Janssen Research & Development *

Statistical Analysis Plan

Continued access to darunavir/ritonavir (DRV/rtv) in HIV-1 infected adults, adolescents and children aged 3 years and above

Protocol TMC114IFD3001; Phase N/A

Prezista®/TMC114 (darunavir)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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TABLE OF CONTENTS

AMENDMENT HISTORY

Not applicable ; this is the initial version of this Statistical Analysis Plan

ABBREVIATIONS

3TC	lamivudine
ABC	abacavir
ADR	adverse drug reaction
AHA	American Heart Association
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARV	antiretroviral
ASR	Annual Safety Report
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{12h}	area under the plasma concentration-time curve from time of intake until 12 hours after dosing
AZT	zidovudine
b.i.d.	twice daily (*bis in die*)
BRAT	bananas, rice, applesauce and toast
CDC	US Centers for Disease Control and Prevention
C_{0h}	predose plasma concentration
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CRF	Case Report Form
DAIDS	Division of AIDS
DCF	Data Correction Form
DILI	drug-induced liver injury
DRV	darunavir (formerly known as TMC114)
DSUR	Development Safety Update Report
FTC	emtricitabine
GCP	Good Clinical Practice
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IUD	intra-uterine device
LC-MS/MS	liquid chromatographic mass spectrometry/mass spectrometry
LDL	low-density lipoprotein
LPV	lopinavir
NCEP	National Cholesterol Education Program
NCR	non-carbon required
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
OBR	optimized background regimen
PI	protease inhibitor

QA	Quality Assurance
QC	Quality Control
q.d.	once daily (*quaque die*)
RAM	resistance-associated mutation
RBC	red blood cell
rtv	low-dose ritonavir
SJS	Stevens-Johnson syndrome
TEN	toxic epidermal necrolysis
ULN	upper limit of laboratory normal range
WBC	white blood cell

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for the CSR analysis (final analysis) of the continued access trial TMC114IFD3001.

1.1. Trial Objectives

Primary Objective

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

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

1.2. Trial Design

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

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

- HIV-1 infected subjects participating in the TMC114-C211(parent) trial or in the pediatric (parent) trial TMC114-TiDP29-C232, after original participation in TMC114-TiDP29-C230 trial were to continue on the DRV/rtv 800/100 mg q.d. dosing regimen as administered in the original (parent) trial.
- HIV-1 infected subjects participating in the pediatric (parent) trial TMC114-TiDP29-C232, after original participation in TMC114-C212 or TMC114-TiDP29-C228 trial were to continue on the selected b.i.d. DRV/rtv dosing regimen as administered in the original (parent) trial, or on an adjusted dose if necessary due to a change in body weight.
- HIV-1 infected subjects participating in the TMC114-C214 or TMC114-TiDP31-C229 (parent) trials were to continue on the DRV/rtv 600/100 mg b.i.d. dosing regimen as administered in the original (parent) trial.

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

- Virologic failure;
- Treatment-limiting toxicity;

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

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

Adverse event reporting was restricted to the following (or all AEs if applicable per local regulation):

- Adverse events considered at least possibly related to DRV/rtv;
- Adverse events leading to discontinuation or treatment interruption;
- Serious adverse events and pregnancies.

Efficacy and safety laboratory assessments were done locally, and were not transferred into the database for formal analysis purposes.

1.3. Statistical Hypotheses for Trial Objectives

Not applicable.

1.4. Sample Size Justification

Not applicable.

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

1.5. Randomization and Blinding

Randomization

Since this was a continued access single arm trial, randomization procedures were not applicable.

Blinding

Since this was an open label, continued access trial, blinding procedures were not applicable.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

2.1.1. Trial Phases

Analysis phases are constructed as per Table 1.

Table 1: **Analysis Phases:**

Trial phase	*Start date*	*End date*
Treatment	*Date of first DRV intake in trial*	*If the subject died: min (date of last DRV + 2 days ; date of death)* *If the subject permanently stopped the trial medication: minimum of:* • *date of last DRV intake + 2 days, if missing, date of discontinuation + 2 days* • *date of last contact*
Follow-up (not defined when derived End date is before Start date of this phase)	*End date of DRV Treatment phase + 1 day*	*If the subject died: date of death* *Otherwise: date of last contact*

2.1.2. Analysis Time points

Visits and assessments were to be performed, according to local generally accepted standard of care, but desirable every 3 months for pediatric subjects and not less frequent than every 6 months for adult subjects. The interval between 2 consecutive visits was not to exceed 6 months for pediatric subjects.

Therefor, no time points for analysis purposes are used.

2.2. Analysis Sets

Full Analysis Set (FAS): the set of all subjects who have taken at least one dose of DRV, regardless of their compliance with the protocol and adherence to the dosing regimen.

2.2.1. Safety Analysis Set

Safety results will be presented for the FAS population only.

2.3. Definition of Subgroups

The following subgroups will be defined for all outputs:

- Population: Pediatric (children <12y and adolescents 12-18y separately) and adults

For listings only, the corresponding DRV/rtv dose (ie. 600/100 mg b.i.d. or 800/100 mg q.d.) will be added; no distinction will be made in tables or figures.

3. SUBJECT INFORMATION

3.1. Demographics and Baseline Characteristics

The following parameters will be analyzed:
Demographic Parameters:

- sex (male, female)
- age at baseline
- country/site
- weight at baseline (kg).

3.2. Disposition Information

The following disposition information will be analyzed:

- Subject disposition by visit, according to actual visits recorded.
- Discontinuations, plus the reasons for discontinuation (from trial).

3.3. Treatment Adherence

No analysis of treatment adherence (based on drug accountability) will be performed.

3.4. Extent of Exposure

Exposure is defined as the duration of DRV treatment during the treatment phase (in days), up to the last DRV date. The extent of exposure will be summarized in years, and the total subject-years-of-exposure will be provided. Treatment duration will be calculated as described below:
Treatment duration (years) = [End of phase – Start of phase +1 (days)]/365.25

The total subject-years-of-exposure will be calculated by taking the sum of the DRV treatment durations (years) over all subjects.

In addition, the proportion of subjects in the study (exposed to DRV) using 24-week intervals will be tabulated, i.e. based on 1 x 24 weeks (=169 days), 2 x 24 weeks (=337 days), etc.

Rtv exposure will be calculated in the same manner.

3.5. Concomitant Medications

Concomitant medications are allocated to each phase (see Section 2.1.1) during which they were actually administered, based on their start and end dates. For phase allocation, the following rules are applied to deal with (partially) missing start or end dates:

- a start date with the day only missing has the day imputed with the first day of the month;
- a start date with the day and month missing has the day imputed with the 1st of January;
- an entirely missing start date is considered as having started before the study;
- an end date with the day only missing has the day imputed with the last day of the month;
- an end date with the day and month missing has the day imputed with the 31st of December;
- an entirely missing end date is considered as having ended after the study.

The dictionaries used for concomitant medications are WHODRUG version 01Mar2011 (enhanced) at trial start, and WHODRUG version 01Sep2019 (enhanced) at trial end.

3.5.1. Antiretroviral Therapy

Frequency (%) of subjects will be provided per class and per ARV, during treatment phase.

All ARV classes will be shown in the table and listing.

The dictionaries used for administration of Antiviral Therapy are the same as for concomitant medications.

3.5.2. Non-Antiretroviral Therapy

All Conmed drug categories and actual medications will be shown in a listing.

The dictionaries used for administration of Antiviral Therapy are the same as for concomitant medications.

3.6. Protocol Deviations

All major protocol deviations will be tabulated and listed.

A listing of major protocol deviations where interruptions of dose occurred will be provided, along with missing dose information.

4. SAFETY

Safety results will be summarized for the Treatment phase; all safety data (including Follow-up phase) will be included in listings.

4.1. Adverse Events

4.1.1. Analysis Methods

AE incidence (count and percentage) will be tabulated, overall and by preferred term/SOC.

Overall AE Summary tables and tables by preferred term/SOC for serious events, AEs leading to discontinuation, AEs at least grade 3, HIV-related AEs, and AEs at least possibly related to DRV will be presented throughout the treatment phase only; any AEs in the Follow-up phase will be listed only.

The dictionary used for adverse events will be MedDRA version 23.0.

4.2. Clinical Laboratory Tests

4.2.1. Overall laboratory safety

Only the following 2 laboratory parameters were collected (pregnancy tests):

- General biochemistry : Creatinine Clearance
- Urinalysis : Human Chorionic Gonadotropin.

These parameters will be listed.