Janssen Research & Development

Statistical Analysis Plan

Continued access to etravirine in treatment experienced HIV-1 infected subjects.

Protocol TMC125-TiDP35-C239; Phase N/A

TMC125 Intelence®/ (Etravirine)

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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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AMENDMENT HISTORY

Not applicable

ABBREVIATIONS

AE	adverse event
ATC	anatomic and therapeutic Class
BMI	body mass index
BSA	body surface area
CI	confidence interval
CRF	case report form
CSR	Clinical Study Report
CV	coefficient of variation
DMC	Data Monitoring Committee
DPS	Data Presentation Specifications
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
IQ	interquartile
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamic
PK	pharmacokinetic(s)
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SMQs	standardised MedDRA queries
TEAE	treatment-emergent adverse event
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary
ITT	Intention-to-Treat

1. INTRODUCTION

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

This statistical analysis plan (SAP) for the TMC125-TiDP35-C239 describes the statistical analysis for subject information and safety data.

1.1. Trial Objectives

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

1.2. Trial Design

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

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

Treatment will be continued until one of the following criteria is met: the investigator determines that the subject no longer benefits from ETR treatment (e.g., based on viral load); treatment limiting toxicity; loss to follow-up; patient withdrawal of consent; pregnancy; termination of the program by the Sponsor; ETR becomes commercially available for the subject's indication, is reimbursed, or can be accessed through another source (e.g. access program, government program) in the region the subject is living in, whichever occurs first. A diagram of the study design is provided below in Figure 1.

Figure 1: Schematic Overview of the Study

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

a Subject will rollover from another trial. Baseline visit will coincide with the last visit of the previous trial. Assessments and results from the last visit of the previous trial will be used for the Baseline Visit of this trial.
b Only for subjects who drop out of the study due to the occurrence of a (S)AE.
c Any AE event ongoing at the end of treatment should be followed up until satisfactory clinical resolution or stabilization at the investigator's discretion, according to the local standard of care.
d Including Subject ID from feeder trial.
e Urine pregnancy test for females of childbearing potential only.
f Other AEs will only be collected if required per local regulations.
g Informed assent only applicable to pediatric subjects.
h Only applicable to pediatric subjects.

1.3. Statistical Hypotheses for Trial Objectives

N/A

1.4. Sample Size Justification

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

1.5. Randomization and Blinding

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

2. GENERAL ANALYSIS DEFINITIONS

2.1. Analysis Sets

Intent-to-treat (ITT) population: the set of all subjects who have taken at least 1 dose of ETR, regardless of their compliance with the protocol and adherence to the dosing regimen.

2.1.1. Safety Analysis Set

All safety results will be presented for the ITT population.

2.2. Study Day and Relative Day

Study Day 1 or Day 1 refers to the start of the first study agent administration. All safety assessments at all visits will be assigned a day relative to this date.

Study day or relative day for a visit is defined as:

- Visit date - (date of Study Day 1) +1, if visit date is ≥date of Day 1
- Visit date - Date of Day 1, if visit date <date of Day 1

There is no 'Day 0'

2.3. Baseline and Endpoint

Baseline is defined as the last observation prior to the start of the first study agent administrations.

2.4. General Analysis Rules

- Data of adult and pediatric subjects will be analyzed separately. For the statistical analysis of TMC125-C239, a pediatric and adult subject will be defined as a subject who entered the previous trial at age < 18 and ≥ 18 years old respectively. Subjects who turn 18 while in the

previous trial or in TMC125-C239 will be considered as pediatric subjects for the statistical analysis.

- Continuous data will be summarized by descriptive statistics, including number of subjects (N), mean, standard deviation (SD), median, and range (minimum; maximum).
- The minimum and maximum will be presented to the same number of decimal places as the original data. The mean, median and 95% CI will be rounded to one additional decimal place than the original data, while SD will be approximated to two additional decimal places.
- If a count is 0, the percentage (0%) should not be displayed. The 0 count will be displayed, but the corresponding percentage should be omitted.
- The percentages (%) in tables will be presented to 1 decimal place unless the sample sizes for the percentages are small enough to warrant presenting as integers.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

There is no interim analysis planned for this study.

4. COVID RELATED DEVIATIONS

All COVID related deviations will be tabulated and listed.

5. SUBJECT INFORMATION

5.1. Demographics and Baseline Characteristics

Table 01 presents a list of the demographic variables that will be summarized by pediatric and adult subjects separately as well as all combined for ITT analysis set.

Table 01: Demographic Variables

Continuous Variables	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum])
Height (cm)	
Weight (kg)	
Categorical Variables	
Sex (male, female)	Frequency distribution with the number and percentage of subjects in each category.

The demographics and baseline characteristics will be listed for all subjects.

5.2. Disposition Information

The number of subjects in the following disposition categories will be summarized:

- Subject didn't fulfill all inclusion/exclusion criteria (screen failures)
- AE/HIV-related event/Cutaneous event/Rash (including death, abnormal lab values, current illnesses)

- Lost to follow-up
- Withdrew consent/assent
- Non-compliant
- Ineligible to continue the trial
- Investigator no longer thinks subject benefits from the ETR treatment
- Sponsor's decision
- Switch to commercially available medication
- Other

5.3. Treatment Compliance

Not applicable for this study

5.4. Extent of Exposure

Not applicable for this study

5.5. Protocol Deviations

If captured, major protocol deviations will be defined. A listing of subjects with a major protocol deviation will be provided.

5.6. Prior and Concomitant Medications

Will be summarized by CMDECODE antiretroviral category

5.7. Medical history

Not applicable

6. EFFICACY

N/A

7. SAFETY

All safety analyses will be based on the safety analysis set.

Safety data of adult and pediatric subjects will be analyzed separately as well as overall.

For all continuous safety variables, descriptive statistics will include the N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

7.1. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the available version of the Medical Dictionary for Regulatory Activities (MedDRA version 23.0). Treatment-emergent adverse events are adverse events with onset during the treatment phase or

that are a consequence of a pre-existing condition that has worsened since baseline. If the event occurs on the day of the initial administration of study agent, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered treatment emergent unless it is known to be prior to the first administration of study agent based on partial onset date or resolution date. All reported adverse events will be included in the analysis. For each adverse event, the number and percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment.

Summary tables will be provided by pediatric and adult subjects separately as well as overall for:

- Mortality
- Serious AEs (SAEs)
- AEs leading to discontinuation of treatment
- AEs possibly related to ETR
- All AEs

From the collected (S)AE data in TMC125-C239, the following events will be summarized:

Skin events
Skin events of interest will be assigned to categories from the following list:

- '(Serious) Rash Cases': a predefined list of selected PTs used for the post-marketing safety monitoring, is used to identify (serious) cases of Rash.

Acrodynia	Rash generalised
Drug eruption	Rash macular
Erythema ab igne	Rash maculo-papular
Erythema	Rash maculovesicular
Erythema elevatum diutinum	Rash morbilliform
Erythema toxicum neonatorum	Rash neonatal
Fixed eruption	Rash papular
Generalised erythema	Rash pruritic
Lupus miliaris disseminates faciei	Rash pustular
Mucocutaneous rash	Rash rubelliform
Necrolytic migratory erythema	Rash scarlatiniform
Rash	Red man syndrome
Rash erythematous	Rash vesicular

- '(Severe) Cutaneous Reactions': the MedDRA SMQ (Severe) Cutaneous Adverse Reactions [Broad scope SMQ code: 20000020], which includes Stevens-Johnson Syndrome, is used
  to identify cases.
- 'Angioedema': the MedDRA SMQ Angioedema (SMQ, broad) is used to identify cases.

- Cardiac
- Hepatobilliary

Hepatic events
Hepatic events of interest (or 'Hepatotoxicity') will be assigned to the subcategories from the following list, with relevant SMQs to identify cases:

– "Cholestasis and jaundice": Cholestasis and jaundice of hepatic origin, broad (SMQ code: 20000009),
– "Hepatic Failure, fibrosis and cirrhosis and other": Hepatic failure fibrosis and cirrhosis and other liver damage-related conditions, broad (SMQ code: 20000013),
– "Hepatitis non-infectious": Hepatitis non-infectious, broad (SMQ code: 20000010),
– "Liver related investigations, signs and symptoms": Liver related investigations signs and symptoms, broad (SMQ code: 20000008).

- Neuropsychiatric

In addition to the summary tables, listings will be provided for subjects who:

- Mortality
- Had SAEs
- Had AEs leading to discontinuation of treatment

7.2. Clinical Laboratory Tests and Vital Signs Findings

Missing baseline values:

The only reference time point for the weight analysis will be baseline. If there is no baseline value available, no changes will be calculated. Observed and change from baseline in weight by visit will be summarized by pediatric and adult subjects separately. Table 2 and Table 3 show the definition of windows used for the weight analysis for pediatric and adult, respectively.

Table 2: Definition of windows for weight (pediatric subjects)

Phase	Visit	Target day	Analysis time point	Time interval (days)
Baseline	1	1	Baseline	<=1
Treatment	2	90	Month 3	2 to 135
	3	180	Month 6	136 to 225
	4+	XX*30	Month XX	[XX*30 days – 44 to XX*30 days + 45]

Table 3: Definition of windows for weight (adult subjects)

Phase	Visit	Target day	Analysis time point	Time interval (days)
Baseline	1	1	Baseline	<=1
Treatment	2	180	Month 6	2 to 270
	3	360	Month 12	271 to 450
	4+	XX*30	Month XX	[XX*30 days – 89 to XX*30 days + 90]

If two (or more) measurements fall within the same time interval, the measurement closest to the target day (in case of equal distances, latest measurement takes precedence) is used for the analysis displays and graphics in order to have only one measurement per subject per analysis time point. However, all data are presented in the listings.

The number of days in the treatment is defined as:

relday = visit day – reference day+1 for visits on or after the reference

relday = visit day – reference day for visits before the reference where the reference day equals the actual start date of intake of ETR.

7.3. Overview of statistical output

COVID related deviations	
TCOV01	COVID-related deviations: Tabulation
LCOV01	COVID-related deviations: Listing
Demographics	
TDEM01	Demographics and baseline characteristics
LDEM01	Listing of demographics and baseline characteristics
Prior and Concomitant Medications	
TSICM01	Prior ARV Therapies; Individual ARVs
TSICM02a	Initial OBR Therapies Individual ARVs
TSICM02b	Initial OBR Therapies Combinations of ARVs
Disposition	
TDIS01	Disposition

LDIS01	Listing of disposition
Safety	
TSFAE01	Adverse Events: Summary Table
TSFAE02	Adverse Events: Tabulation of All Events by System Organ Class and Preferred Term
TSFAE03	Frequency (%) of Serious Adverse Events
TSFAE04	Frequency (%) of Grade 3-4 Adverse Events (Regardless of Causality)
TSFAE05	Frequency (%) of Adverse Events at Least Possibly Related to Etravirine
TSFAE06	Frequency (%) of Adverse Events Leading to Permanent Stop of Study Medication
TSFAE07	Adverse Events of Interest by Event of Interest Group
LSFAE01	Adverse Events: Summary Listing of All Events
LSFAE02	Adverse Events: All Events with Grade 3 to 4 Toxicity
LSFAE03	Adverse Events: All Serious Events
LSFAE04	Adverse Events: All Events at Least Possibly Related to Study Medication
LSFAE05	Adverse Events of Interest: Summary Listing of All Events of Interest
LSFAE06	Adverse Events: All Events Leading to Permanent Stop of Study Medication
TSFVIT01a	Observed and Change from Baseline in Weight by visit (pediatric)
TSFVIT01b	Observed and Change from Baseline in Weight by visit (adult)
TSLWT01a	Listing: Weight (pediatric)
TSLWT01b	Listing: Weight (adult)