NOVARTIS

Clinical Development

LEE011

CLEE011X2102 / NCT01747876

A phase I, multi-center, open-label study of LEE011 in patients with malignant rhabdoid tumors and neuroblastoma

Statistical Analysis Plan (SAP)

Author: Trial Statistician, [redacted]

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List of abbreviations

AE	Adverse event
AESI	Adverse events of special interest
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
bid	bis in diem/twice a day
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
IVR	Interactive Voice Response
IWR	Interactive Web Response
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NCI	National Cancer Institute
o.d.	Once Daily
OS	Overall Survival
PFS	Progression-Free Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
qd	Qua'que di'e / once a day
QoL	Quality of Life
RAP	Report and Analysis Process
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SOC	System Organ Class
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

This document describes the detailed statistical analysis plan for final CSR for study LEE011X2102. The final CSR will be written after the final database lock.

The statistical analyses which are covered in the RAP Module 3 for the primary CSR are not repeated within this document. Refer to [redacted]

All changes to the planned analysis described in this document required before or after database lock will be made through an amendment or addendum, respectively. Note that obvious corrections will be made at the time of analysis to address minor formatting or spelling mistakes present in the TFL shells document without the need to amend.

The SAP, TFL shells and PDS documents may also serve as a reference for the creation of any outputs required outside of the CSR, e.g., PSUR/DSUR, MTD/RDE declaration, IB updates, abstracts, posters, presentations, manuscripts, health authority requests and management updates.

1.1 Study design

See the primary CSR RAP Module 3.

1.2 Study objectives and endpoints

Please see the primary CSR RAP Module 3.

2 Statistical methods

2.1 Data analysis general information

See the primary CSR RAP Module 3.

2.1.1 General definitions

See the primary CSR RAP Module 3.

2.2 Analysis sets

See the primary CSR RAP Module 3.

2.2.1 Subgroup of interest

See the primary CSR RAP Module 3.

2.3 Patient disposition, demographics and other baseline characteristics

Background, baseline and demographic characteristics including age, gender, race, ethnicity, height, weight, body surface area (BSA), body mass index (BMI), Karnofsky/Lansky performance status, etc., are listed individually by patient and summarized by treatment for patients in the FAS.

BMI and BSA (Gehan and Georage formulae) are calculated using the following formulas:

- *BMI [kg/m2] = weight[kg] / (height[m]**2)*
- *BSA [m2] = 234.94*(height[cm]**0.422)*(weight[kg]**0.515)/10000*

BMI may be summarized by categories as appropriate. It is acceptable for the BSA to be calculated up to 7 days in advance of Day 1. Dose adjustments for changes in BSA in subsequent cycles are made as per standard site practice (e.g., if the BSA changes by ± 10% from the previous dose calculation).

Performance status is scored using the Karnofsky (for patients > 16 years old) or Lansky (for patients≤ 16 years old) performance scales (Protocol Appendix 4 and 5).

For patients that have their 17th birthday during the study, performance status will continue to be assessed by the Lansky scale, in order to preserve continuity.

2.3.1 Patient disposition

The following patient disposition information are listed and summarized by treatment for all patients in FAS at the time of final database lock:

- Enrolled patients who remained on treatment or discontinued treatment
- Primary reasons for EOT based on EOT CRF
- Study evaluation completion after EOT:
  - Patients who are either no longer being followed up for study evaluation or who continued to be followed for study evaluation based on EOT CRF
  - Primary reason for study evaluation completion based on Study Evaluation Completion CRF.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Duration of exposure to study drug is categorized into time intervals in days (≤56, 57-≤84, 85-≤140, and ≥ 141) and in cycles (≤1, 2 - ≤3, 4 - ≤5, ≥6), frequency counts and percentages are summarized for the number of patients in each interval.

Duration of exposure to study drug by treatment is listed.

The safety set is used for all summaries tables and listings of study drug.

See the primary CSR RAP Module 3 for more detailed definitions.

2.4.2 Prior, concomitant and post therapies

No analysis of prior, concomitant or post therapient will be performed for the final CSR.

2.5 Analysis of the primary objective

The primary objective of the dose-escalation part was to determine the MTD of LEE011 when administered as a single agent orally to patients aged 12 months to 21 years old with malignant rhabdoid tumors and neuroblastoma.The MTD/RDE of LEE011 was determined prior to halted enrollment.

No analysis related to MTD will be performed for the final CSR as this analysis was fully covered in the primary CSR.

2.5.1 Primary endpoint

See the primary CSR RAP Module 3.

2.5.2 Statistical hypothesis, model, and method of analysis

See the primary CSR RAP Module 3.

2.5.3 Handling of missing values/censoring/discontinuations

See the primary CSR RAP Module 3.

2.5.4 Supportive analyses

The MTD was to be further evaluated for preliminary anti-tumor activity and overall tolerability during the dose-expansion part of the trial. Due to halted enrollment, this analysis will not be performed.

2.6 Analysis of the key secondary objective

No key secondary objective is defined.

2.7 Analysis of secondary efficacy objective(s)

No other secondary efficacy objectives will be analyzed for the final CSR.

2.8 Safety analyses

2.8.1 Adverse events (AEs)

AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Although CTCAE version 4.03 grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening and death, CTCAE grade 5 (death) is not used since this information was collected at the “End of Treatment” and “Study evaluation completion” pages.

Summary tables for AEs include only AEs that started or worsened during the on-treatment period, the **treatment-emergent** AEs. AEs, SAEs, and all deaths (on treatment and post treatment) are tabulated by primary system organ class, preferred term, severity and treatment.

Additional summaries based on causality, study drug discontinuation or study drug interruptions are produced.

All AEs collected in the AE (e)CRF page will be listed along with the information collected on those AEs e.g. AE relationship to study drug, AE outcome etc.

Listing and summaries are produced according to the following rules:

- Patients reporting and experiencing multiple occurrences of a specific AE have occurrences listed but are counted only once in the appropriate event category/class and according to the worst observed grade within summary tables.
- AEs are summarized by presenting the number and percentage of patients having at least one AE sorted by descending frequency then alphabetically (by system organ class and preferred term.

Analysis for clinicaltrials.gov and EudraCT

For the legal requirements of clinicaltrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than and equal to 5% and on treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.8.1.1 Adverse events of special interest / grouping of AEs

An adverse event of special interest is a grouping of adverse events that are of scientific and medical concern specific to compound LEE011. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HGLTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. For each specified AESI, number and percentage of subjects with at least one event of the AESI occurring during on-treatment period will be summarized.
Summaries of these AESIs will be provided by treatment, (specifying grade, SAE, relationship, leading to treatment discontinuation, leading to dose adjustment/interruption, fatal outcome, etc.).

A listing of all grouping levels down to the MedDRA preferred terms used to define each AESI will be generated.

2.8.2 Deaths

Summary of all deaths will be produced by treatment, system organ class and preferred term. All deaths will be listed for the full analysis set, on-treatment deaths will be flagged.

2.8.3 Laboratory data

Summary of notable hepatic laboratory values will be produced by treatment. Liver function test values will be listed. No other laboratory data will be analyzed for the final CSR.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

No ECG and cardiac imaging data will be analyzed for the final CSR.

2.8.4.2 Vital signs

No vital signs data will be analyzed for the final CSR.

2.9 Pharmacokinetic endpoints

No Pharmacokinetic data will be analyzed for the final CSR.

2.10 PD and PK/PD analyses

No PD data will be analyzed for the final CSR.

2.11 Patient-reported outcomes

No patient-reported outcomes will be analyzed for the final CSR.

2.12 Biomarkers

No biomarker data will be analyzed for the final CSR.

2.13 Other Exploratory analyses

No other exploaratory analyses will be be executed for the the final CSR.

2.14 Interim analysis

See the primary CSR RAP Module 3.

3 Sample size calculation

See the primary CSR RAP Module 3.

4 Change to protocol specified analyses

- Due to halted enrollment, all analyses are performed for the dose-escalation part only.
- The analysis of adverse events of special interest is added.
- For the final CSR only limited demographic, disposition, exposure and safety data will be analysed.

5 Appendix

This appendix gives details about statistical methods in addition to the report text.

5.1 Imputation rules

As a general rule, when a date is recorded as a partial date, the missing day is imputed to the 15th of the month (e.g., DEC2007 imputed to 15DEC2007), and if the day and month are both missing then to July 1st of that year (e.g., 2007 imputed to 01JUL2007). Such imputed data are flagged in the listings.

For computation of time intervals (e.g. elapse time between initial diagnosis to first recurrence/relapse), if the imputation rule leads to a negative value, time interval should be set to missing.

Continuing events (e.g. AEs) are summarized using the data cut-off date as the date of completion, with an indication within listings that the event is continuing. For patients who discontinue the study with ongoing events, the discontinuation date is used as the completion date of the event with the appropriate censoring.

Other missing data will simply be noted as missing on appropriate tables/listings

5.1.1 Study drug

The study drug and study treatment refer to the Novartis investigational drug LEE011, an orally bioavailable small molecule inhibitor of CDK4/6.

5.1.2 AE date imputation

See Section 5.1

5.1.3 Concomitant medication date imputation

See Section 5.1

5.1.3.1 Prior therapies date imputation

See Section 5.1

5.1.3.2 Post therapies date imputation

See Section 5.1

5.1.3.3 Other imputations

5.2 AEs coding/grading

AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Although CTCAE version 4.03 grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening and death, CTCAE grade 5 (death) is not used since this information was collected at the "End of Treatment" and "Study evaluation completion" pages.

5.3 Laboratory parameters derivations

All laboratory values are converted into SI units when applicable and the severity grade calculated using CTCAE, version 4.03 unless otherwise indicated. A severity grade of 0 is assigned when the value is within normal limits. In the case when a local laboratory normal range overlaps into the higher (i.e., non-zero) CTC grade, the laboratory value is still considered within normal limits and assigned a CTC grade of zero.

5.4 Statistical models

5.4.1 Primary analysis

See the primary CSR RAP Module 3.

An adaptive BLRM with two parameters guided by the EWOC principle is used to make dose recommendations and estimate the MTD/ RDE during the study. The model is fitted on the Cycle 1 DLT data (i.e. absence or presence of DLT).

The adaptive BLRM model is fitted on the dose-limiting data (i.e. absence or presence of DLT) accumulated in Cycle 1 throughout the dose-escalation part (and possibly during the dose-expansion part), for modeling the dose-DLT relationship of LEE011.

The DLT relationship in the dose-escalation part of the study is described by the following Bayesian logistic regression model:

$$\text{logit}(\pi_{(d)}) = \log(\alpha) + \beta \log(d/d^*), \qquad \alpha>0, \beta>0$$

where $\text{logit}(\pi_{(d)}) = \ln(\pi_{(d)}/(1-\pi_{(d)}))$, and $\pi_{(d)}$ is the probability of a DLT at dose d.

Doses are rescaled as d/d* with reference dose of $d^* = 580$ mg/m^2. As a consequence α is equal to the odds of the probability of toxicity at d*. Note that for a dose equal to zero, the probability of toxicity is zero.

If a different dosing schedule is considered, a Bayesian Meta-analytic approach is used to take into account historical data collected for the initially planned schedule in the actual study, in order to derive an informative prior estimation of the dose-toxicity relationship for the new dosing regimen. This informative prior is combined with DLT data for the new dosing regimen using a two-parameter BLRM. After patients in each cohort have completed at least one cycle of LEE011 treatment, the prior distribution is updated with the cumulated DLT data from Cycle 1. Posterior probabilities for the rate of DLT are summarized; the recommendation for the next dose level is based on these probabilities.

[redacted]

Prior specifications

The Bayesian approach requires the specification of prior distributions for the model parameters. All information currently available about the dose-DLT relationship of LEE011 was summarized in a prior distribution. [redacted]

[redacted]

Operating characteristics of this model and the escalation recommendations for some particular situations are provided in Protocol Appendix 7.

5.4.2 Key secondary analysis

NA

6 Reference

NA