed together with the initial signed and dated ICF/Assent, and a copy of the signed and dated ICF/Assent must be given to the subject.

Pediatric subjects

The special vulnerability of children requires specific measures in the informed consent process sin order to safeguard their interests and to protect them from harm. As a rule, a pediatric subject is legally unable to provide informed consent. Therefore children are dependent on their parent(s)/legal guardian to assume responsibility for their participation in the clinical trial. While children are legally incapable of giving informed consent, they nevertheless may possess the ability to assent or to dissent from participation. Out of respect for children as developing persons, children will be asked whether or not they wish to participate in the research, after having been informed about the trial in a manner that is appropriate to their intellectual and emotional capacities. They will be informed to the fullest extent possible in language and terms they are able to understand. Where appropriate, participants should assent to enroll in a trial (age of assent is to be determined by IEC/IRB or to be consistent with local legal requirements). The parent(s)/legal guardian will be responsible for the actual informed consent, while the child will be asked to assent. The following information forms (including consent/assent form) will be used by the investigational staff:

- parent / legal guardian and adolescent information sheet and consent form

- children information sheet and assent form

The way these forms are composed and used will be in accordance with local laws and regulations (e.g., the age at which adolescents are legally declared 'mature' may differ from country to country, and in case children can not write their names, drawing for example a smiley face to assent is allowed practice in some countries).

All applicable forms will be submitted for review and approval to IECs/IRBs. If local regulations allow, the investigator/trial nurse or social worker could also consider having a private session with the subject to address sensitive issues related to alcohol use, sexual activity, drug screen and any other issues as needed.

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 enrolment of the first subject, following centre completion, and 1 year following trial completion. The investigator should promptly update this information if any relevant changes occur during this period.

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

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

8 DATA QUALITY CONTROL/ASSURANCE

The trial is to be monitored by the sponsor or representative.

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 centre 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., are 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 (see Figure 1), all 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 centre(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

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	25Jul2019, 16:36:01 PM, UTC	Document Approval

Janssen Research & Development *

Clinical Protocol

COVID-19 Appendix

Protocol Title
Continued Access to Etravirine in Treatment Experienced HIV-1 Infected Subjects

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Protocol TMC125-TiDP35-C239; Phase [N/A]

TMC125 (etravirine)

*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 UC; 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.

United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

EudraCT NUMBER: 2009-013126-16

Status: Approved
Date: 15 May 2020
Prepared by: Janssen Research & Development, a division of Janssen Pharmaceutica NV
EDMS number: EDMS-RIM-56255, 1.0

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

COVID-19 APPENDIX

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation with the participant, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the case report form (CRF).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a participant has tested positive for COVID 19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

Drug Supply:

- Normal study drug shipment from the Janssen depots to the sites will continue until further notice.
- Normal study drug dispensation to subject by site.
- If study treatment dispensation to subject at site might be impacted, the local sponsor team should be informed by the site. Direct-to-patient (DTP) process, when permitted by local regulations in the country, will be initiated to allow sites to ship study treatment to the subjects. Only after approval by the sponsor, the granted site may ship treatment to subjects with support of the sponsor's supply team. Where DTP shipments are deemed necessary, the process must be coordinated between the site and sponsor staff following standard DTP procedures for arranging shipment and adhering to associated approvals and documentation requirements.
- Sites are requested to send their SOPs, related to drug supply and dispensation, for sponsor approval prior to implementation.
- Where necessary upon local guidance, subjects will consent upfront before the DTP process will be implemented.
- In case of remote visits, the subject should keep used and un-used kits at home at a secure location. The subject will be requested to bring the used and un-used kits back to the site at the next on-site visit.
- There will be no central study drug return organized by the sponsor.
- Sites need to continue to assess the levels of investigational product (IP) inventory to ensure the site has enough IP to cover all patients for at least 6 months. If the inventory is not sufficient the site is to contact the site manager to organize shipment of new IP.

Verification and Monitoring Visits:

- Interim monitoring visits will be replaced by remote monitoring visits until such time that on-site visits can be resumed.

Remote Assessment Visits:

- Remote assessment visits may be performed until such time that on-site visits can be resumed. Site staff will be asked to collect any assessments that can be made remotely. These assessments are important for the continued evaluation of safety and efficacy as patients complete the study period. Conducting remote assessment visits enables this important data to be collected without risking patient, family, and site staff safety. As allowable per local regulations, these remote assessments can be conducted via telephone with patients in their homes. Assessments that can be completed remotely include a review of adverse events and concomitant medications. Site staff will be asked to adhere to the Time and Events Schedule outlined in the protocol, to the extent feasible, when scheduling remote assessments. Some of the assessments required in the Time and Events Schedule are not in scope for remote visits including weight and urine pregnancy test (if applicable). Drug accountability can be discussed remotely but will be confirmed at the first visit back on site. These data will be missing for patients that are unable to attend site visits.

- The relationship to COVID-19 for missing protocol-specified information/procedures will be documented in the patient source documents.
- Where necessary upon local guidance, subjects will consent upfront before remote visits will be implemented.

Early Withdrawal from the Study:

- If a subject is lost to follow-up, or is unwilling to have a remote assessment performed, the subject will be considered an early withdrawal. Sites will be reminded to follow the procedures outlined in the protocol.

Protocol Deviations:

- All COVID-19 related protocol deviations will be reported and summarized in the Clinical Study Report.

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Magda Opsomer, MD

Institution: Janssen Research & Development

Signature: electronic signature appended at the end of the protocol Date: _____
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.