NOVARTIS

Oncology Early Clinical Development

LEE011

Clinical Trial Protocol CLEE011X2201 / NCT02300987

A randomized, blinded, placebo-controlled, phase II trial of LEE011 in patients with relapsed, refractory, incurable teratoma with recent progression

Statistical Analysis Plan - Amendment 1

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Document type: RAP Documentation

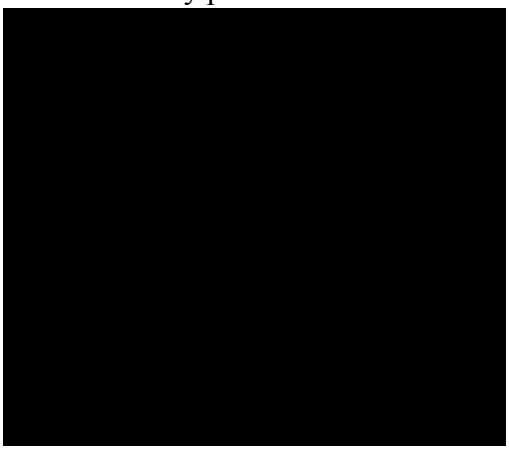
Document status: Final

Release date: 07-Dec-2016

Number of pages: 22

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
24-Jun-2015	Prior to DB lock	Creation of initial version	N/A - First version	NA
07-Dec-2016	Prior to DB lock	Since the enrollment in the study was halted after only a few patients treated, short close-out CSR to be produced.	Aligned to Short close-out CSR guideline	• [Protocol Section 10.3.1 Study Treatment]: The actual dose, dose intensity, relative dose intensity and total daily doses of each agent will not be summarized or listed. • [Protocol Section 10.3.2 Concomitant therapies]: Concomitant medications and significant non-drug therapies prior to and after the start of the study drug treatment will not be summarized or listed. • [Protocol Section 10.3.3 Compliance]: The listing of patients with protocol deviations will be provided; no summary tables will be produced. • [Protocol Section 10.4.2] The primary efficacy endpoint, PFS will not be analyzed. Log-rank test, HR estimates and related confidence interval and Kaplan-Meier estimates with confidence interval for median survival and survival probabilities will not be performed. • [Protocol Section 10.5.2 Other secondary efficacy objectives]: BOR, ORR and DCR will not be summarized and corresponding confidence interval will not be produced. Kaplan-Meier plots for DOR will not be produced and the median DOR will not be estimated. Kaplan-Meier estimates for OS with confidence intervals will not be produce and OS rate

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				and related confidence interval will not be performed. Listing of Overall response, time to progression time to onset and duration of overall response will not be provided. Waterfall plot will not be produced. • [Protocol Section 10.5.3 Safety objectives]: Laboratory abnormalities, ECG, Cardiac Imaging and vital signs summary tables and listings will not be provided. Tolerability of the study drug will not be summarized and reason for dose interruption, dose reduction and dose change will not be listed by patient or summarized. 

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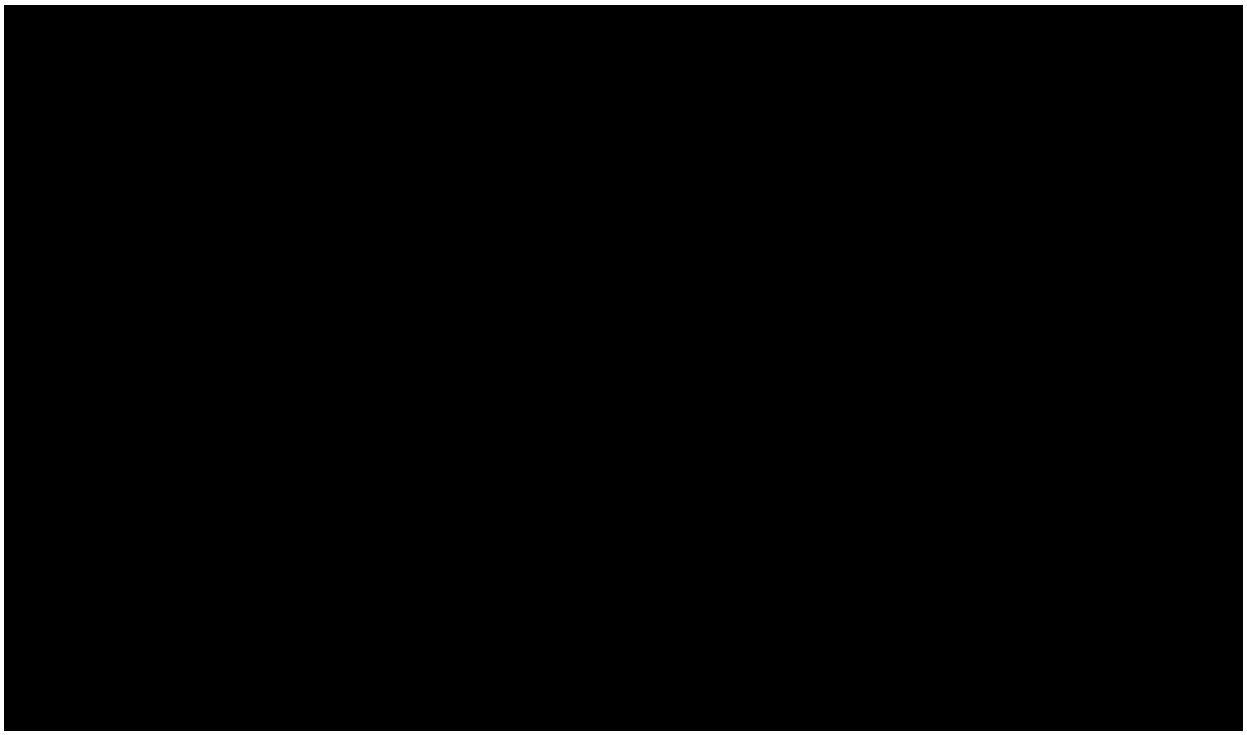
1 Introduction

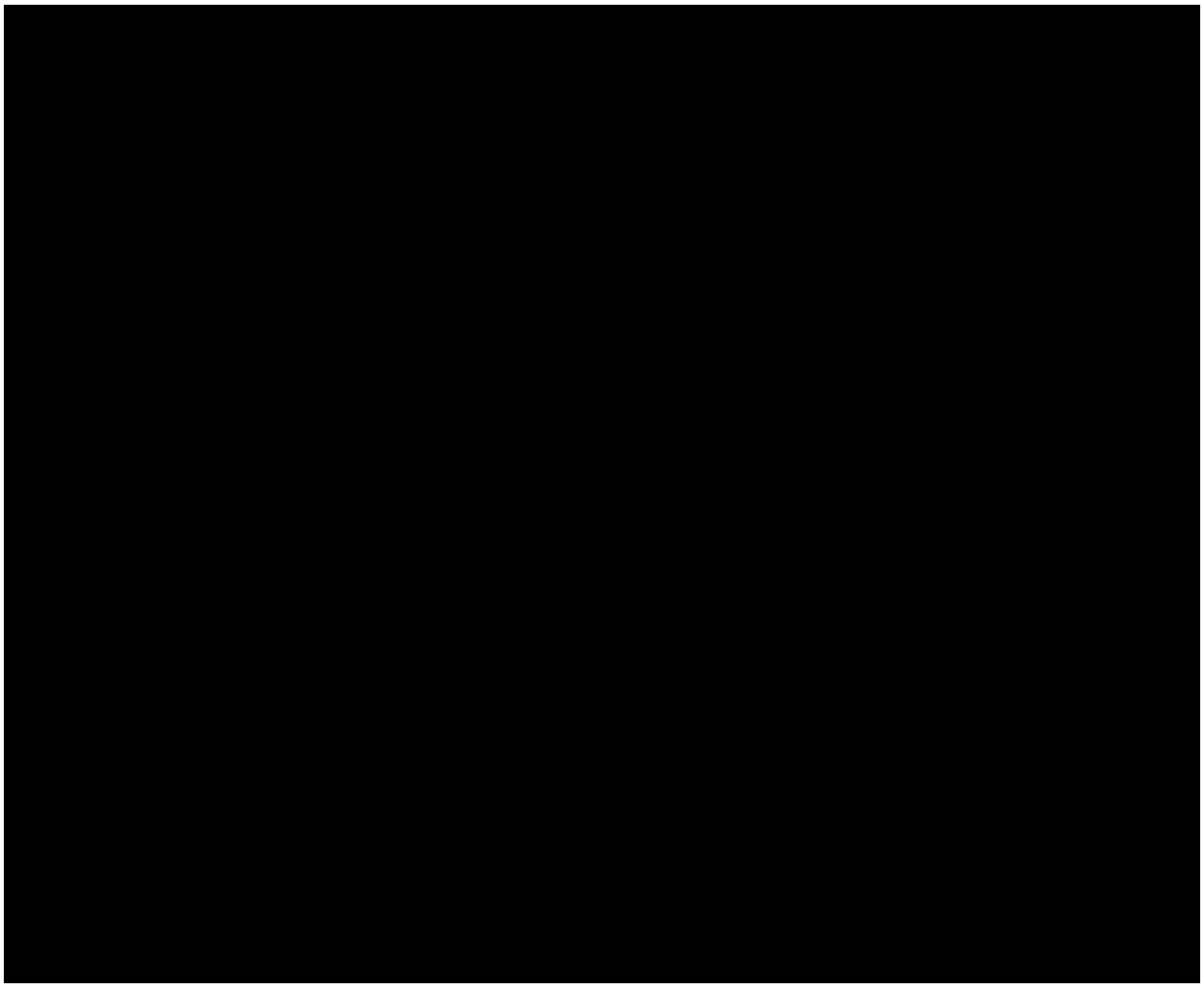
This document describes the detailed statistical methodology for the Report Analysis Plan (RAP) of study CLEE011X2201 Protocol Amendment 2. The data will be analyzed by Novartis and/or designated CRO. It is planned that the data from all centers that participate in this protocol will be used.

The purpose of the CSR is to report the assessment of clinical efficacy and safety of the LEE011 in patients with relapsed, refractory, incurable teratoma with recent progression.

The list of tables to provide at each analysis will be detailed in Module 7.

All changes to the planned analysis described in Modules 3, 7 and 8 required before or after database lock will be made through an amendment or an addendum, respectively. Note that obvious corrections will be made at the time of analysis to address minor formatting or spelling mistakes present in RAP modules without the need to amend these modules.





1.2 Objectives and endpoints

The study objectives and corresponding endpoints are shown in Table 1-1.

Table 1-1 Objectives and related endpoints

Objective	Endpoint
Primary	
To assess the efficacy of LEE011 compared to placebo in patients with relapsed/refractory teratoma with recent progression	PFS as per RECIST v1.1 (by local investigator assessment).
Secondary	
To assess other measures of efficacy of LEE011 compared with placebo	BOR, ORR, DOR, DCR at 4 months as per RECIST v1.1 and OS, OS Rate at 12 months.
To assess safety and tolerability of LEE011	Incidence and severity of adverse events and serious adverse events, changes in

compared with placebo	laboratory values, electrocardiograms, and vital signs will be used to assess the safety as per CTCAE v.4.03. Dose interruptions and changes will be used to assess the tolerability.

1.3 Data Analysis

Data will be analyzed by Novartis and/or designated CRO according to the data analysis section 10 of the clinical study protocol [CLEE011X2201] and will be available in CSR Appendix 16.1. Important information will be given in the following sections and details are provided as applicable in CSR Appendix 16.1.9.

All statistical analysis will be performed using SAS® version 9.3.

1.4 CSR related reporting events

The following points will guide the production of all or subset of the planned analyses:

- The primary CSR includes all outputs described in Module 7 based on all patients' data at the time when there are approximately 23 PFS events for the primary efficacy analysis and all patients have been followed for PFS for at least 6 months or have discontinued prior to this time for disease progression or death, or have withdrawn consent to follow up or have been lost to follow up or if the study is terminated early [Protocol CLEE011X2201 Section 4.4].
- If there will be additional data for patients continuing on study or in survival follow-up past the data cutoff date for the primary CSR, they will be reported in a final CSR once the

treatment period, safety follow-up, disease progression follow-up and survival follow-up periods have ended for all patients as described in [Protocol CLEE011X2201 Section 7.1.4]. The content of the final CSR is determined based on instructions outlined in [OTM Guidelines for Patients that Continue Beyond Study Data Cutoff].

2 Definitions and general methodology

2.1 General definitions

2.1.1 Study drug

Study drug is defined as LEE011 or matching placebo.

Study treatment is defined as LEE011 or matching placebo.

2.1.2 Assessment windows, baseline and post baseline definitions, missing data handling

2.1.2.1 Date of first administration of study drug/ treatment

The date of first administration of study drug is derived as the first date when a nonzero dose of study drug was administered and recorded on the dose administration DAR eCRF. The date of first administration of study drug will also be referred as ***start of study drug***.

2.1.2.2 Date of last administration of study drug/ treatment

The date of last administration of study drug is defined as the last date when a nonzero dose was administered and recorded on DAR (e)CRF.

2.1.2.3 Study drug exposure

The following algorithm will be used to calculate the duration of study drug exposure (in cycles and in days) for patients takes at least 1 dose of the study drug:

Duration of exposure (days) = last date of exposure to study drug – date of first administration of the study drug + 1

For patients who did not take any drug, the duration of exposure is defined as zero.

2.1.2.4 Study day

The study day, describes the day of the event or assessment date, relative to the reference start date (randomization date).

The study day for safety assessments (e.g. adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption etc.) will be calculated as the difference between the date of the assessment and the start of study treatment plus 1. (Note: if an adverse event starts before the start of study treatment the study day displayed on the listing will be negative and will be calculated as the difference between the date of the assessment and the start of study treatment.).

The study day for all other non-safety assessments (i.e., tumor assessment, death, disease progression, tumor response, ECOG performance status, [redacted]) is defined as the difference between the date of the event and the randomization date plus 1. In other words, all efficacy time-to-event variables (e.g. progression-free survival, overall survival, time to response) will be calculated from date of randomization. (Example: if randomization date is 15DEC2013, start of study drug is on 18DEC2013, and the date of death is 28DEC2013 then the study day when the death occurred is 14).

The study day will be displayed in data listings.

Study day is not to be used in numerical computations, for example in calculating exposure.

Cycle definition

The study day for all assessments is calculated using the randomization date as Day 1.

The cycle number and day within cycle attributed to a visits or assessment will be derived according to the following rules:

- C1D1 (cycle 1 day 1) coincides with the start date of drug/treatment
- All pre-treatment assessments are displayed as **Cycle 0** with a negative day (e.g., **Day -1** for the day before the patient started treatment) or with day 1.
- Day 1 of a cycle corresponds to the day reported by investigator on the start of cycle log form.
- For all cycles but the last, the end date of a cycle is defined as the day before Day 1 of the following cycle as recorded on the cycle log form.
- The end date of the last cycle is when treatment administration is permanently discontinued at the latest of the following days:
  - Date of last administration
  - 28 days after the first day of the last cycle or day of patient's death if earlier when date of last administration is not known
- All post-cycles assessments are displayed as follow-up and with, by analogy, Day 1 representing the first day after the end of the last cycle.

The duration (in days) of a cycle is defined as the cycle end date – cycle start date + 1.

Cycle number and day within cycle are computed to be displayed in listings only.

2.1.2.5 Baseline

Baseline is considered as the last available assessment performed or value measured within 28 days before the first administration of study treatment, unless otherwise stated under the related assessment section. Baseline could be the day before first treatment administration or the same day as first treatment administration if a pre-dose assessment/value is available (e.g., ECG, [redacted]).

If time is recorded for the first treatment dose and for a specific assessment performed the day of first dose, this assessment will be considered as baseline only if it is actually performed before the first dose, as checked using both times.

For those patients eligible to crossover to LEE011 treatment after initial progression, baseline will be adjusted to the last assessment prior to secondary treatment phase. Re-baseline could be the day before first treatment after crossover administration or the same day as first treatment administration after crossover if a pre-dose assessment/ value is available.

If time is not recorded, a specific assessment performed the day of first dose administration will be considered as baseline if, according to protocol, it should be performed before the first dose.

If patients have no value as defined above, the baseline results will be set to missing.

2.1.2.6 On-treatment assessment/event

Safety summaries and selected summaries of deaths will summarize only on-treatment assessments/events. On-treatment assessment/event is defined as any assessment/event obtained in the time interval:

Date of first administration of study treatment through the date of last administration of study treatment + 30 days, i.e. including the lower and upper limits. (Note: However, the calculation of study treatment duration may use different rules as specified in Section 3.3.1.1.)

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF.

If the last date of study treatment is missing, on-treatment assessments/events include any assessment/event recorded in the database and which occur after the start date of study treatment.

Data listings will include all assessments/events, flagging those which are not on-treatment assessments/events.

Note: The date of first administration of study treatment in the randomized treatment phase and the date of last administration of study treatment in the randomized treatment phase are defined in sections 2.1.3.1 and 2.1.3.2, respectively.

For patients who crossed over to LEE011, the placebo group will include all events before the date of first administration of LEE011 and will not include the 30 days are described above. While the LEE011 crossed over group will include all events after the date of first administration of LEE011 and will include the 30 days.

2.1.2.7 Last contact date

The last contact date will be derived for patients not known to be dead at the analysis cut-off using the last complete date among the following:

- All assessment dates (e.g. vital signs assessment, performance status/[redacted],).
  Note, only a true on study assessment date or patient contact date will be used. If there is a

visit date without evidence of any actual assessment performed that date will not be used. No dates post cut-off will be used.

- Medication dates including study medications, concomitant medications, and antineoplastic therapies administered after study treatment discontinuation.
- Adverse event dates.
- Last contact date collected on the 'Survival information' eCRF (only if the patient status is not unknown).
- Randomization date.
- The cut-off date will not be used for last contact date, unless an actual assessment or patient contact was performed.

Important note: imputed dates (e.g. the analysis cut-off date programmatically imputed to replace the missing end date of a dose administration record) will not be used to derive the last contact date.

The last contact date will be used for censoring of patients in the analysis of overall survival.

2.1.2.8 Scheduled study visit and window for the analysis

In order to summarize longitudinal data per time point, assessments will be allocated to visits using predefined time windows. Unless otherwise specified, when more than one assessment is available for a visit, all assessments will be listed under the visit while only the assessment closest to the planned day for the visit will be used for summaries and analyses.

Time windows are provided in Table 2-1. Time windows for measurements to be described by visit.

Table 2-1 Time windows

Assessment	Visit	Time Window
Efficacy Assessments		
Tumor response for imaging assessments	Screening	Baseline
	C3D1	Week 8 ± 3 days
	every 8 weeks (2 cycles) during the first 12 month, i.e. C5D1 ± 3 days, C7D1 ± 3 days, C9D1 ± 3 days, C11D1 ± 3 days, C13D1 ± 3 days	
	C16D1	Week 60 ± 3 days
	every 12 weeks (3 cycles) … i.e. C19D1 ± 3 days, C22D1 ± 3 days, C25D1 ± 3 days …	
	EOT	EOT - 28 days

Notes:
C = cycle, D = Day
All other assessments (i.e. laboratory evaluations etc.) the reported visit will be used

2.1.2.9 Imputation rule of partial or missing dates/data

Imputation rule of partial or missing dates

The following rule will be applied to handle partial dates. When the day is missing, it is imputed to the 15th of the month (e.g., DEC2007 imputed to 15DEC2007). When the day and month are both missing then the date is imputed to July 1st of that year (e.g., 2007 imputed to 01JUL2007). All imputed data are flagged in the listings.

Standard imputation rules for adverse events (AEs) and concomitant medications partial or missing dates will be used.

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

As of the date of data cutoff for the purposes of reporting, continuing events (e.g. adverse events, concomitant medication, etc.) will be summarized using the 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 will be used as the completion date of the event with the appropriate censoring.

Handling of missing data

Unless otherwise specified missing data will not be imputed. Handling of missing data will depend on the nature of the data:

- Baseline characteristics: number of patient with missing data will be reported and descriptive statistics will be computed on patients with non-missing data.
- RECIST best overall response (BOR): patients with missing or unknown BOR will be considered as failure in the overall response rate computation (see Section 3.5.1.1)

- Time-to-event endpoints: appropriate statistical methods will be used to account for censored patients (see Section 3.5.1.2)
- [redacted] laboratory data, ECG data, vital signs: number of patient with missing data will be reported and descriptive statistics will be computed on patients with non-missing data.

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

2.2 Analysis sets

For inclusion in any analysis set it is required that a patient has correctly consented and has received at least one dose of study treatment. For those incorrectly consented patients, they will be excluded from all analysis.

The following analysis sets which will be derived prior to database lock will be used.

Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study drug were assigned by randomization. According to the intent to treat principle, patients will be analyzed according to the treatment arm assigned at randomization.

The FAS2 will consist of all patients from the placebo arm who had progression per RECIST v1.1, crossed over to the LEE011 arm and received at least one dose of LEE011.

Note that patients who were screened and are eligible but never started treatment will not be included in the FAS and FAS2.

The FAS and FAS2 will be used for all listings of raw data of placebo and LEE011 arm, and LEE011 crossover arm, respectively. Unless otherwise specified, FAS will be the default analysis set used for all summary tables and figures.

Safety Set

The safety set includes all randomized patients who received at least one dose of study drug, and have at least one valid post-baseline safety assessment. The statement that a patient had no AEs (on the AE eCRF) constitutes a valid safety assessment.

Patients will be classified according to treatment received, which is defined as:

- The treatment assigned if it was received at least once, or
- The first study drug received when starting therapy with study treatment if the assigned treatment was never received.

Table 2-2 summarized protocol deviations leading to exclusion from analysis sets. Severity codes are defined in [Validation and Analysis Planning (VAP) Module 3]. Patients were excluded from the analysis sets defined above based on the protocol deviations entered in the database.

Table 2-2 Summary of protocol deviations leading to exclusion from analysis sets

Analysis set	Protocol deviations [severity codes leading to exclusion]
Full analysis set	Patient not correctly consented [8] Patient who did not receive at least one dose of study drug [8]
Full analysis set 2	Patient who did not receive at least one dose of study drug [8]
Safety set	Patient not correctly consented [8] Patient who did not receive at least one dose of study drug [8] Patient has no safety assessments (including no record that No adverse event occurred) [5]

[8] exclude from all analysis / [5] exclude from all safety analyses / [1] exclude from per protocol set / [redacted]

2.3 Interim analysis

Not applicable.

3 Statistical methods used in reporting

Data will be summarized with respect to demographic and baseline characteristics, and safety observations using descriptive statistics (quantitative data) and contingency tables (qualitative data). They will be reported using FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25^{th} and 75^{th} percentiles, minimum and maximum will be presented.

Listing will be reported separately for:

(a) Patients randomized in placebo arm, until they stop to switch to LEE011 or discontinued the study, whichever occurs first

(b) Patients randomized in LEE011 arm

(c) Patients who crossover to LEE011 arm from the time of first LEE011 dose

Summary tables will be reported only for patients in (a) and (b) specified above.

Listings of all raw data will be produced and ordered by treatment arm, center, country and patient. Unless otherwise specified, if multiple measurements are available for one time point (or period), an average will be provided to represent the time point (or time period). Unless specified otherwise, all percentage is with respect to big N.

Screen failure patients are those who signed the informed consent, but never started the study treatment for any reason. For these patients, the only information collected on the eCRF is the screening log and the demography pages. These will not be included in any analysis, but will be reported in the CSR as separate listings.

3.1 Enrollment status

These analyses will not be provided, since the enrollment in the study was halted after only a few patients treated. See details in Section 4.

3.2 Patient disposition, background and demographic characteristics

The FAS will be used for all baseline disease characteristics and demographic summaries and data listings.

Baseline demographic, reasons for screen failure and serious adverse events will be listed for screened failure patients.

3.2.1 Patient disposition

The FAS will be used for the patient disposition summaries. Based on the four eCRF pages 'End of Treatment Phase Disposition', 'End of Post Treatment Phase Disposition', 'End of Crossover disposition' and 'End of Post Treatment Phase Disposition 2' will be combined by treatment. A listing of study completion by treatment will be produced. Patients are considered to be ongoing if they have not discontinued due to any reason (e.g., disease progression, AE, withdrawn consent).

3.2.2 Protocol deviations

These analyses will not be provided, since the enrollment in the study was halted after only a few patients treated. See details in Section 4.

3.2.3 Background and demographic characteristics

Background and demographic characteristics including age, gender, race, ethnicity, height, weight, ECOG performance status, tumor type and medical conditions will be listed and summarized using descriptive statistics. The summaries will be based on the assessments from the screening visit (baseline). The FAS and FAS2 (for listing) will be used.

In addition, the following derived variables derived from the demographic eCRF will be described:

- age groups summarized by class (<65, ≥65 years)
- Body mass index (BMI) calculated as weight/(height**2) (kg/m^2) where weight is measured in kg and height in m

3.2.4 Medical History

These analyses will not be provided, since the enrollment in the study was halted after only a few patients treated. See details in Section 4.

3.2.5 Prior antineoplastic therapy

These analyses will not be provided, since the enrollment in the study was halted after only a few patients treated. See details in Section 4.

3.2.6 Diagnosis and extent of cancer

These analyses will not be provided, since the enrollment in the study was halted after only a few patients treated. See details in Section 4.

3.2.7 Other baseline characteristics

These analyses will not be provided, since the enrollment in the study was halted after only a few patients treated. See details in Section 4.

3.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

3.3.1 Study medication

These analyses will not be provided, since the enrollment in the study was halted after only a few patients treated. See details in Section 4.

3.3.1.1 Duration of study treatment exposure

The following algorithm will be used to compute the duration of study treatment exposure for patients who took at least 1 dose of any of the components of the study treatment:

Duration of exposure (days) = (last date of exposure to any study treatment component) – (date of first administration of any treatment component) + 1.

Both date of first administration of study treatment and last date of exposure to study treatment are defined in Section 2.1.3.3 and Section 2.1.3.5, respectively.

For patients who did not take any drug the duration of drug exposure is by definition equal to zero.

3.3.2 Prior and concomitant medication

These analyses will not be provided, since the enrollment in the study was halted after only a few patients treated. See details in Section 4.

3.4 Analysis of the primary variable(s)

3.4.1 Primary variable(s)

The primary endpoint of the study is PFS, defined as the time from the date of randomization to the date of the first documented progression or death due to any cause. PFS will be assessed via the local radiology assessment according to RECIST v1.1. If a patient has not had an event, PFS will be censored at the date of the last adequate tumor evaluation [Protocol CLEE011X2201 Appendix 1].

3.4.2 Statistical model

The primary efficacy endpoint, PFS will be formally analyzed at the final analysis time point [Protocol CLEE011X2201 Section 10.8].

If the estimated hazard ratio at the final analysis is 0.48 or below, it will be considered as evidence of clinically relevant efficacy of LEE011 over placebo.

To claim the superiority of LEE011 to placebo, both criteria below need to be satisfied:

- The log-rank test p-value (one-sided) is below 0.05
- The estimated HR is 0.48 or smaller

The distribution of PFS between the **two treatment arms** will be compared using the log-rank test. The HR will be estimated using the Cox proportional hazard regression model. The estimated HR and related two-sided 90% confidence interval (CI) will be provided.

In addition, PFS will be analyzed using Kaplan-Meier estimates [Kaplan and Meier 1958] (including graphical representation) with two-sided 90% confidence interval for median survival and survival probabilities for specific time-points (3, 6, 9, 12, 15, 18, 21 and 24 months) will be presented for each treatment arm.

The final primary analysis of PFS will be conducted when a total of 23 PFS events are observed (See [Protocol CLEE011X2201 Section 10.8] for sample size calculation) and patients have been followed for PFS for at least 6 months or have discontinued prior to this time for disease progression or death, or have withdrawn consent to follow up or have been lost to follow up. This event number is associated with 80% power when the underlying hazard ratio is 0.33 (corresponding to 2 months median PFS for placebo versus 6 months median PFS for LEE011).

These analyses will not be provided, since the enrollment in the study was halted after only a few patients treated. See details in Section 4.

3.4.3 Supportive analyses

These analyses will not be provided, since the enrollment in the study was halted after only a few patients treated. See details in Section 4.

3.4.4 Sample size calculation

The sample size is determined based on the primary efficacy endpoint PFS.

Under the hypothesis in Section 3.4.2, 23 PFS events are required for a one-sided type I error of $\alpha = 0.05$ and 80% power to reject H_0 when the true log hazard ratio is HR = 0.33 using a

log-rank test. It is assumed the median PFS for placebo is 2 months and median PFS for LEE011 is 6 months. Under an exponential survival model, a 3-fold increase of PFS (or a 66.7% reduction in the hazard rate) is expected on treatment of LEE011 against placebo.

[redacted]

The expected study duration is approximately 24 months (completed study) (inflated by 3 months in order to take into account for a 15% drop-out rate).

The sample size calculation was performed using software package EAST 5.4.

3.5 Efficacy evaluation (Secondary [redacted] Objectives)

These analyses will not be provided, since the enrollment in the study was halted after only a few patients treated. See details in Section 4.

3.6 Safety evaluation

The assessment of safety is based on the type of AEs and frequency of AEs as well as on the number of laboratory values that fall outside of pre-determined ranges (Common Toxicity Criteria [CTC] version 4.03 grading limits or normal ranges as appropriate).

The Safety set will be used for summaries and listings of all safety data in Section 14 of the CSR. Safety analyses will be performed per treatment received (see Section 2.1.1.2). The FAS will be used for Section 16 of the CSR, including for safety listings. These listings will be displayed per intended treatment as per all analyses performed on the FAS (see Section 2.2). Differences between treatment received and intended treatment, if any, will be provided in a listing.

The safety summary tables will include only assessments collected no later than 30 days after study treatment discontinuation. All safety assessments will be listed, and those collected later than 30 days after study treatment discontinuation will be flagged.

For patients who crossed over to LEE011, the placebo group will include all events before the date of first administration of LEE011 and will not include the 30 days are described above. While the LEE011 crossed over group will include all events after the date of first administration of LEE011 and will include the 30 days.

3.6.1 Adverse event

Adverse events 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) will not be used since this information will be collected on the “End of Treatment”, “Study evaluation completion” or “Survival information” CRF pages.

Separate summaries and listing for adverse events (AEs) and serious AEs (SAEs) recorded during the study, and all death (on-treatment and post-treatment, with appropriate flag variable to identify on-treatment death) will be provided. Additional summaries and listing based on the relationship to study drug by treatment, study drug discontinuation, requiring dose adjustment or delay will be produced.Listing and summaries will be produced according to the following rules:

- Patients reporting and experiencing multiple occurrences of a specific AE will have occurrences listed but will be counted only once in the appropriate event category/class and according to the worst observed grade within summary tables.
- AEs will be summarized by presenting the number and percentage of patients having at least one AE, and having at least one AE in each primary system organ class and for each preferred. AE will be sorted by descending frequency or alphabetically (system organ class [SOC] and preferred term [PT]).
- 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.

3.6.2 Deaths

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

3.6.3 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.

3.6.4 Tolerability

These analyses will not be provided, since the enrollment in the study was halted after only a few patients treated. See details in Section 4.

[redacted]

[redacted]

4 Change to protocol specified analyses

Since the enrollment in the study was halted after only a few patients treated (10 patients), only the outputs defined in the document "Guidelines for short, closeout CSRs" (released on the 17-Sept-2014) will be produced.

Therefore, the following analyses will not be performed:

- [Protocol Section 10.3.1 Study Treatment]: The actual dose, dose intensity, relative dose intensity and total daily doses of each agent will not be summarized or listed.
- [Protocol Section 10.3.2 Concomitant therapies]: Concomitant medications and significant non-drug therapies prior to and after the start of the study drug treatment will not be summarized or listed.
- [Protocol Section 10.3.3 Compliance]: The listing of patients with protocol deviations will be provided; no summary tables will be produced.
- [Protocol Section 10.4.2] The primary efficacy endpoint, PFS will not be analyzed. Log-rank test, HR estimates and related confidence interval and Kaplan-Meier estimates with confidence interval for median survival and survival probabilities will not be performed.
- [Protocol Section 10.5.2 Other secondary efficacy objectives]: BOR, ORR and DCR will not be summarized and corresponding confidence interval will not be produced. Kaplan-Meier plots for DOR will not be produced and the median DOR will not be estimated. Kaplan-Meier estimates for OS with confidence intervals will not be produce and OS rate and related confidence interval will not be performed. Listing of Overall response, time to progression time to onset and duration of overall response will not be provided. Waterfall plot will not be produced.
- [Protocol Section 10.5.3 Safety objectives]: Laboratory abnormalities, ECG, Cardiac Imaging and vital signs summary tables and listings will not be provided. Tolerability of the study drug will not be summarized and reason for dose interruption, dose reduction and dose change will not be listed by patient or summarized.
- [redacted]
- [redacted]
- [redacted]

5 References

Brookmeyer R and Crowley J (1982). A Confidence Interval for the Median Survival Time, *Biometrics* 38, 29 - 41.

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