Clinical Trial Protocol
Amendment 3

Project No.:	TMC278-TiDP6		
Department:	Clinical R&D	**Generic name:**	rilpivirine hydrochloride
Status:	Approved	**Issued Date:**	28-Nov-2016
Protocol Title:	An open-label trial with TMC278 25 mg q.d. in combination with a background regimen containing 2 nucleoside/nucleotide reverse transcriptase inhibitors in HIV-1 infected subjects, who participated in TMC278 clinical trials.		
Study No.:	TMC278-TiDP6-C222	**Clinical Phase:**	III
Sponsor:	**Janssen Research & Development***		

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Prepared by: Janssen Research & Development, a division of Janssen Pharmaceutica NV
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COMPLIANCE STATEMENT

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

CONFIDENTIALITY STATEMENT

Protocol History[1]
TMC278-TiDP6-C222

Document Type and *File Name*	Issued Date	Amendment Type	Comments
Initial Clinical Trial Protocol *TMC278-TiDP6-C222-CTP*	*30-Jul-2010*		
CTP Amendment I *TMC278-TiDP6-C222-CTPA-GEN-I*	05-May-2011	Substantial	This amendment was created to incorporate the following changes to the clinical trial protocol: 1. Serum pregnancy test at the Roll-over visit was replaced by a urine pregnancy test. 2. A reminder for HLA-B*5701 testing and viral genotype determination were added. 3. From the Roll-over visit onwards switching to background N(t)RTIs other than those used in the previous trials is allowed. 4. A list of established and theoretical drug interactions with commonly used co-medications and TMC278 was added as an attachment. 5. Effective methods of birth control for male and female subjects were updated. 6. Safety follow-up and management of toxicities were updated. 7. Withdrawal criteria were updated. 8. Furthermore, some administrative and textual changes were made.
First Revised Clinical Trial Protocol *TMC278-TiDP6-C222-CTP-v2*	05-May-2011		Integrates Initial Protocol + Amendment I
CTP Amendment II *TMC278-TiDP6-C222-CTPA-GEN-II*	04-Aug-2011	Non-substantial	This amendment was created to make corrections to Attachment 3.
Second Revised Clinical Trial Protocol *TMC278-TiDP6-C222-CTP-v3*	25-Aug-2011		Integrates First Revised Protocol + Amendment II
CTP Amendment III ***TMC278-TiDP6-C222-CTPA-GEN-III***	**This document**	**Substantial**	**See PROTOCOL AMENDMENTS table**

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

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PROTOCOL AMENDMENTS

Amendment 3 (28-Nov-2016)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The TMC278-C222 trial has been ongoing for over 5 years (started in February 2011) and the subjects have been on TMC278 (rilpivirine) + 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs) not only in this roll-over trial but also in the previous trials (TMC278-C209, -C215, and -C204). Therefore, long-term safety and efficacy of rilpivirine have been properly assessed, allowing the trial to be simplified and trial-related activities to be reduced to a minimum for the limited number of subjects remaining in this trial. The main component of this trial will remain to allow subjects who experience and are expected to continue experiencing clinical benefit from rilpivirine treatment to have continued access to rilpivirine in a simplified study setting or to be switched to local (rilpivirine-based) treatment options or local standard of care, as appropriate.

Rilpivirine has received Marketing Authorization in over 85 countries worldwide. In some countries, however, rilpivirine is not registered, or not reimbursed, or cannot be accessed through another source. In those countries, rilpivirine will continue to be provided through this trial until subjects can be switched to locally available rilpivirine (ie, commercially available AND reimbursed, OR accessible through another source [eg, access program or government program]), other local (rilpivirine-based) treatment options, or local standard of care, as appropriate.

This amendment provides details on the process and requirements for this simplified trial setting that will apply after approval of this amendment, which includes the provision of rilpivirine, clinical management of subjects as per local standard of care, more limited adverse event (AE) reporting requirements, and removal of data collection, source verification, and trial monitoring requirements (with the exception of a site closure visit).

The table below gives an overview of the rationale for each change and all applicable sections.

Rationale: Long-term safety and efficacy of rilpivirine have been assessed and the collection of additional data in this trial is unlikely to impact the risk-benefit assessment. Therefore, trial-related data will no longer be collected; medical records should be maintained as per local standard of care and should continue to include details on the use of rilpivirine. In the absence of trial-related data collection, no trial monitoring will be performed (with the exception of a site closure visit) and no trial-related data will be analyzed or reported. The procedures for safety reporting were updated and will continue to include serious adverse events (SAEs) and pregnancies (using trial-specific reporting forms), and non-serious clinically important events (using regular pharmacovigilance reporting).

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Rationale: In some countries, rilpivirine is not registered, or not reimbursed, or cannot be accessed through another source. Rilpivirine will continue to be provided through this trial until subjects can be switched to locally available rilpivirine (ie, commercially available AND is reimbursed, OR can be accessed through another source [eg, access program or government program]). The trial will be stopped when all subjects have switched to locally available rilpivirine, other local (rilpivirine-based) treatment options, or local standard of care, as appropriate.

SYNOPSIS
Time and Events Schedule
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Rationale: Where rilpivirine is available locally, subjects should follow the local prescribing information for rilpivirine under the guidance of the investigator.

4.4 Prohibitions and Restrictions
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Rationale: In line with the simplified trial setting, information on the provision and destruction of study drug supplies was updated. A tool will continue to be available to order additional study drug supplies and will be used to record the date of last study drug intake.

6 DOSAGE AND ADMINISTRATION
9.1.4 Posttreatment Phase (Follow-Up)
14.4 Preparation, Handling, and Storage
14.5 Drug Accountability

Rationale: The name of the sponsor of the trial was changed from Tibotec Pharmaceuticals to Janssen Research & Development because of the transition of the Johnson & Johnson Research & Development companies to a unified Janssen identity.

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9.3.4.1 Rash
14.1 Physical Description of Study Drug
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Attachment 1
SIGNATURE PAGE SPONSOR

Rationale: The background section was updated as more current data have become available. The drug interactions table was deleted as prescribing information for rilpivirine has been approved and can be referenced where available. The references were updated according to the changes made. Minor editorial changes were made.

1 INTRODUCTION
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10.2 Withdrawal From the Study

SYNOPSIS

An open-label roll-over trial with TMC278 (rilpivirine) 25 mg once daily (q.d.) in combination with a background regimen containing 2 nucleoside/nucleotide reverse transcriptase inhibitors (N[t]RTIs) in HIV-1 infected subjects, who participated in TMC278 clinical trials.

TMC278 (formerly known as R278474), a diarylpyrimidine derivative, is a potent non-nucleoside reverse transcriptase inhibitor (NNRTI) with in vitro activity against wild-type as well as NNRTI-resistant human immunodeficiency virus (HIV-1).

OBJECTIVES

Primary Objective

The primary objective of the trial is to provide continued access to TMC278 for subjects who were randomized and treated with TMC278 in the Phase IIb (TMC278-C204 [C204]) or Phase III trials (TMC278-TiDP6-C209 [C209] and TMC278-TiDP6-C215 [C215]), and who, at the time of roll-over, experience and are expected to continue experiencing clinical benefit from TMC278 treatment.

Secondary Objectives

Up to and including Protocol Amendment 2, the secondary objective is to evaluate the long-term safety and tolerability of TMC278 25 mg q.d. in combination with a background regimen containing 2 N(t)RTIs. Available efficacy data will also be collected, including resistance data in case of virologic failure.

Protocol Amendment 3 Objective

As of Protocol Amendment 3, the objective is to provide continued access to TMC278 for subjects who experience and are expected to continue experiencing clinical benefit from TMC278 treatment until subjects can switch to locally available rilpivirine (ie, commercially available AND reimbursed, OR accessible through another source [eg, access program or government program]), other local (rilpivirine-based) treatment options, or local standard of care, as appropriate.

OVERVIEW OF STUDY DESIGN

This is a Phase III, open-label, multicenter, roll-over trial to provide continued access to TMC278 for HIV-1 infected subjects who were randomized and treated with TMC278 in the Phase IIb (C204) or Phase III trials (C209 or C215). At the time of roll-over the investigator should assess whether the subject benefits from TMC278 treatment according to the efficacy and safety criteria as set out in the previous trial protocol. The investigator should also be confident that the subject is expected to continue benefiting from TMC278 treatment.

The Final visit of the previous trial will be the first visit of this trial (= the Roll-over visit). From this visit onwards, all enrolled subjects will continue to receive TMC278 25 mg q.d. in combination with a background regimen of 2 N(t)RTIs until one of the following criteria is met (whichever comes first):

- The subject meets at least one of the withdrawal criteria, or
- Rilpivirine becomes commercially available AND is reimbursed, OR can be accessed through another source (e.g., access program or government program) by the subject in his/her country; or
- The investigator finds it in the subject's best interest to switch to other local (rilpivirine-based) treatment options or local standard of care, as appropriate.

The background regimen of 2 N(t)RTIs can be changed at the investigator's discretion anytime during this study, as long as there is no evidence of resistance to the chosen N(t)RTIs, as determined by the last available genotype results.

As of Protocol Amendment 3, medical records should be maintained as per local standard of care and should continue to include details on the use of TMC278; data will no longer be recorded in the electronic Case Report Form (eCRF).

STUDY POPULATION

It was anticipated that approximately 750 HIV-1 infected subjects would continue to receive TMC278 treatment in combination with 2 N(t)RTIs at the start of this trial. **At the time of execution of Protocol Amendment 3,** most of the subjects involved in this trial will have been switched to locally available rilpivirine, other local (rilpivirine-based) treatment options, or local standard of care.

To be eligible, subjects must satisfy all of the following criteria:

1. Male or female subjects, aged 18 years or older.
2. Subjects must have signed an informed consent form indicating that they are willing to participate in the trial and understand the purpose and procedures required for the trial.
3. Subjects are HIV-1 infected and were previously randomized to receive TMC278 in a TMC278 clinical trial and completed the protocol defined treatment period.
4. Subjects benefit from treatment with TMC278, according to the efficacy and safety criteria as set out in the previous trial protocol, and will continue to benefit from this treatment in the opinion of the investigator.
5. Subjects can comply with the current protocol requirements.
6. The subject's general medical condition, in the investigator's opinion, does not interfere with participation in the trial.

DOSAGE AND ADMINISTRATION

Oral tablets of TMC278 25 mg q.d. should be administered together with a meal.

EFFICACY EVALUATIONS/CRITERIA

It is recommended that subjects are followed as per local standard of care. All tests are to be performed locally. Efficacy measurements will be summarized descriptively. **As of Protocol Amendment 3,** efficacy assessments should still be conducted as per local standard of care but documented in the subject's medical records only; data will no longer be recorded in the eCRF and therefore no further efficacy analyses will be performed.

SAFETY EVALUATIONS

Safety and tolerability will be evaluated throughout the trial (see the Time and Events Schedule for details).

As of Protocol Amendment 3, safety assessments should still be conducted as per local standard of care but documented in the subject's medical records only; data will no longer be recorded in the eCRF. Investigators must continue to report serious adverse events, pregnancies, and non-serious clinically important events to the sponsor.

STATISTICAL METHODS

No formal sample size determination has been performed for this trial: any subject in the TMC278 Phase IIb or Phase III trials, who has given consent to participate and who is eligible and willing, may participate in this trial. Since the trial does not include a comparator, only descriptive statistical analyses will be performed on the data collected.

TIME AND EVENTS SCHEDULE – UP TO AND INCLUDING PROTOCOL AMENDMENT 2

Study Part / Type of Visit	Roll-over Visit	Treatment Period		Post-treatment follow-up visit****
Time of Visit	At Final Visit in trial*	Study Visits**	Final/Withdrawal Visit***	
Informed consent	X			
Inclusion/exclusion criteria	X			
Pregnancy test[1]	X	X	X	
Collection of viral load and CD4+ cell count[2]		X	X	
Collection of the following AEs[3]:				
- AEs considered to be at least possibly related to TMC278;	X	X	X	X
- AEs leading to discontinuations;	X	X	X	X
- SAEs and pregnancies;	X	X	X	X
- Any grade 3/4 rash, regardless of causality	X	X	X	X
Safety laboratory tests	X	X[4]	X[4]	
ARV therapy	X	X	X	
Concomitant therapy administered for (S)AEs[5] or contraception to be recorded	X	X	X	X
Dispensation of TMC278	X	X		
Drug accountability	X	X	X	

AEs: adverse events; ARV: antiretroviral; SAEs: serious adverse events.

* All assessments required in previous trial's Final visit need to be completed first.

** Visits should be performed according to local standard of care, but it is recommended to be no less frequent than every 6 months.

- *** The investigator will conduct the Final/Withdrawal visit when the subject meets at least one of the withdrawal criteria or when TMC278 becomes commercially available, is reimbursed, or can be accessed through another source (e.g., access program or government program) by the subject in his/country (whichever comes first).

In case of loss of virologic response: in order to assist in the selection of a new ARV regimen, determination of the genotype will be performed on the sample collected at the first visit where the viral load is sufficiently high to allow genotyping. Genotyping should be performed at a local/regional certified laboratory facility. In countries where such facilities are not available, the site will arrange for shipment of the sample to Virco Laboratories where a virco®TYPE HIV-1 will be performed. The genotype results will be provided to the investigator who will record these data in the electronic Case Report Form (eCRF).

**** The follow-up visit (30 days ± 2 days) is only performed for subjects who have an ongoing AE or SAE at time of discontinuation.

[1] A urine pregnancy test must be performed at the Roll-over visit (= Final visit in the previous trial). It is also recommended to perform a urine pregnancy test at every subsequent visit if it is not part of local standard of care.

[2] It is recommended that viral load and CD4+ cell count information from procedures performed per local standard of care is collected.

[3] Other AEs will only be collected in the eCRF if required per local regulations.

[4] Recommended to be done at all visits, or more frequently if indicated per local standard of care. Results of routine safety laboratory tests will only be collected in case of AE/SAE.

[5] Only use of concomitant therapy administered for (S)AEs for which information is collected in the eCRF, and use of any oral, injectable, or implantable hormonal contraceptives are to be recorded.

TIME AND EVENTS SCHEDULE – AS OF PROTOCOL AMENDMENT 3

As of Protocol Amendment 3, visits and assessments should still be performed as per local standard of care but documented in the subject's medical records only; data will no longer be recorded in the eCRF.

Sites should continue to report SAEs, pregnancies, and non-serious clinically important events to the sponsor.

Concomitant therapies should be documented in the subject's medical records only, as per local standard of care; data will no longer be recorded in the eCRF.

TMC278 will be provided in this trial until subjects can switch to locally available rilpivirine (ie, commercially available AND reimbursed, OR accessible through another source [eg, access program or government program]), other local (rilpivirine-based) treatment options, or local standard of care, as appropriate.

ABBREVIATIONS

3TC	lamivudine
ABC	abacavir
AE	adverse event
ALT	alanine aminotransferase
ARV	antiretroviral
ASR	annual safety report
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{0-24h}	area under the plasma concentration-time curve from time of administration to 24 hours after dosing
AZT	zidovudine
CTP	Clinical Trial Protocol
DAIDS	Division of Acquired Immunodeficiency Syndrome
ECG	electrocardiogram
eCRF	electronic Case Report Form
eDC	electronic Data Capture
EFV	efavirenz
ESI	events of special interest
FDA	Food and Drug Administration
FTC	emtricitabine
GCP	Good Clinical Practice
HIV-1	human immunodeficiency virus - type 1
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
NNRTI	non-nucleoside reverse transcriptase inhibitor
N(t)RTI	nucleos(t)ide reverse transcriptase inhibitor
PI	protease inhibitor
PQC	Product Quality Complaint
q.d.	quaque die; once daily
QTcF	QT interval corrected for heart rate according to Fridericia
RBC	red blood cell
SAE	serious adverse event
SJS	Stevens-Johnson Syndrome
TDF	tenofovir disoproxil fumarate
TQT	thorough QT
ULN	upper limit of laboratory normal range
WBC	white blood cell

1 INTRODUCTION

Currently, human immunodeficiency virus (type 1) (HIV-1) infected subjects are routinely treated with combinations of 3 or 4 drugs, including nucleo(t)side reverse transcriptase inhibitors (N[t]RTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and/or fusion inhibitors. Improved tolerability, safety, and simple dosing regimens are important drivers of good adherence and hence low rates of resistance development and should, therefore, be considered as major elements in the development of new potent antiretroviral (ARV) compounds with different resistance profiles, especially in the treatment-naïve population.[1,2] The currently approved first generation NNRTIs in the United States and/or Europe are nevirapine (Viramune®), delavirdine (Rescriptor®) and efavirenz (EFV; Sustiva®, Stocrin®). These drugs show cross-resistance and are associated with safety problems (mainly hepatotoxicity, central nervous system symptoms, and/or rash).[2] Novel NNRTIs with an increased in vitro genetic barrier to the development of resistance are being developed. Currently one novel NNRTI, etravirine (Intelence®), is approved for the use in treatment-experienced subjects. TMC278 (rilpivirine, formerly known as R278474), a diarylpyrimidine derivative, is a potent NNRTI with in vitro activity against wild-type HIV-1 and NNRTI-resistant mutants. A median inhibitory activity of HIV-1 reverse transcriptase by TMC278 (50% inhibitory concentration) of 42 nM (15.4 ng/mL) was determined using a primer extension-based scintillation proximity assay. TMC278 is able to combine the convenience of once daily (q.d.) dosing with good antiviral effects and a higher barrier to resistance as compared to currently licensed NNRTIs (with the exception of etravirine).

For the most accurate and current information regarding the efficacy and safety of TMC278 refer to the latest version of the Investigator's Brochure for TMC278.[3]

The term sponsor used throughout this document refers to the entities and their representatives listed in the Contact Information page(s), which will be provided as a separate document.

1.1 Background

Nonclinical Studies

Non-clinical safety and toxicology studies demonstrated that TMC278 is safe for use in clinical testing.[4] In non-clinical studies in rats and dogs, changes in adrenal hormones and histopathology have been observed. In those studies, TMC278 appears to interfere with steroid biosynthesis, leading to decreases in cortisol and increases in progesterone and 17-OH-progesterone and as a result to increases in serum adrenocorticotropic hormone. Preclinical work with TMC278 also identified changes in the thyroid glands in rats. However, to date, no significant effects on adrenal or thyroid function were observed in clinical studies with TMC278.

TMC278 did not show a potential for genotoxicity, teratogenicity, phototoxicity, skin or mucous membrane irritation, or delayed-type sensitization. Fertility, early embryonic development, pre- and postnatal development, and the immune system were not affected by TMC278 at oral doses ranging from 160 to 1600 mg base eq./kg.

Clinical Studies

Human Pharmacokinetics

In humans, TMC278 is well absorbed after single and multiple dosing and maximum concentrations are generally reached at 4 hours postdose. Steady-state concentrations of TMC278 are usually reached within 11 days of dosing. The mean terminal elimination half-life after multiple dosing was approximately 45 hours. There was no indication of changes in the pharmacokinetics of TMC278 over a 96-week period in a trial in HIV-1 infected subjects. TMC278 exhibited linear pharmacokinetics for maximum plasma concentration and area under the plasma concentration-time curve (AUC) after single and multiple dose administration up to a dose of 150 mg q.d. in non-HIV infected subjects. In HIV-1 infected subjects the exposure to TMC278 increased less than proportional to the dose, particularly between 25 mg q.d. and 75 mg q.d. The average exposure (AUC_{0-24h}) to TMC278 after repeated administration (96 weeks) of 25, 75, and 150 mg q.d. in HIV-1-infected subjects was, respectively, 2.8, 5.9, and 10.3 µg.h/mL.

Single dose exposure to TMC278 when administered as the Phase III tablet formulation was approximately 40-50% lower when taken fasting or with a nutritional drink as compared to intake with a standard or high-fat breakfast. Therefore, TMC278 should always be taken with a meal.

Mild induction of CYP2C19 activity was observed after repeated administration of TMC278 150 mg q.d. in non-HIV infected subjects. This effect is unlikely to cause clinically relevant changes in the pharmacokinetics of coadministered drugs that are metabolized by this enzyme. TMC278 at a dose of 75 mg q.d. was shown not to affect CYP3A4 activity in vivo. TMC278 at 25 mg q.d. or higher did not influence the pharmacokinetics of any of the agents evaluated to a clinically relevant extent. The exposure to TMC278 can be affected by modulators of CYP3A4 enzyme activity and by drugs that increase the gastric pH. Drugs that induce CYP3A4 activity (e.g., rifabutin and rifampin) can reduce the TMC278 exposure and should not be coadministered. Proton-pump inhibitors (e.g., omeprazole) should not be coadministered, given the reduced exposure to TMC278. H_2-antagonists should only be administered at least 12 hours before or at least 4 hours after intake of TMC278, and antacids should only be administered either at least 2 hours before or at least 4 hours after intake of TMC278.

Efficacy/Safety Studies

At the time of writing this protocol, 35 clinical trials with TMC278 have been conducted with 1834 HIV-1 infected subjects and 759 non-HIV infected subjects.

In the 30 Phase I trials (774 subjects), short-term administration of TMC278 in single and multiple dose trials has been generally safe and well tolerated. A thorough QT (TQT) trial at the TMC278 25 mg q.d. dose[5] showed that TMC278 did not prolong the QT interval corrected for heart rate according to Fridericia (QTcF) interval at this dose. The upper limit of the 90% confidence interval of the difference versus placebo as well as the difference versus baseline in QTcF interval for TMC278 25 mg q.d. was less than 10 ms at all time points. Higher doses of TMC278 (75 mg and 300 mg q.d.) examined in this previous TQT trial, were associated with maximum mean QTcF prolongations > 10 ms, which were shown to be dose- and plasma concentration-dependent.

The 2 Phase IIa proof-of-principle trials[6,7] (83 subjects) demonstrated the short-term (7 days) antiviral activity in HIV-1 infected subjects who were naïve to ARV therapy as well as in HIV-1 infected subjects with NNRTI experience and/or genotypic evidence of NNRTI resistance and who were failing ARV therapy. These data provided a strong rationale for further development of TMC278 in HIV-1 infected subjects at doses of 25 to 150 mg q.d. The results of these 2 trials demonstrated that TMC278 doses up to 150 mg q.d. for 7 days did not reveal any new or unexpected safety signals that would affect the risk/benefit balance as compared to Phase I trials.

The Phase IIb (C204) trial[8] (368 subjects) was a randomized, active controlled, and partially blinded trial to evaluate the effect on efficacy, safety, and tolerability of TMC278, given at 3 different doses (25 mg q.d.,75 mg q.d., and 150 mg q.d.), when added to a regimen of investigator selected N(t)RTIs. At Week 48 and Week 96, all TMC278 doses were highly active and associated with a substantial and sustained virologic response when considering the percentage of subjects reaching less than 50 HIV-1 ribonucleic acid copies/mL (time to loss of virologic response algorithm) and the mean change in viral load from baseline. TMC278 25 mg q.d. was as effective as the higher doses of 75 mg q.d. and 150 mg q.d. up to 96 weeks of treatment. All TMC278 doses provided a clear immunologic benefit, up to 96 weeks of treatment, in addition to the antiviral effect in HIV-1 ARV-naïve subjects. For subjects receiving the higher doses of TMC278, doses were switched to 25 mg q.d. after Week 96 once results of the TQT trial were available and the dose of 25 mg q.d. was selected for further development. The total treatment duration of the trial was extended to 240 weeks in order to collect long-term efficacy and safety data from subjects who continued to benefit from their treatment. No loss of efficacy was observed when the dose was decreased to 25 mg q.d. There was no clear dose differentiation for adverse events (AEs) or laboratory abnormalities. No clinically relevant effects were observed on adrenal function. Overall, there were no endocrine or cardiovascular signals to suggest safety issues with the use of TMC278. In conclusion, these data showed that TMC278 was generally safe and well tolerated after long-term treatment at all doses tested, compared with EFV, when combined with zidovudine (AZT)/lamivudine (3TC) or tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC). Data from the primary analysis at Week 48 and the analyses at Weeks 96, 144, 192, and 240 are available.[9,10]

The 2 Phase III (ECHO[11] [C209] and THRIVE[12] [C215]) trials (1368 subjects in total) are multi-national, randomized, double-blind, double-dummy, active-controlled trials to compare the efficacy (including antiviral efficacy, immunologic changes, and evolution of HIV-1 genotypic and phenotypic characteristics), safety, and tolerability of TMC278 25 mg q.d. versus EFV both combined with a background regimen of 2 N(t)RTIs in treatment-naïve HIV-1 infected subjects. Data from the primary analysis at Week 48 and the analyses at Week 96 and post-Week 96 are available.[13,14,15,16] These data demonstrated TMC278 to have substantial and sustained efficacy, that was non-inferior to EFV, and to be generally safe and well tolerated. Overall, there were no endocrine or cardiovascular signals to suggest safety issues with the use of TMC278, when combined with TDF/FTC, AZT/3TC or abacavir (ABC)/3TC.

1.2 Overall Rationale for the Study

The trial was designed to allow subjects who have benefited from treatment with TMC278 in a clinical trial to continue this treatment upon completion of this trial. The potential benefit of continuing TMC278 treatment should outweigh the potential risk of experiencing possible AEs

after switching to another (commercially available) NNRTI. Subjects will continue to receive TMC278 in this trial until one of the following criteria is met (whichever comes first):

- The subject meets at least one of the withdrawal criteria, or
- Rilpivirine becomes commercially available AND is reimbursed, OR can be accessed through another source (e.g., access program or government program) by the subject in his/her country, or
- The investigator finds it in the subject's best interest to switch to other local (rilpivirine-based) treatment options or local standard of care, as appropriate.

The design of the trial also allows long-term safety and available efficacy information, including resistance data in case of virologic failure, to be gathered in these subjects. **As of Protocol Amendment 3,** visits and assessments should still be performed as per local standard of care but documented in the subject's medical records only; data will no longer be recorded in the electronic Case Report Form (eCRF).

2 OBJECTIVES

Primary Objective

The primary objective of the trial is to provide continued access to TMC278 for subjects who were randomized and treated with TMC278 in the Phase IIb (C204) or Phase III trials (C209 and C215), and who, at the time of roll-over, experience and are expected to continue experiencing clinical benefit from TMC278 treatment.

Secondary Objectives

Up to and including Protocol Amendment 2, the secondary objective is to evaluate the long-term safety and tolerability of TMC278 25 mg q.d. in combination with a background regimen containing 2 N(t)RTIs. Available efficacy data will also be collected, including resistance data in case of virologic failure.

Protocol Amendment 3 Objective

As of Protocol Amendment 3, the objective is to provide continued access to TMC278 for subjects who experience and are expected to continue experiencing clinical benefit from TMC278 treatment until subjects can switch to locally available rilpivirine (ie, commercially available AND reimbursed, OR accessible through another source [eg, access program or government program]), other local (rilpivirine-based) treatment options, or local standard of care, as appropriate.

3 OVERVIEW OF STUDY DESIGN

3.1 Study Design

This is a Phase III, open-label, multicenter, roll-over trial to provide continued access to TMC278 for HIV-1 infected subjects who were randomized and treated with TMC278 in the

Phase IIb (C204) or Phase III trials, (C209 or C215). At the time of roll-over the investigator should assess whether the subject benefits from TMC278 treatment according to the efficacy and safety criteria as set out in the previous trial protocol. The investigator should also be confident that the subject is expected to continue benefiting from TMC278 treatment. It was anticipated that approximately 750 subjects would participate in this trial. **At the time of execution of Protocol Amendment 3,** most of the subjects involved in this trial will have been switched to locally available rilpivirine, other local (rilpivirine-based) treatment options, or local standard of care.

The Final visit of the previous trial will be the first visit of this trial (= the Roll-over visit). From this visit onwards, all enrolled subjects will continue to receive TMC278 25 mg q.d. in combination with a background regimen consisting of 2 N(t)RTIs until one of the following criteria is met (whichever comes first):

- The subject meets at least one of the withdrawal criteria (see Section 10.2), or
- Rilpivirine becomes commercially available AND is reimbursed, OR can be accessed through another source (e.g., access program or government program) by the subject in his/her country, or
- The investigator finds it in the subject's best interest to switch to other local (rilpivirine-based) treatment options or local standard of care, as appropriate.

The background regimen of 2 N(t)RTIs can be changed at the investigator's discretion anytime during this study, as long as there is no evidence of resistance to the chosen N(t)RTIs, as determined by the last available genotype results.

Visits and assessments performed should be based on the local generally accepted standard of care (see Time and Events Schedule). However, it is recommended that visits be planned no less frequently than every 6 months.

Information regarding AEs considered at least possibly related to the investigational medication (TMC278), AEs leading to discontinuation, serious adverse events (SAEs), and any grade 3/4 rash regardless of causality, should be recorded on the eCRF. Other AEs will be collected only if required as per local regulations.

As of Protocol Amendment 3, visits and assessments should still be performed as per local standard of care but documented in the subject's medical records only; data will no longer be recorded in the eCRF. Safety and tolerability of TMC278 will continue to be documented through the reporting of SAEs, pregnancies, and non-serious clinically important events to the sponsor.

3.2 Study Design Rationale

The Week 48 analysis of the Phase III trials, C209 and C215, demonstrated TMC278 to have substantial and sustained efficacy that is non-inferior to EFV, and to be generally safe and well tolerated. This trial was designed to provide continued access to TMC278 for subjects who were previously treated with TMC278 in the Phase IIb or Phase III trials, and who, at the time of roll-over, experience and are expected to continue experiencing clinical benefit from TMC278 treatment. **Up to and including Protocol Amendment 2,** this trial also allows long-term safety

and available efficacy information, including resistance data in case of virologic failures, to be gathered in these subjects. **As of Protocol Amendment 3,** safety and tolerability of TMC278 will continue to be documented through the reporting of SAEs, pregnancies, and non-serious clinically important events to the sponsor. The objective of this trial does not mandate any comparator drug, hence the open-label design. Efficacy and safety data will be analyzed in a descriptive way. Visits and assessments are recommended by this protocol; however, subjects are to be monitored according to the local standard of care for this subject population.

4 STUDY POPULATION

4.1 General Considerations

The inclusion and exclusion criteria for enrolling subjects in this trial are described in the following sections. If there is any uncertainty about the inclusion or exclusion criteria below, the investigator may consult with the appropriate sponsor representative before enrolling the subject in the trial. Approximately 750 HIV-1 infected subjects are expected to participate in this trial.

For discussion of the statistical considerations, refer to Section 11.3.

4.2 Inclusion Criteria

To be eligible, subjects must satisfy all of the following criteria:

1. Male or female subjects, aged 18 years or older.
2. Subjects must have signed an informed consent form (ICF) indicating that they are willing to participate in the trial and understand the purpose and procedures required for the trial.
3. Subjects are HIV-1 infected and were previously randomized to receive TMC278 in a TMC278 clinical trial and completed the protocol defined treatment period.
4. Subjects benefit from treatment with TMC278, according to the efficacy and safety criteria as set out in the previous protocol, and will continue to benefit from this treatment in the opinion of the investigator.
5. Subjects can comply with the current protocol requirements.
6. The subject's general medical condition, in the investigator's opinion, does not interfere with participation in the trial.

4.3 Exclusion Criteria

Potential subjects who meet any of the following criteria will be excluded from participating in the trial:

1. Use of disallowed concomitant therapy (see Section 8).
2. Females of childbearing potential* who are pregnant, or without the use of effective birth control methods, or not willing to continue practicing these birth control methods during the trial and for at least 1 month after the end of the trial (or after last intake of TMC278).

Effective birth control methods**:

(1) male condom*** in combination with diaphragm or cervical cap **** ("double barrier method"),

(2) intrauterine device or hormonal contraceptive in combination with a barrier contraceptive (i.e., male or female condom***, diaphragm, or cervical cap****),

(3) be non-heterosexually active, practice sexual abstinence or have a vasectomized partner: if no other effective birth control methods are being used, vasectomy should have been performed more than 1 month prior to withdrawal of these other effective birth control methods.

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

** Spermicides should not be used as this can potentially increase the rate of HIV-1 transmission[17].

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

**** A cervical cap has been shown to be less effective in parous women. Therefore, this barrier method is preferably not used in parous women in this trial.

3. Non-vasectomized heterosexually active male subjects without the use of effective birth control methods or not willing to continue practicing these birth control methods during the trial and for at least 1 month after the end of the trial (or after last intake of TMC278).

4.4 Prohibitions and Restrictions

During the conduct of the trial, subjects are not allowed to participate in any other clinical trials that include any blood sampling with a volume higher than 50 mL taken over the course of 6 months, specimen collection, or other interventional procedure. Concurrent participation in non-interventional observational trials is allowed as long as there is no impact on the objectives of this trial.

All HIV-1 infected subjects should be advised to take the necessary precautions to reduce the risk of transmitting HIV.

Potential subjects must be willing/able to adhere to the following prohibitions and restrictions during the course of the trial to be eligible for participation:

1. Women of childbearing potential must remain on a highly effective method of birth control (see Section 4.3). These precautions apply from the Roll-over visit onwards until 1 month after the last intake of TMC278 or 1 month after discontinuation of TMC278 in case of premature discontinuation.
2. Men must use a highly efficient method of birth control and not donate sperm during the trial and for 1 month after receiving the last dose of TMC278 (see Section 4.3).

For details on the existing data with regard to the reproductive toxicity of TMC278, please see the current Investigator's Brochure.

Where rilpivirine is available, investigators should follow the guidance in the local prescribing information for TMC278 regarding any contraindications, precautions for use, and other restrictions. Where local prescribing information is not available, investigators should follow the guidance in the Summary of Product Characteristics[18], United States Prescribing Information[19], or the Investigator's Brochure[3].

5 TREATMENT ALLOCATION

As this is an open-label trial in which all subjects receive the same treatment, randomization and blinding procedures are not applicable.

6 DOSAGE AND ADMINISTRATION

From the Roll-over visit onwards, subjects can either continue the background regimen of 2 N(t)RTIs that they are using or they can switch to another background regimen of 2 N(t)RTIs. The sponsor will not provide the medication for the background regimen. The subject will receive investigator-selected background medication according to locally applicable procedures. Please refer to the current product information for further details.

Subjects planning to use ABC in their background regimen, and who have no prior documented HLA-B*5701 negative results, should test negative for HLA-B*5701 before the start of ABC. In those subjects who test positive for HLA-B*5701, no ABC-containing background regimen can be administered.

Oral tablets of TMC278 25 mg q.d. must be administered together with a meal. Starting on Day 1, whenever possible, TMC278 should be taken around the same time each day (each dose should be separated by approximately 24 hours). When TMC278 is taken with only a protein-rich nutritional drink, exposures are approximately 40-50% lower than when taken with a meal.

Up to and including Protocol Amendment 2, the date of the first intake of TMC278 will be recorded on the eCRF. If a subject misses the intake of TMC278, and this is noticed within 12 hours of the time of usual intake, the subject should take the missed dose as soon as possible, with food. The subject may then continue with the usual dosing schedule. If a subject misses the intake of TMC278, and this is noticed more than 12 hours after the time of usual intake, the subject should not take that dose and simply resume the usual dosing schedule. The subject should not take a double dose to make up for a missed one.

If a subject discontinues the trial early, for whatever reason, TMC278 treatment can immediately stop, with no need for dose modifications.

Subjects will visit the site for assessments as per the Time and Events Schedule.

As of Protocol Amendment 3, a tool will continue to be available to order additional supplies of TMC278. Sites should also use this tool to record the date of last intake of TMC278 for each individual subject in this study.

7 TREATMENT COMPLIANCE

The investigator will discuss the importance of good compliance to the entire treatment regimen, including TMC278 taken in combination with other ARVs. The investigator or designated trial personnel will maintain a log of all drug dispensed and returned. Drug supplies for each subject will be inventoried and accounted for throughout the trial.

8 PRESTUDY AND CONCOMITANT THERAPY

The investigator is responsible for following guidance from product information/package inserts of TMC278 and all background ARVs regarding concomitant treatments, drug interactions, and other data.

The following medications are not allowed at any time during the trial from the Roll-over visit until the end of the study:

- Disallowed medication, as detailed in the most recent version of the Investigator Brochure for TMC278.
- All investigational drugs, except TMC278.
- All disallowed medication as mentioned in the product information/package insert of TMC278 and background ARVs. For any alternative N(t)RTIs in the background regimen, the respective package inserts should be consulted for concomitant use with other medications and for contraindicated medications or medications that are not recommended for concomitant use.

The following ARVs are not allowed at any time during the trial from the Roll-over visit until the end of the study:

- Any investigational ARVs.
- Any PIs.
- CCR5 antagonists.
- Integrase inhibitors.
- Any fusion inhibitor.
- Any NNRTIs, except for TMC278.

Nucleo(t)side reverse transcriptase inhibitors other than ABC/3TC, AZT/3TC, and TDF/FTC will be allowed. At all times, 2 N(t)RTIs must be administered as the background regimen.

Hormone replacement therapy is allowed in postmenopausal women. Applicable procedures and treatment guidance based on package inserts should be respected.

Female subjects of childbearing potential must use birth-control methods as outlined previously in Section 4.3 and must be willing to continue practicing these birth-control methods throughout the trial and for at least 1 month after the last intake of TMC278. **Up to and including Protocol Amendment 2,** the use of oral, injectable, and implantable hormonal contraceptives is to be recorded in the Concomitant Therapy eCRF section.

Other comedication is allowed in the following cases:

- In case of rash and/or an allergic reaction, the use of cetirizine (Zyrtec®), levocetirizine (Xyzal®), topical corticosteroids, or antipruritic agents in the recommended dosing schedule is permitted.
- In case of nausea, the use of antiemetics is permitted.
- In case of diarrhea, the use of loperamide or diphenoxylate is permitted.

As of Protocol Amendment 3, concomitant therapies should be documented in the subject's medical records only, as per local standard of care; data will no longer be recorded in the eCRF.

Where rilpivirine is available locally, subjects should follow the local prescribing information for rilpivirine under the guidance of the investigator. Subjects should not take any medications which are listed as contraindicated in the prescribing information for rilpivirine. Where local prescribing information is not available, investigators should follow the guidance in Summary of Product Characteristics[18], United States Prescribing Information[19], or the Investigator's Brochure[3].

9 STUDY EVALUATIONS

9.1 Study Procedures

9.1.1 Overview

The Time and Events Schedule that follows the Synopsis summarizes the frequency and timing of efficacy and safety measurements applicable to this trial.

9.1.2 Pretreatment Phase

Subjects will continue to receive TMC278 without interruption.

At the Roll-over visit, all assessments required at the Final visit in the previous protocol need to be completed first.

9.1.3 Open-Label Treatment Phase

Up to and including Protocol Amendment 2, assessments will be performed as detailed in the Time and Events Schedule. Visits should be performed according to local standard of care, but it is recommended that visits be planned no less frequently than every 6 months. TMC278 will be dispensed at every visit until the time of the Final/Withdrawal Visit, and drug accountability assessed.

It is recommended to perform a urine pregnancy test at every visit if it is not part of local standard care.

If viral load and CD4+ cell count have been measured per local standard of care, the information will be collected at every visit.

The investigator will conduct the Final/Withdrawal visit when the subject meets at least one of the withdrawal criteria (see Section 10.2) or when TMC278 becomes commercially available, is reimbursed, or can be accessed through another source (e.g., access program or government program) by the subject in his/her country (whichever comes first).

As of Protocol Amendment 3, visits and assessments should still be be performed as per local standard of care but documented in the subject's medical records only; data will no longer be recorded in the eCRF. A tool will be available that sites should use to record the date of last intake of TMC278 for each individual subject.

9.1.4 Posttreatment Phase (Follow-Up)

Up to and including Protocol Amendment 2:

In case of loss of virologic response: in order to assist in the selection of a new ARV regimen, determination of the genotype will be performed on the sample collected at the first visit where the viral load is sufficiently high to allow genotyping. Genotyping should be performed at a local/regional certified laboratory facility. In countries where such facilities are not available, the site will arrange for shipment of the sample to Virco Laboratories where a virco®TYPE HIV-1 will be performed. The genotype results will be provided to the investigator who will record these data in the eCRF.

Upon withdrawal from the trial, subjects with an ongoing AE, that is either considered to be at least possibly related to TMC278, a grade 3/4 rash regardless of causality, an AE leading to discontinuation or an SAE, at time of discontinuation will be followed for an additional 30 days (± 2 days).

Investigators may re-contact the subject to obtain long-term follow-up information to determine the subject's safety or survival status (see Section 16.2.3, Informed Consent).

As of Protocol Amendment 3, safety and efficacy will continue to be assessed as part of the local standard of care but should be documented in the subject's medical records only; data will no longer be recorded in the eCRF. A tool will be available that sites should use to record the date of last intake of TMC278 for each individual subject.

9.2 Efficacy

9.2.1 Evaluations

Up to and including Protocol Amendment 2, assays will be performed locally, as per local practice. The results will be collected in the eCRF.

As of Protocol Amendment 3, efficacy will continue to be assessed as part of the local standard of care but should be documented in the subject's medical records only; data will no longer be recorded in the eCRF.

9.2.2 Criteria

Up to and including Protocol Amendment 2: Efficacy measurements will be summarized descriptively.

9.3 Safety Evaluations

Up to and including Protocol Amendment 2:

Any clinically significant abnormalities persisting at the Posttreatment follow-up visit will be followed by the investigator until satisfactory resolution (i.e., value back to baseline value) or until a clinically stable endpoint is reached (to be agreed upon in collaboration with the sponsor).

The trial will include the following evaluations of safety and tolerability according to the time points provided in the Time and Events Schedule.

As of Protocol Amendment 3, safety will continue to be assessed as part of the local standard of care but should be documented in the subject's medical records only; data will no longer be recorded in the eCRF. Investigators should continue to report SAEs, pregnancies, and non-serious clinically important events to the sponsor.

9.3.1 Adverse Events

Up to and including Protocol Amendment 2:
Starting with signing of the ICF onwards to the Final/Withdrawal visit or 30 days (± 2 days) after the Final/Withdrawal visit for AEs ongoing at this visit, AEs will be followed by the investigator. Adverse events considered to be at least possibly related to TMC278, AEs leading to discontinuation, SAEs, and any grade 3/4 rash regardless of causality, will be collected. Other AEs will be collected only if required as per local regulations. For detailed definitions and reporting procedures of AEs see Section 12.

9.3.2 Pregnancies

Up to and including Protocol Amendment 2:
For female subjects of childbearing potential only, a urine pregnancy test (by means of a dipstick) should be performed at the Roll-over visit (= Final visit in the previous trial). This urine pregnancy test is recommended at all other visits following the Roll-over visit, if it is not part of local standard care. The results of these tests will be collected in the eCRF.

9.3.3 Clinical Laboratory Tests

Up to and including Protocol Amendment 2:

All tests will be performed by local laboratories. The sponsor recommends that the laboratory assessments (including hematology, biochemistry (including aspartate aminotransferase [AST], alanine aminotransferase [ALT], pancreatic enzymes, and lipid analyses), plasma viral load, and CD4+ cell count), are done at all trial visits, or more frequently if indicated per local standard of care. The results of the routine laboratory tests (excluding plasma viral load and CD4+ cell count) will only be collected in case of AEs considered to be at least possibly related to TMC278, AEs leading to discontinuations, grade 3/4 rash regardless of causality, or SAEs. Plasma viral load and CD4+ cell count should be recorded in the eCRF at each trial visit, if available.

In case of grade 3 or 4 lab abnormalities, it is recommended to retest within 48 hours for confirmation (see Section 9.3.4 for further guidance and exceptions). In the case of safety concerns, and/or upon the sponsor's request, the site will provide all relevant laboratory results, in which subject identifiers have been removed and/or masked with the exception of the subject's initials, sex, CRF ID and date of birth. Laboratory safety assessments should be performed according to local standard of care taking into account the subject's current medications and the clinical condition. Recommended laboratory safety assessments for TMC278 may be found in the Investigator's Brochure under "Guidance for the Investigator".

9.3.3.1 PREGNANCY TEST

Up to and including Protocol Amendment 2:
For female subjects of childbearing potential only, a urine pregnancy test (by means of a dipstick) should be performed at the Roll-over visit. This urine pregnancy test is recommended at all other visits following the Roll-over visit, if it is not part of local standard care. The results of these tests will be collected in the eCRF.

9.3.3.2 PLASMA VIRAL LOAD

Up to and including Protocol Amendment 2:
Plasma viral load assessments are performed by a local laboratory, per local standard practice. The results will be collected in the eCRF.

9.3.3.3 IMMUNOLOGY

Up to and including Protocol Amendment 2:
Immunology assessments (CD4+ cell count analysis) are performed by a local laboratory, per local standard practice. The results will be collected in the eCRF.

9.3.3.4 RESISTANCE DETERMINATIONS

Up to and including Protocol Amendment 2:
When selecting an ARV regimen to be used in combination with TMC278, careful consideration must be given to previous ARV treatment history, allowed and disallowed ARVs and any information from resistance testing (including any genotype report available from the previous trial in which the subject was enrolled).

In case of loss of virologic response: in order to assist in the selection of a new ARV regimen, determination of the genotype will be performed on the sample collected at the first visit where the viral load is sufficiently high to allow genotyping. Genotyping should be performed at a

local/regional certified laboratory facility. In countries where such facilities are not available, the site will arrange for shipment of the sample to Virco Laboratories where a virco®TYPE HIV-1 will be performed. The genotype results will be provided to the investigator who will record these data in the eCRF.

9.3.4 Specific Toxicities

Up to and including Protocol Amendment 2, management of toxicities will be at the discretion of the investigator, taking into account the following protocol defined procedures, and should follow local standard of care.

As of Protocol Amendment 3, safety should be assessed as part of the local standard of care and documented in the subject's medical records only; data will no longer be recorded in the eCRF.

9.3.4.1 RASH

Since in this trial only subjects who have been exposed to TMC278 for > 48 weeks are included, the emergence of TMC278-related rash is considered very unlikely. Therefore the safety management of rash will be less stringent than in the initial trials. However, specific attention will be given to severe rash of grade 3 or 4 and additional assessments will be required in those cases.

In case of severe (grade 3/4) rash, visits and assessments should be performed as described below and in the "Visit Schedule for Grade 3/4 Rash Management" (see Attachment Attachment 2). **Subjects should be informed that they should contact their doctor and visit the clinic immediately, preferably within 24 hours after the onset of the grade 3/4 rash.** Unscheduled follow-up visits for close follow-up of rash will be performed in case of grade 3/4 rash. At the investigator's discretion, additional visits and assessments can be performed. The rash event, regardless of causality, should be captured in the Adverse Events Section of the eCRF. In case of severe (grade 3/4) rash, safety blood samples need to be taken, and processed by the local laboratory. These samples need to be taken during the unscheduled visits as described below and in Attachment Attachment 2. The values of the local laboratory assessments need to be transcribed in the eCRF by the site staff.

The following parameters need to be tested: AST, ALT, red blood cell (RBC) sedimentation rate and a complete blood cell count (including hemoglobin, hematocrit, RBC count, white blood cell [WBC] count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet count). The subject may be treated symptomatically until the rash resolves. If the rash is considered to be most likely due to concomitant illness or medication other than TMC278, standard management, including discontinuation of the likely causative agent, should be undertaken, and the continuation of the subject in the trial should be discussed with the sponsor. Dermatologist fees for evaluating subjects who experience a rash will be reimbursed by Tibotec. The following grades are based on the Division of Aquired Immunodeficiency Syndrome (DAIDS) grading table, with adaptations made by the sponsor (see Attachment 1).

Grade 1/2 Rash

A grade 1 rash is defined as localized macular rash.

A grade 2 rash is defined as the following: diffuse macular, maculopapular, or morbilliform rash, OR target lesions.

- Subjects may continue the intake of TMC278 (at the investigator's discretion).
- No unscheduled visits are required.

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

In case the rash evolves to grade 3 or 4 unscheduled visits have to be conducted according to the guidelines for grade 3/4 rash.

Grade 3/4 Rash

A grade 3 rash is defined as the following:

- Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR
- Rash with superficial ulcerations of mucous membranes limited to 1 anatomical site (revised by the sponsor) OR
- Rash with at least one of the following (revised by the sponsor):
    - Elevations in AST/ALT more than 2 x baseline value and at least 5 times upper limit of normal (ULN)
    - Fever > 38°C or 100°F.
    - Eosinophils > 1000/mm^3.
    - Serum sickness-like reaction.

A grade 4 rash is defined as the following: 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**.**

For grade 3/4 rash:

Subjects will permanently discontinue the intake of TMC278 and be withdrawn from the trial if in the investigator's opinion, the rash is at least possibly related to TMC278. In that case no rechallenge will be allowed.

Unscheduled visits for rash evaluation are required as follows:

Day 0 (preferably within 24 hours after the onset of the rash) and Day 1:

- Assessment of vital signs by the investigator and safety blood samples by the local laboratory is required. The values of these and all subsequent local laboratory assessments need to be transcribed in the eCRF by the site staff.
- Digital pictures can only be taken if the subject gave consent. If the subject is taking ABC, digital pictures are required; otherwise they are the investigator's discretion.

- Referral to a dermatologist is required on Day 0. A copy of the dermatologist's report should be made anonymous and will be collected by the monitor.
- For grade 4 rash a biopsy should be performed on Day 0. For grade 3 rash a biopsy can be performed at the dermatologist's discretion. A copy of the biopsy report should be made anonymous and will be collected by the monitor.

Days 2, 3, 4, and 5:

- Additional safety blood samples are to be taken by the local laboratory, only if the subject's AST/ALT on Day 0 and/or Day 1 of rash ≥ 2 x baseline value and/or ≥ 5 x ULN and/or in case of rash progression.
- On Day 5 additional safety blood samples are to be taken by the local laboratory regardless of the Day 0 and/or Day 1 AST/ALT levels or rash progression.
- Digital pictures are to be taken under the same conditions as on Day 0/1.

Weekly follow-up:

- Thereafter, weekly follow-up visits are required (or more frequently at the investigator's discretion) as long as grade 3/4 rash is present.
- Weekly assessment of safety blood samples is required only if the subject's AST/ALT on Day 5 of rash is still ≥ 2 x baseline value and/or ≥ 5 x ULN and/or in case of rash progression, until resolution or stabilization of the AST/ALT elevations.
- Digital pictures are to be taken under the same conditions as on Day 0/1.
- Once grade 3/4 rash has resolved to ≤ grade 2 rash, follow-up should be done at the investigator's discretion.

Upon resolution/stabilization of the rash (to be agreed upon in collaboration with the sponsor), the final Cutaneous Reaction/Rash form should be completed. Digital pictures are to be taken under the same conditions as on Day 0/1.

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

A complete summary of the guidelines for grade 3/4 rash management is given in Attachment Attachment 2.

9.3.4.2 ACUTE SYSTEMIC ALLERGIC REACTION

Grade 1 (Localized Urticaria [Wheals] With no Medical Intervention Indicated)

Subjects may continue the intake of TMC278.

Cetirizine, levocetirizine, topical corticosteroids or antipruritic agents may be prescribed, as long as these are in line with the package inserts of the ARV background regimen.

Subjects should be advised to contact the investigator immediately if there is any worsening of the acute systemic allergic reaction.

Grade 2 (Localized Urticaria With Medical Intervention Indicated or Mild Angioedema With no Medical Intervention Indicated)

Subjects may continue the intake of TMC278.

Cetirizine, levocetirizine, topical corticosteroids or antipruritic agents may be prescribed, as long as these are in line with the package inserts of the ARV background regimen.

Subjects should be advised to contact the investigator immediately if there is any worsening of the acute systemic allergic reaction.

Grade 3 (Generalized Urticaria, Angioedema With Medical Intervention Indicated, Symptomatic Mild Bronchospasm) and Grade 4 (Acute Anaphylaxis, Life-Threatening Bronchospasm, or Laryngeal Edema)

Subjects will permanently discontinue the intake of TMC278 and be withdrawn from the trial. Rechallenge is not allowed.

Subjects will be treated as clinically appropriate. Subjects should be followed until resolution of the AE and standard management should be undertaken.

9.3.4.3 AST AND ALT ELEVATION

Grade 1 (≥ 1.25 to ≤ 2.5 x ULN) or Grade 2 (> 2.5 to ≤ 5.0 x ULN) AST or ALT elevation with Grade 1 or 2 total bilirubin elevation (≥ 1.1 to ≤ 2.5 x ULN):

Subjects may continue the intake of TMC278.

Subjects should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation (to be agreed upon with the sponsor).

Grade 3 AST or ALT elevation (> 5.0 to ≤ 10.0 x ULN) with Grade 1 or 2 total bilirubin elevation (≥ 1.1 to ≤ 2.5 x ULN):

Subjects are to interrupt the intake of TMC278. Upon resolution of the laboratory abnormality to at least the lower grade level (≤ grade 2), the subject may resume the intake of TMC278 under the guidance of the investigator and after the investigator has consulted with a sponsor's physician.

If a subject was required to interrupt the intake of TMC278 due to a grade 3 AST or ALT elevation, and after restarting the intake of TMC278 he/she has a recurrence of grade 3 or grade 4 AST or ALT elevation, he/she will permanently discontinue the intake of TMC278 and be withdrawn from the trial.

Grade 3 AST or ALT elevation (> 5.0 to ≤ 10.0 x ULN) with at least Grade 3 total bilirubin elevation (> 2.5 x ULN) or Grade 4 AST or ALT elevation (> 10.0 x ULN):

Subjects will permanently discontinue the intake of TMC278 and be withdrawn from the trial.

It is recommended that the investigator contacts the sponsor to discuss the case. Subjects should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation.

9.3.4.4 PANCREATIC AMYLASE OR LIPASE ELEVATIONS

For confirmed asymptomatic grade 1 and grade 2 pancreatic amylase or lipase elevations, and confirmed asymptomatic grade 3 pancreatic amylase elevations with no history or concomitant disease of pancreatitis, subjects should be carefully evaluated and followed closely. An overview of the laboratory ranges to assign grading to a laboratory value for pancreatic amylase and lipase is provided in Attachment 1: DAIDS table.

For confirmed asymptomatic grade 4 elevations of pancreatic amylase or confirmed asymptomatic grade 3 or grade 4 elevations of lipase, subjects should interrupt the intake of TMC278 until pancreatic amylase returns to grade ≤ 3 or lipase returns to grade ≤ 2, at which time TMC278 therapy could be reintroduced. If asymptomatic grade 4 elevations of pancreatic amylase or asymptomatic grade 3 or 4 lipase levels recur with reintroduction of TMC278, the subject should permanently discontinue the intake of TMC278 and be withdrawn from the trial.

If the subject experiences symptomatic pancreatitis that is considered at least possibly related to TMC278, the subject should permanently discontinue the intake of TMC278 and be withdrawn from the trial.

9.3.4.5 CLINICAL HEPATITIS

Non-viral hepatitis

Subjects taking TMC278 should be monitored for the development of signs and symptoms of hepatitis which include but are not limited to fatigue, malaise, anorexia, nausea, dark urine and clay colored stools, bilirubinuria, jaundice, liver tenderness, or hepatomegaly, with or without initially abnormal serum transaminase levels.

Subjects with these signs and symptoms must seek medical attention immediately and have hepatic parameters assessed. Relevant markers of viral hepatitis should also be assessed.

At the discretion of the investigator, subjects may permanently discontinue the intake of TMC278 and be withdrawn from the trial. Subjects need to be followed until resolution of the AE.

Viral Hepatitis

If a subject is diagnosed with acute clinical hepatitis A, B, or C infection (with signs and symptoms present) during the trial, the subject should permanently discontinue the intake of TMC278 and be withdrawn from the trial.

9.3.4.6 RENAL COMPLICATIONS

If renal complications develop, subjects should be closely monitored for disturbances in serum creatinine and for abnormalities in urine analysis (e.g., proteinuria). Additional investigations can be performed at the investigator´s discretion. Subjects must be treated as clinically appropriate.

Subjects, who develop a renal complication considered to be at least possibly related to TMC278, will permanently discontinue the intake of TMC278 and should be followed appropriately until resolution of AE or toxicity. Rechallenge is not allowed.

9.3.4.7 NEURO-PSYCHOLOGICAL SYMPTOMS

Subjects should be informed that the investigational medication may cause dizziness, impaired concentration, drowsiness, sleeplessness, and/or abnormal dreaming, and instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery.

There have been reports of delusions and inappropriate behavior in subjects receiving licensed NNRTIs, predominantly in subjects with a history of mental illness or substance abuse. Severe acute depression (including suicidal ideation/attempts) has also been infrequently reported. Subjects who experience these symptoms should contact the investigator immediately because discontinuation of the investigational medication may be required. Investigators should refer subjects reporting such symptoms for immediate psychiatric evaluation/medical intervention.

In case of grade 3 alterations in personality behavior or in mood (alteration causing inability to perform usual social and functional activities) and grade 4 alterations in personality behavior or in mood (behavior potentially harmful to self or others [e.g., suicidal and homicidal ideation or attempt, acute psychosis] or causing inability to perform basic selfcare functions): if the neuro-psychological symptoms are considered to be at least possibly related to TMC278, the investigational medication will be permanently discontinued, and the subject withdrawn from the trial.

9.3.4.8 GASTROINTESTINAL NAUSEA (WITH OR WITHOUT VOMITING)

Although common, nausea following initiation of therapy with (antiretroviral) medication usually subsides or resolves during the first few weeks of treatment.

Grade 1 (Transient [< 24 Hours] or Intermittent Nausea With No or Minimal Interference With Oral Intake) and Grade 2 (Persistent Nausea Resulting in Decreased Oral Intake for 24 to 48 Hours)

Subjects may continue the intake of TMC278 and may be treated as needed with antiemetics given orally or rectally.

Grade 3 (Persistent Nausea Resulting in Minimal Oral Intake for > 48 Hours, or Aggressive Rehydration Indicated) and Grade 4 (Life-Threatening Consequences)

Subjects will permanently discontinue the intake of TMC278 and be withdrawn from the trial if nausea is considered to be at least possibly related to TMC278. Rechallenge is not allowed. Subjects should be followed until resolution of the AE.

9.3.4.9 DIARRHEA

Grade 1 (Transient or Intermittent Episodes of Unformed Stools, or Increase of ≤ 3 Stools Over Baseline per 24-Hour Period) or Grade 2 (Persistent Episodes of Unformed to Watery Stools, or Increase of 4 to 6 Stools Over Baseline per 24-Hour Period)

Subjects may continue the intake of TMC278. Loperamide or diphenoxylate can be administered.

Grade 3 (Bloody Diarrhea, Increase of ≥ 7 Stools per 24-Hour Period, or i.v. Fluid Replacement Indicated), or Grade 4 (Life-Threatening Consequences)

Subjects will permanently discontinue the intake of TMC278 and be withdrawn from the trial if diarrhea is considered to be at least possibly related to TMC278. Rechallenge is not allowed. Subjects should be followed until resolution of the AE.

9.3.4.10 OTHER TOXICITIES

Grade 1

Subjects who develop a grade 1 AE or laboratory toxicity may continue intake of the ARV medication (TMC278 and background regimen).

Grade 2

Subjects who develop a grade 2 AE or laboratory toxicity may continue intake of the ARV medication (TMC278 and background regimen) based on the investigator's clinical judgment.

Grade 3

Subjects who develop a grade 3 AE or laboratory toxicity should temporarily interrupt all ARV medication (TMC278 and background regimen) and may resume all therapy when the AE or laboratory abnormality resolved to within one grade level of the subject's baseline but not higher than grade 2.

The following exceptions apply:

- subjects with pre-existing diabetes who experience a glucose elevation of grade 3.
- subjects who experience asymptomatic glucose, triglyceride or cholesterol elevations of grade 3.
- subjects who experience asymptomatic pancreatic amylase elevations of grade 3 with no history or concomitant disease of pancreatitis (see Section 9.3.4.4).
- subjects who experience an AE or laboratory toxicity that is considered not related or doubtfully related to TMC278.

Grade 4

Subjects experiencing a grade 4 AE or laboratory toxicity will permanently discontinue all ARV treatment (TMC278 and background regimen) and will be withdrawn from the trial (see Section 10.2).

The following exceptions apply:

- subjects with pre-existing diabetes who experience a glucose elevation of grade 4.
- subjects who experience asymptomatic glucose or triglyceride elevations of grade 4.

- subjects who experience asymptomatic pancreatic amylase and lipase elevations of grade 4 (see Section 9.3.4.4).
- subjects who experience an AE or laboratory toxicity that is considered not related or doubtfully related to TMC278 (except for allergic reaction: all subjects experiencing this type of grade 4 AE should be permanently discontinued, regardless of causality).

If the subject has pre-existing diabetes and experiences persistent grade 3 or 4 glucose elevations despite appropriate antidiabetic medication/management, the subject should permanently discontinue the intake of TMC278 and be withdrawn from the trial.

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

10 SUBJECT COMPLETION/WITHDRAWAL

10.1 Completion

A subject will be considered to have completed the trial if:

- Rilpivirine becomes commercially available AND is reimbursed, OR
- Rilpivirine can be accessed through another source (e.g., access program or government program) by the subject in his/her country, OR
- The investigator finds it in the subject's best interest to switch to other local (rilpivirine-based) treatment options or local standard of care as appropriate.

10.2 Withdrawal From the Study

Treatment with TMC278 must be discontinued and the subject must be withdrawn from the trial if any of the following apply:

- Termination of the trial by the sponsor.
- The subject no longer benefits from TMC278 treatment, in the opinion of the investigator.
- The subject dies.
- The subject is lost to follow-up. In case a subject is lost to follow-up, every reasonable effort must be made by the trial site personnel to contact the subject and determine the reason for discontinuation/withdrawal The measures taken to follow-up must be documented.
- The subject withdraws consent.
- The investigator believes that for safety reasons (e.g., AE) it is in the best interest of the subject to stop treatment.
- The subject becomes pregnant.
- The subject demonstrates loss of virologic response, defined as per local standard practice.

- The subject develops tuberculosis during the trial. He/she will be withdrawn from the trial to allow appropriate tuberculosis therapy to be installed.
- The subject changes the ARV underlying regimen he/she is receiving while continuing to receive TMC278 treatment, with the exception of within class N(t)RTI substitutions and dose adjustments for tolerance reasons.
- The subject fails to comply with the protocol or trial staff requirements.
- The subject meets any of the criteria for withdrawal specified in Section 9.3.4.

Up to and including Protocol Amendment 2: Upon withdrawal from the trial, subjects with an ongoing AE, that is either considered to be at least possibly related to TMC278, a grade 3/4 rash, an AE leading to discontinuation, or SAE, at time of discontinuation will be seen for a withdrawal visit and a follow-up visit at 4 weeks posttreatment (except in the case of withdrawal of consent). For these subjects, the date and reason for withdrawal are to be documented in the eCRF and in the source document. Remaining data should be completed on the date of the last scheduled follow-up visit.

After the last trial visit, the Investigator's Signature page of the eCRF must be completed and signed.

TMC278 assigned to the withdrawn subject will not be assigned to another subject. Subjects who withdraw will not be replaced.

As of Protocol Amendment 3, visits and assessments should still be performed as per local standard of care, but documented in the subject's medical records only.

11 STATISTICAL METHODS

As of Protocol Amendment 3, safety and efficacy will continue to be assessed as part of the local standard of care but should be documented in the subject's medical records only; data will no longer be recorded in the eCRF and therefore no further analyses will be performed.

11.1 Subject Information

An intent-to treat analysis will be performed, i.e., all subjects who have signed an ICF and received at least 1 dose of TMC278 in this trial will be included in this analysis. Tabulations and descriptive statistics will be provided.

11.2 Efficacy Analyses

Tabulations and descriptive statistics analyses on collected viral load and CD4+ cell count data will be provided.

11.3 Sample Size Determination

No formal sample size determination has been performed for this trial: any subject in the TMC278 Phase IIb or Phase III trials, who has given consent to participate and who is eligible and willing, may participate in this trial.

11.4 Safety Analyses

Adverse Events

Up to and including Protocol Amendment 2: Starting with signing of the ICF onwards to the Final/Withdrawal visit or 30 days (± 2 days) after the Final/Withdrawal visit for AEs ongoing at this visit, AEs will be followed by the investigator. Adverse events considered to be at least possibly related to TMC278, AEs leading to discontinuation, SAEs, and any grade 3/4 rash regardless of causality, will be collected. Other AEs will be collected only if required as per local regulations. The original terms used in the eCRFs by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities. All collected AEs with onset during the treatment period (i.e., treatment-emergent AEs) will be included in the tabulations. For each AE, the percentage of subjects who experienced at least 1 occurrence of the given event will be summarized.

As of Protocol Amendment 3, safety will continue to be assessed as part of the local standard of care but should be documented in the subject's medical records only; data will no longer be recorded in the eCRF. Investigators should continue to report SAEs, pregnancies, and non-serious clinically important events to the sponsor.

12 ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical trials are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical trials conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

As of Protocol Amendment 3, safety will continue to be assessed as part of the local standard of care but should be documented in the subject's medical records only. Investigators should continue to report SAEs, pregnancies, and non-serious clinically important events to the sponsor.

12.1 Definitions

12.1.1 Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical trial subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product (definition per International Conference on Harmonisation [ICH]).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs starting with the signing of the ICF (refer to Section 12.2.1, All Adverse Events, for time of last AE recording).

Changes in viral load should not be reported as an AE/SAE.

Changes in CD4+ cell counts, either decreases or increases, should not be reported as an AE/SAE.

Serious Adverse Event

An SAE as defined by ICH is any untoward medical occurrence that at any dose meets any of the following conditions:

- Results in death.
- Is life-threatening
  (the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

Note: Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in situations other than those listed above. For example, important medical events may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above (e.g., suspected transmission of an infectious agent by a medicinal product should be reported as an SAE). Any AE is considered an SAE if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An unlisted AE is one of which the nature or severity is not consistent with the applicable product reference safety information. For an investigational product, the expectedness of an AE will be determined by whether or not it is listed in the Investigator's Brochure and possible Addenda.

Associated With the Use of the Drug

An AE is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2.

12.1.2 Attribution Definitions

Not related

An AE that is not related to the use of the drug.

Doubtful

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

Possible

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

Probable

An AE that 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), concomitant disease(s).

Very likely

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

12.2 Procedures

12.2.1 All Adverse Events

Up to and including Protocol Amendment 2:

Starting with signing of the ICF onwards to the Final/Withdrawal visit or 30 days (± 2 days) after the Final/Withdrawal visit for AEs ongoing at this visit, AEs will be followed by the investigator.

Adverse events considered to be at least possibly related to TMC278, AEs leading to discontinuation, SAEs, and any grade 3/4 rash regardless of causality, will be recorded in the eCRF. Other AEs will be collected only if required as per local regulations. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of TMC278, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All AEs collected at any time during the trial will be followed until satisfactory resolution (e.g., value back to baseline value) or stabilization or until final database lock.

Certain long-term AEs related to therapy cannot be followed until resolution within the setting of this trial. In these cases follow-up will be the responsibility of the treating physician.

All events that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments. All AEs considered to be at least possibly related to TMC278, AEs leading to discontinuation, SAEs, and any grade 3/4 rash regardless of causality must be recorded using medical terminology in the source document and the eCRF. All other AEs must be recorded in the source document as required per local regulations. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as “upper respiratory infection”). Investigators must record in the eCRF their opinion concerning the relationship of the AE to trial therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator all SAEs that are unlisted (unexpected) and associated with the use of the drug. The investigator (or sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

Adverse events reporting, including suspected unexpected serious adverse reactions, will 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, will be reported by the sponsor as soon as possible to the competent authority(ies) concerned together with proposed actions.

Subjects (or their designees, if appropriate) must be provided with a “study card” indicating the name of the investigational study drug, the study number, the investigator’s name, a 24-hour emergency contact number, and excluded concomitant medications.

As of Protocol Amendment 3, safety will continue to be assessed as part of the local standard of care but should be documented in the subject’s medical records only; data will no longer be

recorded in the eCRF. Investigators should continue to report SAEs, pregnancies, and non-serious clinically important events to the sponsor.

12.2.2 Serious Adverse Events

All SAEs occurring during clinical trials (between signing of informed consent and end of the study) must be reported to the appropriate sponsor contact person by investigational staff within 24 hours of their knowledge of the event. For the names and contact details of the contact persons, see Contact Information pages provided separately. Any SAEs with at least a possible relationship to TMC278 occurring after the end of the trial must be reported, and will be handled by the sponsor.

The cause of death of a subject in a clinical trial, whether or not the event is expected or associated with the investigational agent, is considered an SAE. Suspected transmission of an infectious agent by a medicinal product should be reported as an SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a clinical trial must be reported as an SAE, except hospitalizations for the following:

- Social reasons in absence of an AE.
- Surgery or procedure planned before entry into the trial (must be documented in the eCRF) ***Note***: Hospitalizations that were planned prior to the signing of informed consent, and where the underlying condition for which the hospitalization was planned has not worsened will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a member of the investigational staff, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax).

The first report of an SAE may also be made by telephone. The investigator must provide the minimal information: i.e., study number, subject's initials and date of birth, medication code number, period of intake, nature of the AE, and investigator's attribution.

This report of an SAE by telephone must always be confirmed by a written, more detailed report (the Serious Adverse Event Form) to be completed and signed by the investigator. 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.

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

All SAEs that have not resolved by the end of the trial or that have not resolved upon discontinuation of the subject's participation in the trial, must be followed until any of the following occurs:

- The event resolves.
- The event stabilizes.
- The event returns to baseline, if a baseline value is available.
- The event can be attributed to agents other than TMC278 or to factors unrelated to trial conduct.
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

12.2.3 Pregnancy

All initial reports of pregnancy must be reported to the sponsor by the investigational staff within 24 hours of their knowledge of the event using the appropriate pregnancy notification form/a Serious Adverse Event Form. Abnormal pregnancy outcomes are considered SAEs and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the trial must be promptly withdrawn from the trial.

Because the effect of TMC278 on sperm is unknown, pregnancies in partners of male subjects included in the trial will be reported by the investigational staff within 24 hours of their knowledge of the event using the appropriate pregnancy notification form/ a Serious Adverse Event Form.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.3 Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the trial are listed in the Contact Information page(s), which will be provided as a separate document.

13 PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, i.e., any dissatisfaction relative to the identity, quality, durability, reliability of a product, including its labeling or package integrity. A product quality complaint may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from clinical trials are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements

worldwide to ensure appropriate reporting of PQC information; all clinical trials conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1 Procedures

All initial PQCs must be reported to the sponsor by the investigational staff as soon as possible after being made aware of the event.

If the defect is combined with an SAE, the investigational staff must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 12.2.2). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2 Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed on the Contact Information page(s), which will be provided as a separate document.

14 STUDY DRUG INFORMATION

14.1 Physical Description of Study Drug

The investigational medication, TMC278, will be manufactured and provided under the responsibility of the sponsor. TMC278 is formulated as an oral tablet (F006), containing 27.5 mg of TMC278 as the hydrochloric acid salt R314585, equivalent to 25 mg of TMC278 as the free base, in combination with lactose monohydrate, croscarmellose sodium, povidone (K30), polysorbate 20, silicified microcrystalline cellulose, and magnesium stearate, and coated with a white coating powder and purified water (processing solvent, minimized in final formulation).

14.2 Packaging

TMC278 25 mg oral tablets will be packaged in 30 count, child-proof bottles under the responsibility of the sponsor.

Background regimen will not be provided by the sponsor.

14.3 Labeling

TMC278 labels will contain information to meet the applicable regulatory requirements.

Labels will contain the protocol number, batch or reference number, storage caution statements, dispensing instructions and ‘keep out of reach of children’ warning.

No medication can be relabeled without prior approval from the sponsor.

14.4 Preparation, Handling, and Storage

Storage conditions will be detailed on the label. Supplies need to be stored in the original container.

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

- study number.
- reference or batch number(s).
- kit number.
- site number.
- temperature log (including date and duration of the deviation, and the minimum temperature below the range and/or maximum temperature above the range that the product was exposed to).
- used units (°C or °F).

Deviations in storage conditions will be evaluated by the sponsor/stability manager.

Antiretroviral medication must be handled strictly in accordance with the protocol and the packaging labels and will be stored in a limited access area or in a locked cabinet under appropriate environmental conditions. Storage and dosing instructions and an expiration date will be supplied with TMC278. Used medication packs should be returned by the subject and should be kept at the site for drug accountability purposes. Access to ARV medication should be restricted to designated trial personnel.

Background medication must be stored according to locally applicable procedures and conditions and as stipulated in the prescribing information.

Up to and including Protocol Amendment 2, the monitor will periodically check the supplies of TMC278 held by the investigator or pharmacist to ensure accountability and appropriate storage conditions.

As of Protocol Amendment 3, the investigator or pharmacist remains responsible for accountability and appropriate storage conditions of TMC278 supplies but supplies will no longer be checked by the monitor. At the end of the trial, all unused TMC278 medication will be returned to the sponsor unless other arrangements have been agreed to with the sponsor.

14.5 Drug Accountability

The investigator is responsible for ensuring that all TMC278 received at the site is inventoried and accounted for throughout the trial. The dispensing of TMC278 to the subject, and the return of TMC278 from the subject (if applicable), must be documented on the drug accountability form. Subjects must be instructed to return all original containers, whether empty or containing TMC278. TMC278 returned by trial subjects will be stored and disposed of according to the sponsor's instructions. Site staff must not combine contents of TMC278 containers.

TMC278 must be handled in strict accordance with the protocol and the container label and will be stored in a limited access area or in a locked cabinet under appropriate environmental conditions.

Up to and including Protocol Amendment 2, unused TMC278, and TMC278 returned by the subject (if applicable), must be available for verification by the sponsor's site monitor during on-site monitoring visits.

The return to the sponsor of unused TMC278, or used returned TMC278 for destruction, will be documented on the Drug Return Form. When the site is an authorized destruction unit and TMC278 supplies are destroyed on site, this must also be documented on the Drug Return Form.

Returned TMC278 must not be dispensed again, even to the same subject. TMC278 may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense TMC278 from, nor store it at, any location other than the trial sites agreed upon with the sponsor.

As of Protocol Amendment 3, unused TMC278 and TMC278 returned by the subject will not be verified by the sponsor.

15 STUDY SPECIFIC MATERIALS

Investigators will be provided with the latest version of the Investigator's Brochure for TMC278.

16 ETHICAL ASPECTS

16.1 Study-Specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the trial and, during the trial, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the trial is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential AEs of the trial, and provide their consent voluntarily will be enrolled.

This trial is designed to provide continued access to TMC278 to HIV-1 infected subjects who were previously treated with TMC278 in a clinical trial, and who, at the time of roll-over, experience and are expected to continue experiencing clinical benefit from TMC278 treatment. In addition, information on the long-term safety and tolerability of oral doses of TMC278 25 mg q.d. in combination with a background regimen containing 2 N(t)RTIs will be collected **up to and including Protocol Amendment 2**.

Subjects will only continue to receive TMC278 25 mg q.d. in the trial until one of the criteria detailed in Section 10.2 is met.

16.2 Regulatory Ethics Compliance

16.2.1 Investigator Responsibilities

The investigator is responsible for ensuring that the clinical trial is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies 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 originated in the Declaration of Helsinki, and that the clinical trial data are credible.

16.2.2 Independent Ethics Committee or Institutional Review Board (IEC/IRB)

Before the start of the trial, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents:

- Final protocol and, if applicable, amendments.
- Sponsor-approved ICF (and any other written materials to be provided to the subjects).
- Investigator's Brochure (or equivalent information) and addenda.
- Sponsor-approved subject recruiting materials.
- Information on compensation for trial-related injuries or payment to subjects for participation in the trial, if applicable.
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by IEC/IRB).
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects.
- Any other documents that the IEC/IRB requests to fulfill its obligation.

This trial will be undertaken only after the IEC/IRB has given full approval of the final protocol, substantial/major amendments (if any), the informed consent form, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the trial, the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Substantial/major protocol amendments.

- Revision(s) to informed consent form and any other written materials to be provided to subjects.
- If applicable, new or revised subject recruiting materials approved by the sponsor.
- Revisions to compensation for trial-related injuries or payment to subjects for participation in the trial, if applicable.
- Investigator's Brochure addenda or new edition(s).
- Summaries of the status of the trial at intervals stipulated in guidelines of the IEC/IRB (at least annually).
- Reports of AEs that are serious, unlisted, and associated with the investigational drug.
- New information that may adversely affect the safety of the subjects or the conduct of the trial.
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects.
- Report of deaths of subjects under the investigator's care.
- Notification if a new investigator is responsible for the trial at the site.
- Annual Safety Report, Short Term Study Specific Safety Summary and Line Listings, where applicable.
- Any other requirements of the IEC/IRB.

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or trial conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s), except when necessary to eliminate immediate hazard to the trial subjects. If a deviation from, or a change to the protocol was implemented to eliminate an immediate hazard to trial subjects, then the implemented deviation or change, the reasons for it, and, if appropriate, the protocol amendment should be submitted to the IEC/IRB as soon as possible.

At least once a year, the IEC/IRB will be asked to review and reapprove this clinical trial. The reapproval should be documented in writing.

At the end of the trial, the investigator (or sponsor where required) will notify the IEC/IRB about the trial completion.

16.2.3 Informed Consent

Each subject must give written consent according to local requirements after the nature of the trial has been fully explained. The consent form must be signed before performance of any trial-related activity. The consent form that is used must be approved by both the sponsor and by the reviewing IEC/IRB. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

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

The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the trial, consent should be appropriately recorded by means of the subject's personally dated signature. After having obtained the consent, a copy of the informed consent form must be given to the subject.

If the subject is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject is obtained, if permitted by local law.

Written assent should be obtained from subjects who are able to write. After having obtained the assent, a copy of the assent form must be given to the subject.

16.2.4 Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this trial will be limited to those data that are necessary to investigate the efficacy, safety, quality, and utility of the investigational study drug(s) used in this trial.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of trial subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator to allow direct access to his or her original medical records for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the trial, and the applicable laws and regulations. However, this access to personal data may be postponed until the end of the trial if such access would interfere with the conduct of the trial. Even if the subject withdraws consent, certain personal data obtained within the scope of this trial may still be processed by the sponsor if permitted by the applicable legislation. If the results of the trial are published, the identity of the subjects will remain confidential. If reference is made to specific subjects, this will only be done by using code numbers.

16.2.5 Country Selection

Unless explicitly addressed as a specific ethical consideration in Section 16.1 this trial will only be conducted in those countries where the intent is to help ensure access to the developed product.

17 ADMINISTRATIVE REQUIREMENTS

17.1 Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Substantial/major protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor or its designee. When the change(s) involves only logistic or administrative aspects of the trial, the IRB (and IEC where required) only needs to be notified.

During the course of the trial, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (see Contact Information pages provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2 Regulatory Documentation

17.2.1 Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A trial may not be initiated until all local regulatory requirements are met.

17.2.2 Required Prestudy Documentation

The following documents must be provided to the sponsor or its representative before shipment of TMC278 to the investigational site:

- Protocol and amendment(s), if any, signed and dated by the investigator.
- A copy of the dated and signed written IEC/IRB approval of the protocol, amendments, informed consent form, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed by the chairman or authorized designee.
- Name and address of the IEC/IRB including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the investigational staff is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the trial.
- Regulatory authority approval or notification, if applicable.
- Signed and dated statement of investigator (e.g., Form FDA 1572), if applicable.
- Documentation of investigator qualifications (e.g., curriculum vitae).
- Completed investigator financial disclosure form from the investigator, where required. ***Note:*** **The investigator should promptly update this information if any relevant changes occur up to 1 year following trial completion.**
- Signed and dated clinical trial agreement, which includes the financial agreement.
- Any other documentation required by local regulations.

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators.
- Documentation of subinvestigator qualifications (e.g., curriculum vitae).
- Photocopy of the site signature log, describing delegation of roles and responsibilities at the start of the trial.

- Name and address of any local laboratory conducting tests for the trial, and a dated copy of current laboratory normal ranges for these tests.
- Local laboratory documentation demonstrating competence and test reliability (e.g., accreditation/license), if applicable.

17.3 Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the trial. This document will be reviewed by the sponsor site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the trial file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the trial will identify subjects by initials and/or assigned number only.

The investigator must also complete a subject-screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the trial.

17.4 Source Documentation

Up to and including Protocol Amendment 2:

At a minimum, source documentation must be available for the following to confirm data collected in the eCRF: subject identification, eligibility, and trial identification; trial discussion and date of informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs; and follow-up of AEs; concomitant medication; drug receipt/dispensing/return records; TMC278 administration information; and date of trial completion, and reason for early discontinuation of trial drug or withdrawal from the trial, if applicable. Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded on the eCRF are consistent with the original source data.

In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a trial subject should be consistent with that commonly recorded at the site as a basis for standard medical care. Specific details required as source data for the trial will be reviewed with the investigator before the trial and will be described in the monitoring guidelines (or other equivalent document). The nature and location of all source documents will be identified in the Source Document Identification Form.

All data recorded in the eCRF must have a source in the subject's medical records.

17.5 Case Report Form Completion

Up to and including Protocol Amendment 2:

Case report forms are provided for each subject in electronic format.

Electronic Data Capture (eDC) will be used for this trial. The trial data will be transcribed by trial personnel from the source documents onto an electronic CRF, and transmitted in a secure manner to the sponsor within 7 days of the subject's visit. The electronic file will be considered to be the eCRF.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documentation. Such worksheets should not resemble an eCRF and should not be generated by the sponsor. All data relating to the trial must be recorded in eCRFs prepared by the sponsor. Data must be entered into eCRFs in English. Designated site personnel must complete eCRFs as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

The investigator must verify that all data entries in the eCRFs are accurate and correct.

All eCRF entries, corrections, and alterations must be made by the investigator or other authorized trial-site personnel.

If necessary, queries will be generated in the eDC tool. The investigator or an authorized member of the investigational staff must adjust the eCRF (if applicable) and complete the query. If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in 3 different ways:

- Site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Site manager can generate a query (field Data Correction Form) for resolution by the investigational staff.
- Clinical data manager can generate a query for resolution by the investigational staff.

As of Protocol Amendment 3, visits and assessments should still be performed as per local standard of care but documented in the subject's medical records only; data will no longer be recorded in the eCRF.

17.6 Data Quality Control

Up to and including Protocol Amendment 2:

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate trial centers, review of protocol procedures with the investigator and associated personnel before the trial, and periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from the selected laboratory into the sponsor's data base. Written instructions will be provided for collection, preparation, and shipment of blood, plasma, and urine samples.

Guidelines for eCRF completion will be provided and reviewed with trial personnel before the start of the trial.

The sponsor will review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the clinical trial database they will be verified for accuracy.

As of Protocol Amendment 3, no data collection will take place.

17.7 Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRFs and all source documents that support the data collected from each subject, as well as all trial documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all trial documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must 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 until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the trial records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any trial documents before having obtained written approval from 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.

17.8 Monitoring

Up to and including Protocol Amendment 2:

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a trial center visit log that will be kept at the site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to substantiate the eCRF are known to the sponsor and investigational staff and are accessible for verification by the sponsor site contact. If electronic records are maintained at the investigational site, the method of verification must be discussed with the investigational staff.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data. Findings from this review of eCRFs and source documents will be discussed with the investigational staff. The sponsor expects that, during monitoring visits, the relevant investigational staff will be available, the source documentation will be accessible, and a suitable environment will be provided for review of trial-related documents. The monitor will meet with the investigator on a regular basis during the trial to provide feedback on the trial conduct.

As of Protocol Amendment 3, no data collection will take place, hence study monitoring and source data verification will not be performed (with the exception of a site closure visit).

17.9 Study Completion/Termination

17.9.1 Study Completion

The trial is considered completed when all subjects have switched to locally available rilpivirine (ie, commercially available AND reimbursed, OR accessible through another source [eg, access program or government program]), other local (rilpivirine-based) treatment options, or local standard of care, as appropriate.

The trial is considered completed with the last visit of the last subject participating in the trial. The final data from the investigational site will be sent to the sponsor (or designee) after completion of the final subject visit at that site, in the time frame specified in the Clinical Trial Agreement.

17.9.2 Study Termination

The sponsor reserves the right to close the investigational site or terminate the trial at any time for any reason at the sole discretion of the sponsor. 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.

Investigational sites will be closed upon trial completion. An investigational site is considered closed when all required documents and trial supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of an investigational site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the investigator.

- Discontinuation of further drug development.

The sponsor is committed to provide TMC278 in a participating country until all subjects have switched to locally available rilpivirine (ie, commercially available AND reimbursed, OR accessible through another source [eg, access program or government program]), other local (rilpivirine-based) treatment options, or local standard of care, as appropriate.

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.

17.10 On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the site at any time during or after completion of the trial to conduct an audit of the trial in compliance with regulatory guidelines and company policy. These audits will require access to all trial records, including source documents, for inspection and comparison with the eCRFs. Subject privacy must, however, be respected. The investigator and staff are responsible for being present and available for consultation during routinely scheduled site audit visits conducted by the sponsor or its designees.

Similar procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this trial in support of a regulatory submission. The investigator should immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

17.11 Use of Information and Publication

All information, including but not limited to information regarding TMC278 or the sponsor's operations (e.g., patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic research data, generated as a result of this trial, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this trial, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the clinical trial will be used by the sponsor in connection with the continued development of TMC278 and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the trial.

The sponsor will create an Annual Safety Report (ASR) and Line Listings in accordance with the European Community Clinical Trials Directive, with a data lock date of 19 May. This trial TMC278-TiDP6-C222 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 trial approval date, and in all subsequent ASRs, as appropriate, until trial closure.

The results of the trial will be reported in a Clinical Research Report generated by the sponsor and will contain eCRF data from all investigational sites that participated in the trial. Only limited safety data are being collected as of **Protocol Amendment 3,** which will be included in an addendum to the Clinical Research Report; additionally, appropriate safety reports will continue to be provided to IECs/IRBs and regulatory authorities, as required.

Recruitment performance or specific expertise related to the nature and the key assessment parameters of the trial will be used to determine a coordinating investigator.

Clinical narratives will be written for the following events (if applicable):

- All deaths (irrespective of drug relationship).
- All other SAEs with an at least possible relationship to the active investigational drug (i.e., only for the treatment arm[s] with active investigational drug[s]).
- All discontinuations due to AEs with an at least possible relationship to TMC278 (including investigational drug[s] and any other study drugs [e.g., control drug, background regimen/standard of care]).
- All grade 3 or 4 events of special interest (ESI) as defined in the Clinical Trial Protocol (CTP) (irrespective of drug relationship) occurring in the active investigational drug treatment arm(s) and starting during the treatment period with the investigational drug(s). For some of these ESIs, which are specified in the CTP, narratives will also be written for grade 1 and 2.
- At the discretion of the team and after statistical analysis of the data, certain discontinuations not related to AEs of treatment failure, i.e., related to lost to follow-up or withdrawal of consent (irrespective of treatment arm).
- Any additional ESIs explicitly requested by the regulatory agencies.
- Any additional ESIs (and severity grades) identified after statistical analysis of the data as potential safety hazards, occurring in the active investigational drug treatment arm(s) and starting during the treatment period with the investigational drug(s).

One investigator will be appointed for signing off the final Clinical Research Report. The selection of this investigator will be determined by recruitment performance and specific expertise related to the nature of the trial and the key assessment parameter(s). A summary of this final version will be provided to the investigators, to the applicable regulatory authorities, and IECs/IRBs, if required by the applicable regulatory requirements, within 1 year of the end of the trial (LastPatientLastVisit).

The sponsor shall have the right to publish such data and information without approval from the investigator. If an investigator wishes to publish information from the trial, a copy of the

manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter trial designs and substudy approaches, results may need to be published in a given sequence (e.g., substudies should not generally be published before the primary endpoints of a trial have been published). Similarly, investigators will recognize the integrity of a multicenter trial by not publishing data derived from the individual site until the combined results from the completed trial have been published in full, within 12 months after conclusion, abandonment, or termination of the trial at all sites, or the sponsor confirms there will be no multicenter trial publication. Authorship of publications resulting from this trial will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the trial or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

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ATTACHMENT 1: DAIDS TABLE

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

Quick Reference

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

General Instructions

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

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

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

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

Definitions

Basic self-care functions	Adult: activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding. Young children: activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).
Usual social & functional activities	Adult: adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc. Young Children: activities that are age and culturally appropriate (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.

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.

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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.

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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

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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 Genitourinary for Vulvovaginitis See also Dysphagia-Odynophagia and Proctitis	Erythema of the Mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (e.g., aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 – 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (e.g., 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

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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.

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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

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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

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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
GENITOURINARY				
Cervicitis (symptoms) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Cervicitis (clinical exam) (For use in studies evaluating topical study agents) For other cervicitis, see Infection: Infection (any other than HIV infection)	Minimal cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption < 25% of total surface	Moderate cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption of 25% – 49% total surface	Severe cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption 50% – 75% total surface	Epithelial disruption > 75% total surface
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

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CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Vulvovaginitis (symptoms) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Vulvovaginitis (clinical exam) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Minimal vaginal abnormalities on examination OR Epithelial disruption < 25% of total surface	Moderate vaginal abnormalities on examination OR Epithelial disruption of 25% – 49% total surface	Severe vaginal abnormalities on examination OR Epithelial disruption 50% – 75% total surface	Vaginal perforation OR Epithelial disruption > 75% total surface
OCULAR/VISUAL				
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)
ENDOCRINE/METABOLIC				
Abnormal fat accumulation (e.g., back of neck, breasts, abdomen)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA

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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).

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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) [c,d]	≥ 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)[c]	≥ 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 lifethreatening consequences	pH > 7.5 with lifethreatening 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*

ATTACHMENT 2: VISIT SCHEDULE FOR GRADE 3/4 RASH MANAGEMENT (RASH FULLY CHARACTERIZED)

This visit schedule summarizes the visits and assessments to be performed in case of grade 3/4 rash. At the investigator's discretion, additional visits and assessments can be performed. **Local laboratory blood sample assessments will be documented/collected as described.**

	Grade 3 or 4 Rash
Day 0[1] (preferably within 24 hours after onset of rash)	• TMC278 **MUST** be permanently **DISCONTINUED**, if in the investigator's opinion, the rash is at least possibly related to TMC278. Rechallenge is **NOT ALLOWED**. • Unscheduled visit for initial rash evaluation **REQUIRED**. • Assessment of vital signs by the investigator and safety blood sample by local laboratory **REQUIRED**. • Digital pictures can only be taken if subject gave consent. **REQUIRED** if subject is taking ABC; otherwise they are the investigator's discretion. • Referral to dermatologist **REQUIRED**. • Biopsy **REQUIRED** for grade 4 rash. Biopsy at the dermatologist's discretion for grade 3 rash.
Day 1	• Follow-up visit **REQUIRED**. • Assessment of safety blood sample by local laboratory **REQUIRED**. • Digital pictures[2].
Day 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[2].
Day 3	• 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[2].
Day 4	• 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[2].
Day 5	• Follow-up visit **REQUIRED**. • Assessment of safety blood sample by local laboratory **REQUIRED**. • Digital pictures[2].
Further Visits	• Weekly follow-up visits **REQUIRED** (or more frequently at the investigator's discretion) until resolution/stabilization of grade 3/4 rash to grade ≤ 2 rash • 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. • Digital pictures[2].
Upon Rash Resolution/ Stabilization[3]	• Digital pictures[2]. • Final Cutaneous Reaction/Rash form should be completed.

[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] Digital pictures can only be taken if subject gave consent. They are required if subject is taking ABC; otherwise they are the investigator's discretion.
[3] Stabilization: to be agreed upon in collaboration with the sponsor.

SIGNATURE PAGE SPONSOR

Sponsor's Responsible Medical Officer:

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

Name:	Rodica Van Solingen-Ristea, M.D.
Affiliation:	Janssen Research & Development

See Attached Electronic Signature Page

INVESTIGATOR AGREEMENT

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

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

LAST PAGE

SIGNATURES

Signed by	Date	Justification
Rodica Van Solingen-Ristea	29Nov2016, 15:53:10 PM, UTC	Document Approval