STATISTICAL ANALYSIS PLAN

Clinical Trial Protocol CMEK162X2114

A phase Ib/II, multicenter, open-label, study of LEE011 in combination with MEK162 in adult patients with NRAS mutant melanoma

STUDY DRUG: MEK162/LEE011

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Approval Signatures

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List of abbreviations

ADI	Actual dose intensity
AE	Adverse event
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomic-Therapeutic-Chemical classification
AUC0-24h	Area under the curve from time zero to 24 hours
AUCinf	Area under the curve from time zero to infinity
AUClast	Area under the curve from time zero to the last measureable concentration time
BID	Twice daily (Bis in diem in Latin)
BLRM	Bayesian logistic regression model
BMI	Body Mass Index
BOR	Best overall response
BUN	Blood Urea Nitrogen
CBC	Complete blood count
CDK	Cyclin-Dependent Kinase
CK	Creatinine Kinase
CL/F	Total body clearance of drug from the plasma
Cmax	Maximum plasma concentration after a single dose
CPK	Creatinine phosphokinase
CR	Complete response
CRF	Case Report/Record Form
CRO	Contract Research Organization
CSR	Clinical Study Report
Css	Plasma concentration during steady state
CT	Computed tomography
CTCAE	NCI common terminology criteria for adverse events (version 4.0)
DAR	Dose Administration Record
DDS	Dose-determining set
DI	Dose intensity
DLT	Dose-limiting toxicity
DOR	Duration of Response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOT	End of Treatment
ETDRS	Early treatment diabetic retinopathy study
EWOC	Escalation with overdose control
FAS	Full analysis set
HR	Heart rate
IB	Investigational Brochure
INR	International normalized ratio
IOP	Intraocular pressure
IU	International units
Kg	Kilogram
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantification

MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multiple gated acquisition scan
NA	Not assessed
NRAS	Neuroblastoma RAS viral oncogene homolog
OCT	Optical coherence tomography
ORR	Objective response rate
OS	Overall survival
PAS	PK analysis set
PD	Pharmacodynamics/Progressive disease
PDI	Planned dose intensity
PFS	Progression-free survival
PK	Pharmacokinetics
CCI	[redacted]
PPS	Per-Protocol Set
PR	Partial response
PT	Prothrombin time/Preferred term
QD	One a day (quaque die in Latin)
QTc	Corrected QT interval
QTcB	QT corrected with Bazett's formula
QTcF	QT corrected with Fredericia's formula
Racc	Accumulation ratio
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria for Solid Tumors
RPED	Retinal pigmented epithelial detachment
RVO	Retinal vein occlusion
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation/Stable disease
SOC	System Organ Class
STL	Standard table and listing
T1/2	Half life
T1/2,acc	Effective elimination half-life
TLFs	Tables, Listings and Figures
Tmax	Time to reach maximum (peak) plasma concentration
TSH	Thyroid-stimulating hormone
TTP	Time to progression
TTR	Time to response
ULN	Upper limit of normal
UNK	Unknown
WBC	White blood cell
WHO	World Health Organization
WHO ATC	WHO Anatomical Therapeutic Chemical
WHO DRL	WHO Drug Reference Listing

1 Introduction

This document provides the detailed statistical methodology for the analysis of data from study CMEK162X2114. The output shells corresponding to this document can be found in separate documents.

All changes to the planned analysis 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 shells documents without the need to amend these documents.

This document and shells may also serve as a reference for the creation of any outputs required outside of the CSR, e.g., IB updates, abstracts, poster presentations, or management updates.

This document and shells were created based on final protocol version released 26-AUG-2015.

1.1 Study design

1.1.1 Description of study design

This is a multi-center, open-label Phase Ib/II study in patients with locally advanced or metastatic NRAS mutant melanoma. The study has 2 parts – phases Ib and II.

MEK162 will be administered orally twice daily (BID) and LEE011 orally once daily (QD). The starting doses of MEK162 and LEE011 will be 45 mg BID and 200 mg QD respectively. LEE011 will be administered for 21 days followed by a 1 week break and MEK162 will be administered on a continuous dosing schedule (28-day cycle).

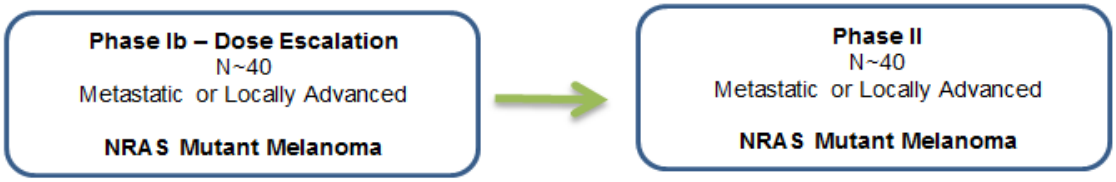
Should safety and PK data from the dose escalation part of this study and/or other MEK162/LEE011 study(s) indicate that alternate dosing regimens of MEK162 and LEE011 may be more appropriate, the following schedules will be considered:

- LEE011 QD and MEK162 BID, both administered for 3 weeks followed by a 1 week planned break (28-day cycle)
- LEE011 QD and MEK162 BID, both administered for 2 weeks followed by a 1 week planned break (21-day cycle)

Phase Ib is the dose escalation part where successive cohorts of 3-6 newly enrolled patients receiving various dose pairs considering the recommendation from an adaptive Bayesian logistic regression model (BLRM) incorporating the Escalation With Overdose Control (EWOC) principle until Maximum Tolerated Dose (MTD) / Recommended Phase II dose (RP2D) is defined. Once the MTD/RP2D have been determined for each tested schedule, the Phase II part will begin at the RP2D on the chosen schedule to assess antitumor activity of the LEE011 and MEK162 combination.

Patients will continue to receive treatment until disease progression, occurrence of unacceptable toxicity that precludes any further treatment, or if treatment is discontinued at the discretion of the investigator or by patient's withdrawal of consent. Analysis of the study data will occur after all patients have had the opportunity to complete at least six cycles of treatment.

Figure 1-1 Study design



1.1.2 Definition of end of the study

Phases Ib and II of the study will end when the treatment period, safety follow-up, disease follow-up, and survival follow-up (only for Phase II) have ended for all patients as described in Protocol Section 7.1.5, or when the study is terminated early.

1.2 Objectives and endpoints

Objectives and related endpoints are described in Table 1-1 below.

Table 1-1 Objectives and related endpoints

Objective	Endpoint
Primary	
Phase Ib: To estimate the MTD(s)and/or to identify the RP2D and schedule of LEE011 and MEK162 in combination	Incidence of dose limiting toxicities in cycle 1
Phase II: To describe the anti-tumor activity of the LEE011 and MEK162 in combination at the RP2D	ORR (CR and PR) according to RECIST 1.1
Secondary	
Phase Ib: To characterize the PK profiles of LEE011 and MEK162 as well as any other clinically significant metabolites that may be identified.	Plasma concentration-time profiles of LEE011 and MEK162, PK parameters, including but not limited to AUC_{tau}, $AUC_{tau,ss}$, $C_{min,ss}$, C_{max}, $C_{max,ss}$,T_{max}, $T_{max,ss}$, accumulation ratio (R_{acc}), and $T_{½,acc}$, CL/F
Phases Ib and II: To characterize the safety and tolerability of LEE011 and MEK162	Incidence and severity of adverse drug reactions and serious adverse drug reactions. Changes in hematology and chemistry values, vital signs, electrocardiograms (ECGs), and dose interruptions, dose reduction and dose intensity.
Phases Ib and II: To assess clinical efficacy of the LEE011 and MEK162 combination	Duration of response (DOR), Time to progression (TTP), Progression Free Survival (PFS) and Overall Survival (OS) as per RECIST 1.1. Best Overall

Response (BOR) according to RECIST 1.1

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1.3 Data Analysis

1.3.1 Data analysis environments and general methodologies

Data will be analyzed by Array Biopharma and/or designated CRO.

The statistical analysis of this study will be performed by Array BioPharma personnel and/or a designated CRO. SAS® version 9.2 or higher will be used in all analyses other than Bayesian analyses. For Bayesian modeling, R version 2.13.2 or higher and WinBUGS version 1.4.3 will be utilized. PK parameters will be calculated using non-compartmental methods available in Phoenix WinNonlin version 5.2 or higher.

1.3.2 Data included in the analysis

The study data will be analyzed and reported based on all patients' data of the dose escalation (Phase Ib) and Phase II parts. The CSR will include all outputs planned within table, listing, and figure shells.

No formal interim analyses are planned.

1.3.3 Data analyses

It is planned that the data from participating centers in this protocol will be combined, so that an adequate number of patients will be available for analysis. No center effect will be assessed.

The following rules will be followed for reporting results unless stated otherwise:

- **Phase Ib dose escalation data**: Cohorts of patients treated with the same dose combination and regimen during the dose escalation part will be pooled into a common treatment group. All summaries, listings, figures, and analyses will be displayed/performed by treatment group

unless otherwise specified. Both pre- and post-intra-patient dose escalation data will be listed and summarized together under the one dose level/treatment group.

- **Phase II data**: All summaries, listings, figures, and analyses will be performed at RP2D.

Patients from the Phase Ib and Phase II parts will **NOT** be pooled for the primary ORR analysis.

The data will be summarized with respect to demographic and baseline characteristics, efficacy and safety assessments, PK, CCI [redacted] measurements.

2 Definitions and general methodology

2.1 General definitions

2.1.1 Naming conventions and definitions

Study drug /treatment

Study drug 1 = LEE011 (in capsule for oral use)

Study drug 2 = MEK162 (in film-coated tablet for oral use)

Study treatment = LEE011 + MEK162 for both Phase Ib and Phase II

The study drugs will be administered as a flat-fixed dose, and **NOT** by body weight or body surface area.

Original dosing regimen

LEE011 QD "3 weeks on/1 week off" + MEK162 BID on a continuous dosing schedule (28-day cycle)

Alternative dosing regimens for consideration

Should safety and PK data from the dose escalation part of the study and/or other MEK162/LEE011 study(s) indicated that alternate dosing schedules of MEK162 and LEE011 may be more appropriate, the following schedules will be considered:

- LEE011 QD and MEK162 BID, both "2 weeks on/1 week off" (21-day cycle)
- LEE011 QD and MEK162 BID, both "3 weeks on/1 week off" (28-day cycle)

Treatment group

Treatment group is the combination of the first actual dose recorded in the Dose Administration Record (DAR) electronic Case Report Form (eCRF) of each component of the combination.

Treatment groups will be presented by dosing regimen; within the same regimen the treatment groups will be presented by ascending LEE dose and then by ascending MEK dose.

In Phase Ib, cohorts of patients treated with the same dose combination and regimen during the dose escalation part will be pooled into a common treatment group.

In Phase II, based on the safety, tolerability, and efficacy, a single treatment group with RP2D and regimen will be selected to assess antitumor activity of the LEE011 and MEK162 combination.

MTD(s)

The MTD will be established for all tested dosing regimens in Phase Ib. It is defined as the highest combination drug dosage not causing medically unacceptable dose-limiting toxicity (DLT) in more than 35% of the treated patients in the first cycle of treatment.

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

2.1.2.1 Date of first and last administration of study drug

The date of first administration of study drug (LEE011 or MEK162) is derived as the first date when a non-zero dose of study drug was administered and recorded on the DAR eCRF. For the sake of simplicity, the date of first administration of study drug will also be referred as ***start of study drug***.

The date of last administration of study drug is the last date when a non-zero dose of study drug is administered and recorded on DAR eCRF.

Dosing is reported in a continuous fashion. Week off (i.e., for 3+1 and 2+1 regimens) are not reported in data (one **does not** enter a new '0 dose' record and new start date to indicate patient is in 'off week').

2.1.2.2 Date of first and last administration of study treatment

The date of first administration of study treatment is derived as the first date when a nonzero dose of the study drug is administered and recorded on DAR eCRF. (i.e., earliest date between first LEE011 dose and first MEK162 dose). For the sake of simplicity, the date of first administration of study treatment will also be referred as ***start of study treatment***.

The date of last administration of study treatment is derived as the latest date of the last administration of non-zero dose of the study drug and recorded on DAR eCRF. (i.e., latest date between last LEE011 dose and last MEK162 dose).

2.1.2.3 Study day

The study day for all assessments/events will be calculated using the start date of study treatment as reference. For assessments/events (both efficacy and safety) occurring on or after the start date of study treatment, study day will be calculated as:

Study day (days) = Event date – Start date of study treatment + 1.

Therefore, the first day of study treatment is study day 1.

For all assessment/events occurring prior to the start of the study treatment, study day will be negative and will be calculated as:

Study day (days) = Event date – Start date of study treatment.

Therefore, the last day prior to the first study treatment is study Day -1.

Unless specified otherwise, the study day will be displayed in the data listings.

2.1.2.4 Baseline

Baseline is considered as the last available assessment performed or value measured within 14 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, PK samples, CCI [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.

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.

Patients with no data on a particular parameter before the first treatment administration will have a missing baseline for this parameter.

On cycle 1 day 1 (pre-dose), 3 ECG recordings must be taken at a minimum of 2-minute intervals. The combined QTc values from these 3 ECGs will be averaged to provide a single baseline value for each patient. If there are no available pre-dose ECG results on the same day as first treatment administration, baseline is the mean of pre-dose records on the last day before start date of treatment.

2.1.2.5 Study evaluation completion

The study evaluation completion eCRF (titled 'Study Phase Completion') records the end of study for every individual patient and is completed for all patients enrolled in the Phase Ib part and those patients enrolled in the Phase II part who have disease progression during study treatment, once the 30-day safety follow-up period is completed. For patients enrolled in Phase Ib who discontinue treatment for a reason other than disease progression, study evaluation completion will be recorded after safety follow-up (30 days after study discontinuation); for Phase II patients who discontinue study treatment for any reason other than disease progression, the study evaluation completion eCRF should be completed upon disease progression, the initiation of subsequent anticancer therapies, or death. Note, the survival follow-up assessments do continue beyond the study evaluation completion for all patients enrolled in the Phase II part.

Any of the following reasons may be provided for study discontinuation if study evaluation completion status is anything other than "completed":

- Adverse event
- Lost to follow-up

- Non-compliance with study treatment
- Physician decision
- Pregnancy
- Progressive disease
- Protocol deviation
- Study terminated by sponsor
- Technical problems
- Subject/guardian decision
- Death
- New therapy for study indication

2.1.2.6 On-treatment assessment/event

An on-treatment assessment/event is defined as any assessment/event obtained in the time interval from the start date of study treatment until the last date of study treatment + 30 days inclusive.

2.1.2.7 End of treatment (EOT)

Patients may voluntarily withdraw from the study treatment or may be taken off the study treatment at the discretion of the investigator at any time. The end of treatment assessments should occur within 14 days of the last study treatment.

Patients may discontinue study treatment for any of the following reasons:

- Adverse event
- Lost to follow-up
- Non-compliance with study treatment
- Physician decision
- Pregnancy
- Progressive disease
- Protocol deviation
- Study terminated by sponsor
- Technical problems
- Subject/guardian decision
- Death

2.1.2.8 Imputation rule of partial or missing dates

For computation of time intervals (e.g., elapsed time between date of first study treatment to progression), the time interval should be set to missing when the imputation rule leads to a negative value.

For patients who discontinue the study with ongoing events, the discontinuation date will be used as the completion date of the event.

For AEs, concomitant medications and antineoplastic therapies, imputation rules for partial or missing dates are described below:

Adverse event date imputation

Missing and partial start and end dates for AEs will be handled according to Section 3.5.1.

Concomitant medication date imputation

The imputation of the start date and end date of concomitant medication use will follow the same conventions as for AE start date and end dates.

Antineoplastic therapies date imputation

Prior therapies

Start date:

In general, follow the same rules that are applied to the imputation of an AE/concomitant medication start date, except:

- Completely missing start dates are imputed as treatment start date - 1;
- If only day is missing, and month and year match that of the treatment start date, impute as treatment start date -1;
- If both day and month are missing, and the year matches that of the treatment start date, then impute as treatment start date - 1.

End date:

Imputed date = min(treatment start date - 1, last day of the month), if day is missing;

Imputed date = min(treatment start date - 1, 31DEC), if month and day are missing.

Completely missing end dates will not be imputed.

Post therapies

Start date:

Imputed date = max(last date of study drug + 1, first day of the month), if day is missing;

Imputed date = max(last date of study drug + 1, 01JAN), if day and month are missing.

Completely missing start dates will be imputed as last date of study drug + 1.

End date: No imputation.

Date of initial diagnosis of cancer and date of most recent recurrence

For date of initial diagnosis of cancer, missing day is defaulted to 15 and missing month and day is defaulted to July 01 respectively. For date of most recent recurrence, if only day is missing then day is set to 15. If both month and day are missing, then month and day will be set to July 01.

2.2 Analysis sets

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the Screening Log eCRF, and each patient's demographic information will be captured in the Demography eCRF. No other data will be entered into the clinical database for screen failure patients.

A patient must have given informed consent to participate in the study before being included in any analysis set.

The number of patients in each analysis set will be summarized by treatment group, as well as listed by patient.

Full Analysis Set

The Full Analysis Set (FAS) includes all patients who received at least one dose of LEE011 or MEK162. Patients will be analyzed according to the planned treatment combination. The FAS will be used for all listings of raw data. Unless otherwise specified the FAS will be the default analysis set used for all analyses.

Safety Set

The safety set includes all patients who received at least one dose of LEE011 or MEK162, and have at least one valid post-baseline safety assessment.

Patients will be analyzed according to treatment received, where treatment received is defined as:

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

Per-protocol Set

The Per-Protocol Set (PPS) consists of a subset of the patients in the FAS who are compliant with the following requirements of the clinical study protocol:

- Diagnosis corresponds to that defined in inclusion criteria (Protocol Section 5.2); prior treatment corresponds to that defined in inclusion criteria (Protocol Section 5.2).
- The patient received at least 50% of the planned dose of each compound (taken together) within the first 8 weeks of study for the 28-day cycle regimen or the first 6 weeks of study for the 21-day cycle regimen. For example, a patient discontinuing after 2 weeks will be excluded from the PPS even if no combination doses were missed.
- The patient was evaluated for primary efficacy variable at or beyond week 10, or discontinued due to an AE, disease progression, or died prior to the first evaluation of the primary efficacy variable.

Patients will be evaluable for efficacy under the PPS if they have at least one tumor evaluation with an overall lesion response assessed differently from 'unknown' or 'not assessed' under the RECIST 1.1 at or beyond week 10.

A patient who discontinued the study prior to being evaluated for the primary efficacy variable at the week 10 evaluation for a reason(s) other than AE, PD, or death, or for whom the evaluation(s) at week 10 and beyond were all of 'unknown' or 'not assessed' status per RECIST 1.1 will not be included in the per-protocol set.

The PPS will be used in the Phase II part of the study only and will define the patients used in the sensitivity analysis of the primary endpoint (Protocol Section 10.4).

Dose-determining analysis set

The dose-determining set (DDS) includes all Phase Ib patients from the safety set who either complete a minimum exposure requirement or have experienced a dose limiting toxicity (DLT) during Cycle 1.

A patient is considered to have met the minimum exposure criterion if they receive at least 75% of the planned daily or a higher combination doses of MEK162 (BID), 75% of the planned or a higher daily combination doses of LEE011, and at least 50% of the planned or a higher daily combination doses of the two compounds administered together (in the same day) within the first 21/28 days of treatment. The length of the DLT evaluation period is one cycle (i.e., Cycle 1).

Pharmacokinetic analysis set

The PK analysis set (PAS) consists of all patients who have at least one blood sample providing evaluable PK data and received at least one dose of study drug. The PAS will be used for summaries (tables and figures) and listings of PK data.

Note: patients will be removed from the estimation of certain PK parameters on an individual basis depending on the number of available blood samples. These patients will be identified at the time of the analyses. When emesis is observed for a patient within 4 hours after dosing, the PK parameters will be flagged and presented only in the listings, but will not be summarized.

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2.3 Sample size and power considerations

Phase Ib

Cohorts of 3 to 6 evaluable patients will be enrolled in the dose-escalation part including approximately 15 patients in total and at least six patients at the MTD(s)/RP2D level per dosing regimen, as described in the Protocol Section 6.2.3. Multiple cohorts may be sequentially or alternatively enrolled to the same dose level. Additional cohorts of 1 to 6 patients may be enrolled at any dose level below the estimated MTD/RP2D for further elaboration of safety and pharmacokinetic parameters as required. Approximately 15 patients are expected to be treated per each dosing regimen in the dose escalation part for the model to have reasonable operating characteristics relating to its MTD(s) recommendation.

Phase II

Based on the prior distribution for the ORR specified in Protocol Appendix 5 and efficacy intervals described in Protocol Section 10.4.2, it is estimated that, given an observed ORR equal to 35%, approximately 40 patients should be enrolled for the model to have less than 10% posterior risk of the true ORR being less than 25% (i.e., unacceptable efficacy).

3 Statistical methods used in reporting

Unless noted otherwise, summaries described in this section will be based on the FAS. Summaries will be produced by treatment group and overall. Data will be listed individually by patient based on the FAS, unless noted otherwise.

Unless specified otherwise, tables and figures will be generated in pairs, one for Phase Ib by treatment group for different dosing regimens (see below) and the other one for Phase II.

For Phase Ib, dosing regimens will be presented in the following order: 28-day-cycle schedule followed by 21-day-cycle schedule. Within each dosing regimen, treatment groups will be presented in ascending order of LEE011 dose levels first, then ascending order of MEK162 dose levels. The last three columns will be "All 28-day patients", "All 21-day patients", and "All patients" if appropriate. For efficacy, the outputs will be presented by regimen (28-day, 21-day, overall) and within each regimen, by treatment group.

Qualitative data (e.g., gender, race, etc.) will be summarized by frequency count and percentages. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator.

Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (e.g., mean, standard deviation (SD), median, minimum, and maximum).

Table 3-1 Treatments

MEK162		LEE011	
Dosing	**Regimen**	**Dosing**	**Regimen**
45 mg	Continuous	200 mg	3 weeks on/1 week off
45 mg	Continuous	250 mg	3 weeks on/1 week off
30 mg	Continuous	300 mg	3 weeks on/1 week off
45 mg	Continuous	300 mg	3 weeks on/1 week off
30 mg	2 weeks on/1 week off	100 mg	2 weeks on/1 week off
30 mg	2 weeks on/1 week off	200 mg	2 weeks on/1 week off
30 mg	2 weeks on/1 week off	300 mg	2 weeks on/1 week off
45 mg	2 weeks on/1 week off	200 mg	2 weeks on/1 week off
45 mg	2 weeks on/1 week off	300 mg	2 weeks on/1 week off
45 mg	2 weeks on/1 week off	400 mg	2 weeks on/1 week off
45 mg	2 weeks on/1 week off	450 mg	2 weeks on/1 week off
45 mg	2 weeks on/1 week off	600 mg	2 weeks on/1 week off

Note: the continuous regimen is considered as a 28-day regimen for the table presentation.

3.1 Patient disposition, background and demographic characteristics

3.1.1 Patient disposition

The FAS will be used for the patient disposition summary tables and listings. The number of patients who enrolled, completed, or discontinued the study will be summarized by treatment group. Specifically, the following will be tabulated using FAS as the denominator:

- Number (%) of patients who are still on-treatment (based on non-completion of the 'End of Treatment' page),
- Number (%) of patients who discontinued treatment (based on completion of the 'End of Treatment' page with discontinuation date and reason entered),
- Primary reasons for study treatment discontinuation (based on discontinuation reason entered in the 'End of Treatment' page),
- Number (%) of patients who discontinued from study (based on completion of the 'Study Phase Completion' eCRF page with discontinuation date and reason entered),
- Primary reasons for study evaluation completion (based on discontinuation reason entered in the 'Study Phase Completion' eCRF page).

Patient disposition will also be listed.

Screen failure patients are those who have been screened, but never started the study treatment for any reason. The data collected on these patients will not be included in any analyses. A listing of patients and the reasons for screen failure will be presented.

3.1.2 Protocol deviations

Protocol deviations will be tabulated and listed by treatment group.

3.1.3 Background and demographic characteristics

Background and demographic characteristics including age, sex, race, ethnicity, height, weight, body mass index (BMI), and Eastern Cooperative Oncology Group (ECOG) (Oken et al., 1982) performance status will be listed and summarized by treatment group.

BMI is derived using the following formula:

BMI [kg/m^2] = weight[kg] / (height[m]**2)

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

- age groups summarized by group (<65, ≥65 years),
- weight summarized by group (<55, 55-<75, ≥75 kg).

3.1.4 Medical history

Medical history and current (ongoing) medical conditions, including cancer-related conditions and symptoms will be summarized and listed by treatment. Separate summaries will be presented for current and historical medical conditions by primary system organ class and preferred term.

Medical history and current medical conditions are coded using the Medical Dictionary for Regulatory Activities (MedDRA).

3.1.5 Prior antineoplastic therapy

Prior antineoplastic therapy will be listed in three separate listings: (i) medications, (ii) radiotherapy, and (iii) surgery.

Prior antineoplastic medications will be summarized by treatment. The summary will include the total number of regimens (note: there can be more than one medication per regimen), setting at last medication, best response at last medication, time (in *days*) between end of last medication to start of study treatment, reason for discontinuation at last medication, and time (in months) from start of last medication to disease progression. The last medication is defined based on the last end date of all prior regimen components. Prior antineoplastic medications will also be summarized by Anatomical Therapeutic Chemical (ATC) class and preferred term.

The summary of prior antineoplastic radiotherapy will include information about the last radiotherapy: time (in months) between radiotherapy and start of study treatment, locations, (including all locations recorded for each patient), and setting.

The summary of prior antineoplastic surgery will include information about the last surgery: the time (in months) between surgery (non-biopsy procedure) and start of study treatment and presence of residual disease.

Last surgery is determined based on the date of surgery. Last radiotherapy is determined based on the radiotherapy end date.

3.1.6 Diagnosis and extent of cancer

Number (%) of patients in each of the categories will be summarized for the following variables:

- melanoma type [cutaneous melanoma, non-cutaneous melanoma]
- predominant histology/cytology [desmoplastic, nodular, lentigo maligna, superficial spreading, unknown, other]
- stage at initial diagnosis and at time of study entry [stage: 0, I, IA, IB, IC, II, IIA, IIB, IIC, III, IIIB, IIIC, IV, IVA, IVB, IVC]
- types of lesions (target, non-target)
- metastases status and sites
- NRAS molecular status (if mutated, type of mutation)

In addition, the following continuous time intervals in days will be computed and summarized:

- time since initial diagnosis of primary site to first dose of study treatment, calculated as (date of study treatment start – date of initial diagnosis of primary site + 1)
- time since initial diagnosis of primary site to most recent recurrence/relapse, calculated as (date of most recent recurrence/relapse – date of initial diagnosis of primary site + 1)
- time since most recent recurrence/relapse to first dose of study treatment, calculated as (date of study treatment start - date of most recent recurrence/relapse + 1)

Disease history will also be listed for each patient.

3.2 Treatments

3.2.1 Study medication

Exposure to study drugs or study treatment will be summarized on the Safety Set in terms of the following derivations:

- duration of study drug exposure,
- duration of study treatment exposure,
- cumulative dose for each study drug,
- dose intensity (DI) and/or relative dose intensity (RDI) for each study drug,
- percentage of actual days dosed during the treatment period,
- percentage of days received planned doses during the treatment period.

All doses of each study drug along with reasons for dose change/dose interruption will be listed.

3.2.1.1 Duration of study drug exposure

For patients who take at least 1 dose of the study drug:

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

3.2.1.2 Duration of study treatment exposure

For patients who take at least 1 dose of any of the components of the study treatment:

Duration of exposure of study treatment (days) = *max*(last date of exposure to LEE011, last date of exposure to MEK162) – *min*(date of first administration of LEE011, date of first administration of MEK162) + 1.

The exposure duration may include periods of temporary interruption.

3.2.1.3 Cumulative dose

The following definitions will be used:

- Actual cumulative dose (mg) = sum of all actual doses of study drug taken during the dosing period (i.e., from first date of treatment administration until last date of treatment administration, including planned interruptions)
- Planned cumulative dose (mg) = sum of all doses of study drug that was intended to have been taken during the treated period (planned interruptions are taken into account)

The planned cumulative dose is obtained by multiplication of the treatment exposure in days by the planned dose per day (e.g., if treatment duration = 10 days, then planned cumulative dose = 10 × daily dosing). Any planned interruptions will not be excluded for the planned cumulative dose calculations.

3.2.1.4 Dose intensity and relative dose intensity

Actual dose intensity (ADI; mg/day), planned dose intensity (PDI; mg/day), and RDI (%) will be summarized by treatment group and overall (using exposure duration) for each study drug.

DI for patients with non-zero duration of exposure is defined as follows:

ADI (mg/day) = actual cumulative dose (mg) / duration of exposure (days)

PDI (mg/day) = planned cumulative dose (mg) / duration of exposure (days)

RDI = ADI [mg/day] / PDI [mg/day]

The number and proportion of patients who fall in the following categories for RDI will also be presented:

- <0.5
- 0.5 - <0.75
- 0.75 - <0.9
- 0.9 - <1.1
- ≥1.1

The calculation of planned dose is based on the initial assigned dose regardless of dose interruption. For patients who did not take any drug, the DI is by definition equal to zero.

Duration of exposure, cumulative dose, actual dose intensity, and relative dose intensity will also be listed for study drug by patient.

3.2.1.5 Dose interruption and dose reduction

Dose interruption

When the actual dose equals zero (where the planned dose is not zero), between the first and last non-zero doses it will be considered a dose interruption. Note that for LEE011/MEK162, the 7-day rest period is not to be considered a dose interruption.

Frequency counts and percentages of patients who have dose interruptions, and the corresponding reasons, will be provided. The number of dose interruptions per patient, and the duration of dose interruptions (*days*) will be summarized.

Dose reductions

For LEE011 and MEK162, the corresponding eCRF allows the recording of dose changes including dose reduction and dose interruption.

For MEK162 dose records, a dose reduction is identified as a non-zero actual dose that is less than the last previous non-zero dose that is divisible by 30, and (for cases where both the current and previous non-zero records are both not divisible by 30) less than the immediate previous non-zero actual dose. For LEE011 dose records, a dose reduction is identified as a non-zero actual dose that is less than the immediate previous non-zero actual dose. For both MEK162 and LEE011 dose records, in cases where a patient's first non-zero dose record is below the treatment planned dose, this dose will be counted a dose reduction as well.

Frequency counts and percentages of patients who have dose reductions, and the corresponding reasons, will be provided.

3.2.2 Prior and concomitant therapy

Concomitant therapies are defined as any medications (excluding study treatment or prior antineoplastic treatments) and significant non-drug therapies (including physical therapy and blood transfusions) administered during the study and are recorded in the Concomitant Medications/significant non-drug therapies eCRF. These therapies will be coded using the WHO Drug Reference Listing (WHO DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (WHO ATC) classification system.

Prior and concomitant medications/significant non-drug therapies will be listed and summarized by treatment group in the safety set. Separate tables and listings will be produced for medication that were stopped prior to start of study drug, medications that started prior to study drug and continued during study, and medication that were started after start of study drug.

Antineoplastic therapies since discontinuation of study drug will be listed by ATC class and preferred term by means of frequency counts and percentages in separate summaries using the safety set.

3.2.3 Anti-neoplastic therapies after discontinuation of study treatment

Anti-neoplastic therapies since discontinuation of study treatment will be listed and tabulated by ATC class and preferred term.

3.3 Analysis of the primary endpoints

3.3.1 Phase Ib

The primary variable is the incidence of dose limiting toxicities (DLTs) in Cycle 1. Patients who are ineligible for the DDS will be removed from the primary analysis and additional patients may be recruited. Their data will be used for all remaining analyses.

The following outputs will be presented:

- DLTs occurring during the first cycle will be listed and summarized by primary system organ class, preferred term, and treatment group.
- A summary of the posterior distribution of DLT rates at the end of Phase Ib will be presented.
- A summary of the prior and posterior parameter estimates for the BLRM will be produced.

3.3.2 Phase II

The primary variable is the ORR, defined as the proportion of patients with a best overall response (BOR) of CR or PR as assessed per RECIST 1.1.

The primary analysis of the ORR will be based on the investigator's assessment of overall lesion responses per RECIST 1.1.

Reporting of ORR to describe the anti-tumor activity in Phase II

Patients with BOR categorized as unknown (UNK) response or not assessed (NA) will be considered as failures in the primary analyses of ORR using the FAS.

Summary tables for ORR per RECIST 1.1 at RP2D, along with 2-sided exact binomial 95% CIs will be produced in FAS and PPS.

Individual lesions evaluation per RECIST v1.1 will be listed in FAS.

Supportive analyses

If deemed necessary, a sensitivity analysis to the investigators assessment CT/MRI scans readings will be performed using the central CT/MRI assessments (RECIST v1.1) mentioned in Protocol Section 7.2.1. The same method of analysis as for the primary analysis will be applied, using the FAS.

CCI [redacted]

3.4 Efficacy evaluation per RECIST 1.1 for secondary endpoints

The FAS and Per-Protocol Set will be used for all efficacy outputs.

Tumor response will be evaluated locally by the Investigator based on RECIST version 1.1. All radiological assessments obtained for patients enrolled during the Phase II part of the study will be centrally collected and subjected to quality checks by an imaging CRO. The site manual provided by the designated imaging CRO will provide further details regarding image collection. For the definition and derivation of all efficacy endpoints, refer to RECIST version 1.1 (Eisenhauer et al., 2009).

3.4.1 General methods for anti-tumor assessments as per RECIST 1.1

3.4.1.1 Analyses of time-to-event data

The following section presents the general methodology used to analyze time-to-event variables (including PFS, OS, DOR, TTP, and TTR).

Start and end dates/censored dates for time to event variables

Refer to Protocol Appendix 2 for details.

Start dates

For all "time to event" variables, other than the duration of response (DOR), the date of treatment start will be used as the start date.

For the calculation of duration of response the following start date should be used:

- Date of first documented response is the assessment date of the first overall lesion response of CR / PR when this status is later confirmed.

End dates

The end dates which are used to calculate 'time to event' variables are defined as follows:

- Date of death (during treatment as recorded on the treatment completion page, or during follow-up as recorded on the 'Study Phase Completion' page or the survival follow-up page).
- Date of progression is the first assessment date at which the overall lesion response was recorded as progressive disease.

  Refer to Protocol Appendix 2 for cases when there is no documentation of radiologic evidence of progression and the patient discontinued for 'Disease progression' due to documented clinical deterioration of disease. The date of discontinuation is used as date of progression in this case.
- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of CR, PR, or SD which was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred), then the date of start of treatment is used.
- Date of discontinuation is the date of the end of treatment visit.
- Date of last contact is defined as the last date the patient was known to be alive. This corresponds to the latest date for either the visit date, lab sample date, or tumor assessment date. If available, the last contact date from that survival follow-up page is used. If no survival follow-up is available, then the date of discontinuation is used as the last contact date.
- Date of secondary anti-cancer therapy is defined as the start date of any additional (secondary) antineoplastic therapy or surgery.

The censoring and event date options to be considered for the PFS/DOR/TTP analysis are presented in Table 3-2.

Table 3-2 Options for event dates/censored dates used in PFS/DOR/TTP

Situation		Date	Outcome
A	No baseline assessment	Date of first administration of study treatment [a]	Censored
B	Progression at or before next scheduled assessment	Date of progression	Progressed
C1	Progression or death after exactly one missing assessment	Date of progression or death	Progressed
C2	Progression or death after two or more missing assessments	Date of last adequate assessment [b]	Censored
D	No progression	Date of last adequate assessment [b]	Censored

E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim		Information ignored. Outcome derived based on radiology data only.
F	New anticancer therapy given	Date of last adequate assessment [b]	Censored

[a] The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

[b] Last adequate tumor assessment is defined in Protocol Section 7.2.1

Kaplan-Meier plot and estimates

An estimate of the survival function will be constructed using the Kaplan-Meier (product-limit) method (Kaplan & Meier, 1958) as implemented in PROC LIFETEST.

The median survival is obtained along with 95% confidence intervals as calculated from the PROC LIFETEST output (using method of [Brookmeyer & Crowley, 1982]).

Kaplan-Meier estimates with 95% confidence intervals at specific time points will be summarized. The confidence intervals are constructed using Greenwood's formula for the standard error of the Kaplan-Meier estimate. When the estimated survival function is close to zero or unity, symmetric intervals are inappropriate since they can lead to confidence limits that lie outside the interval [0, 1]. Any limit that is greater than unity will be replaced by 1.0. Any limit that is less than zero will be replaced by 0.0.

3.4.1.2 Construction of waterfall graphs

The waterfall graph is used to depict anti-tumor activity. This plot displays both BOR and the best percentage change from baseline in the sum of the longest diameter of all target lesions for each patient.

The assessments with an unknown overall response will not be excluded as long as the sum of the longest diameter is correctly computed on the same lesions assessed at baseline.

The best overall response will be shown above each of the displayed bars in the graph.

Patient with missing/unknown best percentage change from baseline represented by a special symbol (e.g., *) in the waterfall graph.

Patients will be ordered in the graph using the following display (from left to right):

- Bars above the horizontal axis representing tumor growth
- Bars under the horizontal axis representing tumor shrinkage
- "Zero" bars with the * symbol representing patients with missing best percentage change

Waterfall plots will show the cut-off limits for target lesions for PR (-30%) as dotted lines.

3.4.1.3 Confidence intervals for Overall Response Rate

ORR is the proportion of patients with a best overall response of CR or PR. Patients will be summarized in terms of percentage rate with 95% confidence interval. An exact binomial confidence interval (implemented using the SAS procedure FREQ with the EXACT statement for one-way tables) will be calculated (Clopper & Pearson, 1934).

3.4.2 Handling of missing data and special cases

No measurable lesion at baseline

Evaluation using RECIST 1.1 criteria implies that patients have a measurable lesion at baseline. However, patient without a measurable lesion may be enrolled in the study. According to RECIST 1.1 guidelines, the overall response should be UNK or PD.

In Phase I studies when the presence of target lesions is not mandatory for enrollment, to avoid the presence of too many "UNK", the overall response will be derived based on non-target lesions only when no target lesion is available. For patients with only non-target lesions at baseline, the overall response will be determined based on post-baseline non-target lesions and new lesions as shown in Table 3-3 below. In general, the non-CR/non-PD response for these patients is considered equivalent to an SD response in endpoint determination. As a result, the overall lesion response can be CR, Non-CR/Non-PD, PD or UNK. Hence, the BOR can be derived as CR, Non-CR/Non-PD, PD or UNK according to RECIST 1.1 guideline for these patients.

Table 3-3 Overall lesion response at each assessment: patients with non-target disease only

Non-target lesions	New Lesions	Overall lesion response
CR	No	CR
Non-CR/Non-PD[1]	No	Non-CR/non-PD
UNK	No	UNK
PD	Yes or No	PD
Any	Yes	PD

[1] As defined in Protocol Appendix 2.

3.4.3 Reporting of BOR, DOR, TTR, TTP, PFS and OS per RECIST as secondary endpoints

Response and progression evaluation will be performed according to the RECIST version 1.1 (as described in detail in Protocol Appendix 2) whenever it applies.

Best overall response (BOR) is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started), death, or early study discontinuation. Only overall tumor assessments reported by investigator and performed before the start of any further anti-neoplastic therapies (i.e. any additional secondary anti-neoplastic therapy or surgery) will be considered in the assessment of best overall response.

Confirmation of complete and partial responses (CR and PR, respectively) must be made at least 4 weeks apart. Stable disease must occur >6 weeks after the start of treatment. Patients with an unknown clinical response will be treated as non-responders.

As a default, any assessments taken more than 30 days after the last dose of study treatment will not be included in the BOR derivation.

If any alternative cancer therapy is taken while on study any subsequent assessments will be excluded from the BOR determination.

The BOR for each patient is determined from overall (lesion) responses.

Duration of response (DOR) is defined as the time from the first day of overall response (CR/PR) to the first documented disease progression or date of death due to underlying cancer. Only patients with confirmed response (CR/PR) will be included in the analysis. If progression or death has not occurred, the patient is censored at the date of last adequate tumor assessment other than unknown. The censoring and event date options to be considered for the DOR analysis are presented in Table 3-2.

Time to overall response (TTR) is the time between treatment start date until the first documented, confirmed response of CR or PR. Patients who do not achieve a confirmed PR or CR will be censored as follows:

- at the last adequate tumor assessment date when they do not have a PFS event (i.e., did not progress or die due to any cause). In this case patients have not yet progressed so they theoretically still have a chance of responding;
- at maximum follow-up (i.e., first patient first visit (FPFV) to last patient last visit (LPLV) used for the analysis) when they have a PFS event (i.e., progressed or died due to any cause). In this case the PFS event is the worst possible outcome as it means the patient cannot subsequently respond. Since the statistical analysis makes use of the ranking of times to response it is sufficient to assign the worst possible censoring time which could be observed in the study which is equal to the maximum follow-up time (i.e., time from FPFV to LPLV).

Time to progression (TTP) is the time from date of start of treatment to the date of first documented progression or death due to melanoma. If a patient has not had an event, TTP is censored at the date of last adequate tumor assessment other than unknown. The censoring and event date options to be considered for the TTP analysis are presented in Table 3-2.

Progression-free survival (PFS) is defined as the time from the date of first study treatment intake to the date of the first radiologically documented disease progression or death due to any cause. In the case where a patient does not have documented progression but has disease progression as the reason for end of treatment/study evaluation completion, i.e., clinical progression, it will not be considered as a PFS event. A patient who has not progressed or died at the last patient last visit (LPLV) date will be censored at the date of last adequate tumor assessment other than unknown.

By default, if disease progression or death is documented after one single missing tumor evaluation, the actual event date of disease progression/death will be used for the PFS event date. If disease progression is documented after two or more missing tumor evaluations, the PFS time

of these patients will be censored at the date of the last tumor evaluation with overall lesion response of CR, PR or SD.

Overall survival (OS) is defined as the time from start date of treatment to date of death due to any cause.

All patients should be followed until death or until patient has had adequate follow-up time as specified in the protocol whichever comes first. The follow-up data should contain the date the patient was last seen alive / last known date patient alive, the date of death and the reason of death ("Study indication" or "Other").

If a patient is not known to have died, survival will be censored at the date of last known date patient alive. The follow-up data should contain the date the patient was last seen alive / last known date patient was alive, or the date of death and the reason of death

3.4.4 Phase Ib

The following Phase Ib listings will be presented for all available dosing regimens.

- individual lesion measurements (by RECIST 1.1 criteria)
- overall and best lesion response
- time to onset and DOR per RECIST v1.1 for patients who experience a CR or PR at any time on study
- time to disease progression and death

In addition, a summary table for BOR per RECIST 1.1 will be provided by treatment group in FAS. A Kaplan-Meier analysis of PFS will be provided in table and figure form, where Phase Ib 28-Day schedule patients are grouped together and 21-Day schedule patients are grouped together.

Waterfall plots for best overall response and best percentage change from baseline for all target lesions for each patient will be produced by treatment group.

3.4.5 Phase II

All of the tables, listings, and figures described above for Phase Ib will also be presented for Phase II, by patient at RP2D.

PFS, TTP, DOR, TTR, and OS will be presented graphically using Kaplan-Meier plots at RP2D.

Summary statistics from the Kaplan-Meier distribution will be presented at RP2D, including the median, 25th percentile, 75th percentile, and estimates at 2 months, 4, 8, and 12 months for PFS, TTP, DOR, TTR, and OS (OS only for 4 and 12 months, TTR confirmed responders subset only for 2, 3, and 4 months). These statistics will be provided as point estimates with 95% confidence intervals. The confidence intervals are constructed using Greenwood's formula (Collett 1944, p. 23) for the standard error of Kaplan-Meier estimate. Number of events and number of censored for PFS, TTP, TTR, DOR, and OS will be summarized as well. The same descriptive summary of TTR on confirmed responders (i.e., patients achieving at least one confirmed CR or PR) only will also be presented.

3.5 Safety evaluation for secondary endpoints

The assessment of safety will be based mainly on the type and frequency of AEs, and on the number of laboratory values that fall outside of pre-determined ranges (CTCAE version 4.03 grading limits or normal ranges, as appropriate). Other safety data (e.g., ECG, vital signs) will be presented, as appropriate. All safety data will be listed.

The overall observation period will be divided into three mutually exclusive segments:

- Pre-treatment period: from day of patient's informed consent to the day before first dose of study medication.
- On-treatment period: from day of first dose of study medication to 30 days after last dose of study medication.
- Post-treatment period: starting at day 31 after last dose of study medication.

The Safety Set will be used for summaries and listings of all safety data, with the exception of DLTs for which the DDS will be used and will be presented by treatment groups for Phase I.

The safety summary tables will include assessments collected no later than 30 days after study treatment discontinuation.

3.5.1 Adverse event

Adverse events will be 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) was not used since this information was collected on the "End of Treatment" or "Study phase completion" pages.

Separate listings for AEs, serious AEs (SAEs), AEs leading to study drug discontinuation, and death recorded during the study will be provided. Summary tables for AEs will include only AEs that started or worsened during the on-treatment period (treatment-emergent AEs [TEAEs]). However, all safety data (including those from the pre- and post-treatment periods) will be listed and safety data collected during the pre-treatment and post-treatment periods are to be flagged. All AE summaries will be summarized (frequency counts and percentages) by system organ class and/or preferred term, and maximum severity grades, except where otherwise noted.

The following AE summaries will be produced:

- AEs regardless of study drug relationship (including CTC grade 3/4)
- AEs suspected to be study drug related (including CTC grade 3/4)
- AEs leading to discontinuation of any study drug
- AEs requiring dose adjustment or study drug interruption
- AEs requiring dose adjustment, by outcome
- AEs requiring study drug interruption, by outcome
- AEs leading to discontinuation of any study drug, by outcome
- SAEs regardless of study drug relationship
- SAEs suspected to be study drug related
- AEs that are not serious, regardless of study drug relationship

- Dose limiting toxicities
- Deaths, with cause of death by primary system organ class and preferred term.

Missing and partial dates for AEs will be handled according to rules specified below.
There will be no attempt to impute the following:

- Completely missing AE start dates;
- AE start dates missing the year.

For a partial AE start date, the date imputation will be based on the temporal relationship between the partial date and start of treatment date.

For a partial AE end date or completely missing end date (AE is ongoing), the date imputation will be based on the temporal relationship between the partial date, the last contact date, and the 30-day follow-up date.

A missing AE start date will be imputed using the following logic matrix described in Table 3-4.

Table 3-4 AE start date imputation example scenarios

Partial AE start date	Treatment start date	Temporal relationship compared to treatment start	Imputed Date
12mmyyyy	20OCT2001	Uncertain	<blank>
ddmmm2000	20OCT2001	Before	01JUL2000
ddmmm2002	20OCT2001	After	01JAN2002
ddmmm2001	20OCT2001	Uncertain	21OCT2001
ddSEP2001	20OCT2001	Before	15SEP2001
ddOCT2001	20OCT2001	Uncertain	21OCT2001
ddNOV2001	20OCT2001	After	01NOV2001

Table 3-5 provides examples of the different considered imputations for AE end date.

Table 3-5 AE end date imputation example scenarios

Partial AE end date	Minimum (Last contact date, 30-day FU date)	Ongoing	Imputed Date
Missing	20OCT2001	Yes	20OCT2001
ddmmm2000	20OCT2001	No	31DEC2000
ddmmm2002	20OCT2001	No	31DEC2002
ddmmm2001	20OCT2001	No	20OCT2001

Partial AE end date	Minimum (Last contact date, 30-day FU date)	Ongoing	Imputed Date
ddmmm2001	20OCT2001	Yes	31DEC2001
ddSEP2001	20OCT2001	No	30SEP2001
ddOCT2001	20OCT2001	No	20OCT2001
ddOCT2001	20OCT2001	Yes	31OCT2001

3.5.2 Laboratory data

Samples for laboratory tests will be collected and analyzed by the study site's local laboratory. More frequent examinations may be performed at the investigator's discretion if medically indicated; results should be recorded on the Unscheduled Lab eCRFs.

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

When not collected, Corrected Calcium will be derived from Calcium and Albumin results as per the following formula:

*Corrected Calcium (mmol/L) = [4*Calcium(mmol/L) – 0.8*(0.1*Albumin(g/L) – 4)]/4*

The following summaries will be produced for the laboratory data by laboratory parameter:

- shift tables from baseline to the worst post-baseline value (expressed in CTC grades);
- shift tables from baseline to the worst post-baseline value using the low/normal/high classifications based on laboratory reference ranges for laboratory parameters where CTC grades are not defined;
- frequency table of laboratory abnormalities: number and percent of patients with newly occurring or worsening post-baseline CTC grade of 3 or 4.

In addition, a summary of the number and percentage of patients with notable hepatic laboratory values will be produced.

The following listings will be produced for the laboratory data:

- laboratory abnormalities of CTC grade 3 and 4;
- laboratory normal ranges by laboratory identification number and laboratory group;
- all laboratory data with values flagged to show corresponding CTC grades and/or the classifications relative to the laboratory reference ranges (i.e., High [H] or Low [L]);
- newly occurring notable hepatic laboratory values.

Table 3-6 Clinical Laboratory Parameters Collection Plan

Test Category	Test Name
Hematology	Complete blood count (CBC) with differential - white blood count (WBC), absolute neutrophil count (including bands), lymphocyte, monocyte, eosinophil, and basophil counts, hemoglobin, hematocrit, and platelet count.
Chemistry	Sodium, potassium, chloride, bicarbonate, urea or BUN, creatinine, glucose, aspartate aminotransferase (AST [SGOT]), alanine aminotransferase (ALT [SGPT]), total bilirubin (if a total bilirubin elevation ≥ Grade 2 occurs then direct and indirect bilirubin should be measured), lactate dehydrogenase (LDH), albumin, calcium, corrected calcium, magnesium, phosphate, alkaline phosphatase
Coagulation	Prothrombin time (PT), activated partial thromboplastin time (aPTT) and International normalized ratio (INR) will be collected at Screening and C1D1
Cardiac/Muscle Enzymes	Brain natriuretic peptide (BNP), troponin I and/or troponin T. Total creatine phosphokinase (CK). If total CK ≥3 X ULN, then measure isoenzymes and myoglobin in blood or urine weekly
Thyroid	Thyroid stimulating hormone (TSH) only. If TSH abnormal, T3 and free T4 to be performed.
Pregnancy	Serum beta-hCG test at screening/baseline, serum or urine every other cycle, and atEOT

Table 3-7 Laboratory parameters to be presented in grade shift tables based on CTC grade

Hematology		Chemistry		Cardiac enzymes	
White Blood Cells (WBC)	↑↓	AST (SGOT)	↑	Creatine phosphokinase	↑
Hemoglobin	↑↓	ALT (SGPT)	↑		
Platelet count	↓	Phosphate	↓		
Absolute Neutrophils	↓	Total Bilirubin	↑		
Absolute Lymphocytes	↑↓	Albumin	↓		
		Creatinine	↑		
		Alkaline Phosphatase	↑		
		Glucose (hyper & hypo)	↑↓		
		Corrected Calcium (hyper & hypo)	↑↓		
		Sodium (hyper & hypo)	↑↓		
		Magnesium (hyper & hypo)	↑↓		
		Potassium (hyper & hypo)	↑↓		

↑ Indicates that CTC grade increases as the parameter increases, these parameters are to be included in the summary of maximum post-baseline lab parameters

↓ Indicates that CTC grade increases as the parameter decreases, these parameters are to be included in the summary of minimum post-baseline lab parameters

Table 3-8 Laboratory parameters to be presented in shift tables based on local laboratory normal ranges

Hematology	Chemistry	Thyroid function test	Cardiac enzymes
Absolute eosinophils	Urea	TSH	BNP
Absolute basophils	Blood urea nitrogen (BUN)	Free T4	Troponin I
Absolute monocytes	LDH	Total T3	Troponin T
Hematocrit	Indirect bilirubin		
RBC	Direct bilirubin		
	Bicarbonate		
	Chloride		

Time to resolution of AST/ALT elevations is defined as the time from the first day of AST or ALT elevation (grade 3 or higher) to the day of first resolution (ALT grade 2 or less if the ALT was elevated or AST grade 2 or less if the AST was elevated). Only patients with elevated AST or ALT will be included in the analysis. If resolution has not occurred, the patient is censored at the date of last record available.

Patients with elevated ALT only ==> Time to resolution of ALT

Patients with elevated AST only ==> Time to resolution of AST

Patients with elevated AST and ALT ==> Lowest {Time to resolution of ALT; Time to resolution of AST}.

Time to resolution of AST/ALT elevations (grade 3 or higher) will be presented graphically. Three groups will be presented separately in a plot:

- Phase I - 21-day schedule
- Phase I – 28-day schedule
- Phase II – 28-day schedule

Plots will only be presented for each of the above groups if there are at least 10 patients in that group with elevated AST or ALT.

Number and percentage of patients will be provided for predefined categories of notable hepatic lab values (Table 3-9) which includes ALT, AST, alkaline phosphatase (ALP), and total bilirubin (TBL) parameters.

Table 3-9 Laboratory parameters to be presented based on local laboratory normal ranges

Parameter	Criterion
ALT	>3xULN; >5xULN; >8xULN;>10xULN;>20 ULN
AST	>3xULN; >5xULN; >8xULN >10xULN;>20 ULN
AT (ALT or AST)	>3xULN; >5xULN; >8xULN >10xULN;>20 ULN
TBL	>1.5xULN, >2xULN
ALP	>2xULN, >3xULN
AT & TBL	AT >3xULN & TBL >2xULN; AT >5xULN & TBL >2xULN;

Parameter	Criterion
	AT >10xULN & TBL >2xULN
ALP & TBL	ALP >3xULN & TBL >2xULN
AT & TBL & ALP	AT >3xULN & TBL >2xULN & ALP <2xULN

3.5.2.1 Pregnancy test

Pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive serum βHCG laboratory test (> 5 mIU/mL).

The following pregnancy tests are to be performed for childbearing potential females (see details in Protocol Section 7.2.2.5.5):

- Screening/baseline – within 72 hours of initial study treatment (serum)
- Follow-up - every other cycle (serum or urine) [Cycle 3, 5, 7 and etc.]
- End of treatment (serum or urine)

Pregnancy test results by treatment will be listed. A positive pregnancy test is cause for immediate withdrawal from the study.

3.5.3 Vital signs, weight, and physical examinations

All vital signs measures (oral temperature, sitting/supine blood pressure, and sitting/supine pulse, height, and weight) will be listed by parameter, treatment group, patient and time point (cycle), and the notable values will be flagged.

The rate of newly occurring or worsening vital sign abnormalities as defined in the Table 3-10 will be summarized and displayed in the listings.

The number and percentage of patients with at least one post-baseline vital sign abnormality (in both directions, i.e., both clinically notable high and low values) will be displayed in summary tables.

Summary statistics for baseline, last value, and change from baseline to last value, will be provided for each parameter. In addition, a shift table of baseline to worst post-baseline results will be presented.

Table 3-10 Notable vital signs ranges

Vital sign	Criteria for clinically notable ranges
Systolic blood pressure [mmHg]	≥160 mmHg / ≤90 mmHg with increase/decrease from baseline of ≥20 mmHg
Diastolic blood pressure [mmHg]	≥100 mmHg / ≤50 mmHg with increase/decrease from baseline of ≥15 mmHg
Pulse rate [bpm]	≥120 bpm / ≤50 bpm with increase/decrease from baseline of ≥15 bpm
Weight [kg]	≥20% decrease from baseline or >=10% increase from baseline
Oral body Temperature [°C]	≥37.5 °C / ≤36 °C

Significant findings that were present prior to the signing of informed consent must be included in the Relevant Medical History/Current Medical Conditions page on the patient's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the AE page of the patient's eCRF.

3.5.4 WHO/ECOG performance status

Performance status will be scored using the Eastern Cooperative Oncology Group (ECOG) performance scale (see Table 3-11) (Oken et al, 1982).

ECOG data will be collected at screening, C1D1, C2D1, C3D1 and subsequent CxD1 and EOT. (see Protocol Table 7-1 and Table 7-2) .

Patients must have an ECOG performance status of 0 – 1 to be enrolled in the study.

Frequencies and percentages for the categories of ECOG performance scale will be summarized at baseline. ECOG values collected over the study period will be listed by patient.

Table 3-11 ECOG performance status scale

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

3.5.5 Electrocardiogram (ECG)

All ECGs will be transmitted to a central laboratory and will be centrally reviewed by an independent reviewer.

If an abnormal ECG is obtained at any time, patients' electrolytes must be reviewed and repeat ECG measurements must be done after correction of electrolyte abnormalities.

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Data from ECG will be listed, notable values will be flagged and any other information collected will be listed as appropriate. Furthermore, combined QTc values from the triplicate ECGs will be averaged to provide a single value for each patient to be used in the summary tables.

Change from baseline in QT intervals by treatment will be summarized for each visit. Moreover notable change from baseline in all ECG parameters for the worst change from baseline will be summarized. The frequency and percentage of patients with notable ECGs and newly occurring qualitative ECG abnormalities will be tabulated by treatment group and mutually exclusive categories of QTcF, QTcB, QT, HR, PR, and QRS (see Table 3-14).

QT or QTc values will also be also considered notable when >450 msec, >480 msec, and > 500 msec. They will be flagged as such in listings.

The difference between baseline and maximum post-baseline QTcF, QTcB, and QT values will also be summarized. Post-baseline values will be presented in the following categories: an increase from baseline of > 30 msec or > 60 msec, or new absolute values > 450 msec, > 480 msec, or > 500 msec. A frequency table for such categories will be presented by treatment.

In addition, a shift table from baseline to worst post-baseline value based on notable values will be provided for QT, QTcF, and QTcB.

The following two listings will also be produced:

- QT prolonging concomitant medications
- ECG evaluations for all patients with at least one abnormality

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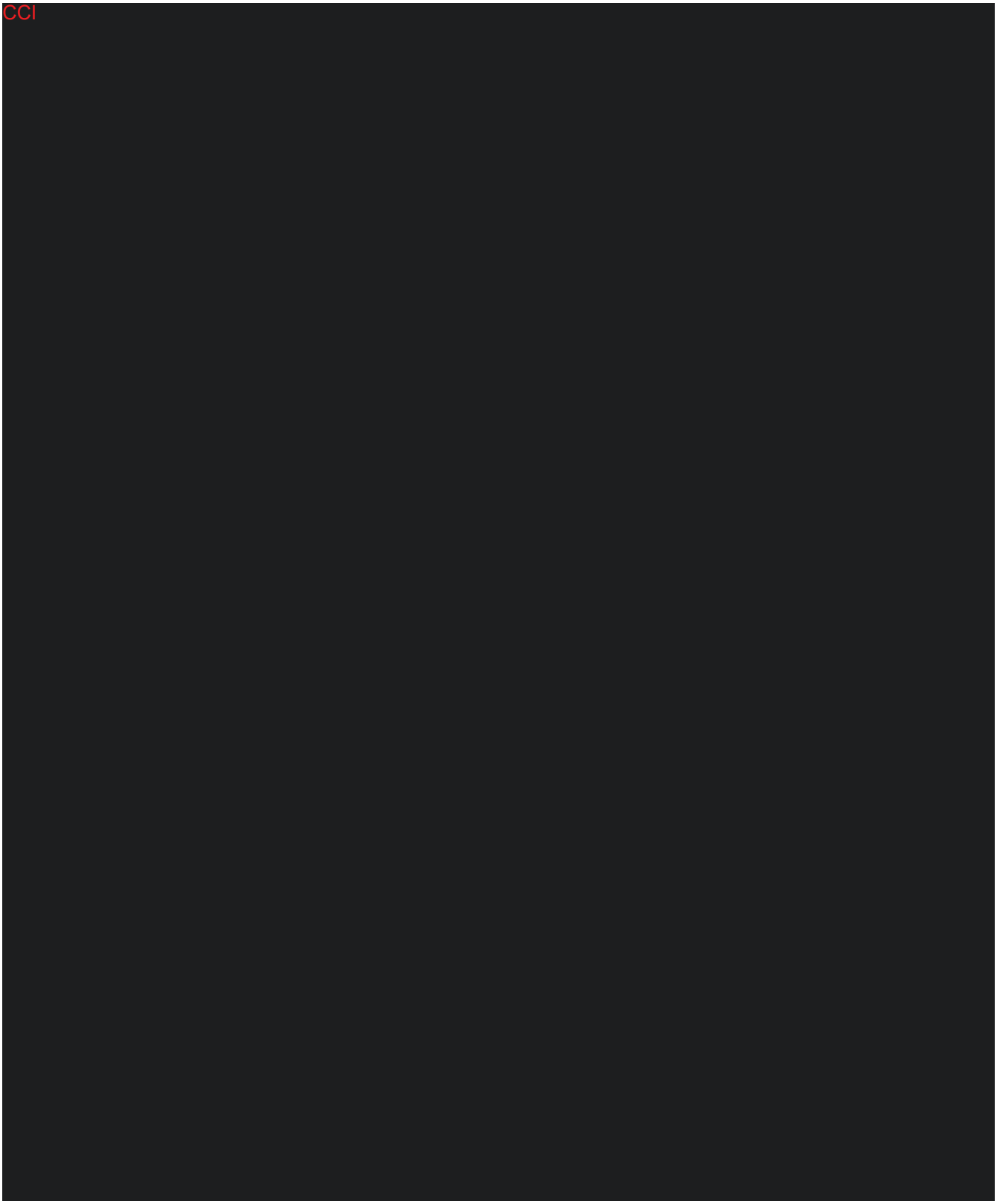

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Table 3-14 ECG parameters and abnormal values

ECG Parameter	Abnormal values
QT, QTcF and QTcB	New absolute values >450, >480 and >500
	Changes from baseline >30 and >60
HR	Decrease from baseline >25% and to a HR < 50
	Increase from baseline >25% and to a HR > 100
PR	Increase from baseline >25% and to a value >200
QRS	Increase from baseline >25% and to a value >110

3.5.6 Ophthalmic examination

Full ophthalmic examinations are required to be performed by trained ophthalmologist including slit lamp examination, color vision test, visual acuity testing, visual field testing, tonometry, optical coherence tomography (OCT), dilated indirect fundoscopy and color fundus photography with attention to retinal abnormalities, especially retinal pigmented epithelial detachment (RPED) and retinal vein occlusion (RVO).

All of the ophthalmic results will be listed, including the additional evaluation results for patients with clinical suspicion of retinal abnormalities.

For the fundoscopy, slit lamp examination, visual field testing, and optical coherence tomography, the incidence of abnormalities at baseline along with the incidence of new abnormalities reported post-baseline will be summarized by type of abnormality and treatment group. At baseline an abnormality will be indicated by an abnormality being present in either or both eyes. At post-baseline assessments an incident of a new abnormality will be indicated by an abnormality present in either eye that was not present in that eye at baseline.

For the summary of visual acuity, recorded values will be transformed into logMAR (minimum angle of resolution) values. It is these logMAR values that will be summarized.

The Visual Acuity Score (Snellen equivalent) will be recorded as decimal or fractional acuity, the formula to use is:

$\text{logMAR} = -\log_{10}(\text{decimal acuity})$

Note that fractional acuity is simply converted to decimal acuity by performing the division.

The logMAR values will be categorized based on change from baseline:

Table 3-15 Categorization of visual acuity loss

	Severity	Loss on LogMAR scale
Grade 1	Mild	<0.1
Grade 2	Mild/moderate	0.1-<0.2
Grade 3	Moderate/severe	0.2-<0.3
Grade 4	Severe	≥0.3

The total visual acuity score as measured by logMAR will be summarized by scheduled time point, by change from baseline by scheduled time point, and by worst change from baseline at any time. A patient's score at any time point will be the average score across assessed eyes at that time point (i.e., if only one eye is assessed the value recorded for that eye will be used, if two eyes are assessed then the average of those two assessed values will be used). Total visual acuity score will also be assessed by identifying clinically meaningful deteriorations in logMAR. The incidence of decreases in the average score of <0.1, 0.1-<0.2, 0.2-<0.3, and 0.3 logMAR by scheduled time point and at any time will be summarized.

Note that a minimum of 10 overall patients in the study with the visual baseline evaluation and at least 1 post baseline visual assessment will be necessary in order to produce the tables explained above. Moreover, only the treatments with a minimum of 3 patients with baseline visual evaluation and at least 1 post baseline visual assessment will be shown.

3.5.7 Cardiac image - MUGA/ bilateral ECHO

Cardiac imaging by MUGA/ ECHO are collected at screening, C2D1, C3D1, at every other cycle, and at EOT or as clinically indicated.

Cardiac imaging results (i.e., left ventricular ejection fraction (%) and overall interpretation) during the study will be listed by treatment.

3.6 Pharmacokinetic data

PK parameters will be determined for all PK-evaluable patients using non-compartmental method(s) using Phoenix WinNonlin version 6.4 or higher (Certara USA, Inc., Princeton, NJ). PK parameters listed in Table 3-15 will be estimated and reported, when feasible. The parameters that require terminal phase determination may not be adequately calculated by non-compartmental methods. CCI [redacted]

For plasma LEE011, its metabolite LEQ803, MEK162, and its metabolite AR00426032, the LLOQ is 1.0 ng/ml. All concentrations below the LLOQ or missing data will be labeled as such in the concentration data listings. Concentrations below the LLOQ will be treated as zero in summary statistics.

For presentation purposes, PK parameters will be identified as parameters of primary or secondary interest, as follows:

Primary

- AUCinf, AUClast, AUClast,ss, AUCtau, AUCtau,ss, Cmax, Cmax,ss, T1/2, T1/2,ss, Racc (AUC and Cmax), T1/2,acc,

Secondary

- CL/F, CL/F,ss, Vz/F, Vz/F,ss, Tmax, Tmax,ss, Tlast, Tlast,ss, Ctrough,ss

Table 3-15 Non-compartmental pharmacokinetic parameters

Variable	Definition
Cmax	Maximum observed plasma concentration after drug administration (mass x volume^{-1})
Cmax,ss	Maximum observed plasma concentration during a dosing interval at steady state (mass x volume^{-1})
Ctrough,ss	Measured concentration at the end of a dosing interval at steady state (taken directly before next administration) (mass x volume^{-1})
Tmax	Time to reach C_{max} (time)
Tmax,ss	Time to reach C_{max} at steady state (time)
Tlast	Time at which the last measurable concentration was observed [time]
Tlast,ss	Time at which the last measurable concentration was observed at steady state [time]
AUClast	Area under the concentration-time curve from time zero to the last measurable concentration sampling time [mass x time x volume-1]
AUClast,ss	Area under the concentration-time curve from time zero to the last measurable concentration sampling time at steady state [mass x time x volume-1]
AUCinf	Area under the concentration-time curve from time zero to infinity with extrapolation of the terminal phase [mass x time x volume-1]
AUCtau	Area under the concentration-time curve during a dosing interval (mass x time x volume^{-1})
AUCtau,ss	Area under the concentration-time curve during a dosing interval at steady state (mass x time x volume^{-1})
CL/F	Apparent total plasma clearance of drug after oral administration (volume x time^{-1})
CL/F,ss	Apparent total plasma clearance of drug after oral administration at steady state (volume x time^{-1})
Vz/F	Apparent volume of distribution during terminal phase (associated with λz) after oral administration (volume)
Vz/F,ss	Apparent volume of distribution during terminal phase (associated with λz) after oral administration at steady state (volume)
T1/2	Elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve [time]
T1/2, ss	Elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve at steady state [time]
Racc_AUC	Accumulation ratio calculated as $AUC_{tau,ss}/AUC_{tau}$
Racc_Cmax	Accumulation ratio calculated as $C_{max,ss}/C_{max}$
MR_AUC	Metabolite ratio based on AUC_{tau} on Day 1 and steady-state AUC_{tau} for the metabolite compared to parent ratio, corrected for molecular weight, calculated for AR00426032 and LEQ803
MR_Cmax	Metabolite ratio based on C_{max} on Day 1 and steady-state C_{max} for the metabolite compared to parent ratio, corrected for molecular weight, calculated for AR00426032 and LEQ803
T1/2,acc	Effective elimination half-life (time)

3.6.1 Data handling principles

3.6.1.1 Analysis sets

The PAS will be used to report PK data. Only PK blood samples with the date and time and for which the last prior dose dates and times are adequately recorded will be included in the PK analyses. Plasma concentrations and PK parameters will be flagged in concentration and PK parameter data listings and excluded from all summary tables, mean figures, and statistical analyses of PK data if the following occur:

- Samples taken from patients who vomited within 4 hours of dosing.
- The planned dose was not administered (i.e., a change in dose occurred before the sampling occasion).
- Steady state was not deemed to have been achieved (i.e. dosing is required for a minimum 2 consecutive days prior to the collection of steady state samples).

3.6.1.2 Descriptive statistics

PK concentration data and PK parameters will be listed and summarized. In addition, descriptive statistics (number of observations, mean, standard deviation, CV%, geometric mean, CV% geometric mean, median, minimum, and maximum) will be presented by treatment and study day. When a geometric mean is presented, it will be stated as such. CL/F and Vz/F will be assessed for MEK162 and LEE011, and only median values and ranges will be given for T_{max}/ $T_{max,ss}$.

Table 3-16 PK parameters – descriptive statistics

Parameters	Descriptive statistics
AUC(1) , Cmax, Cmax,ss, CL/F, CL/F,ss, Ctrough,ss, T1/2, T1/2,ss, Racc (AUC and Cmax), MR (AUC and Cmax), T1/2,acc, Vz/F, Vz/F,ss	Number of observations, mean, standard deviation, CV% mean, geometric mean, CV% geo-mean, median, minimum, and maximum.
Tmax, Tmax,ss, Tlast, Tlast,ss	Median, minimum, and maximum.
(1) AUCtau, AUCtau,ss, AUClast, AUClast,ss, AUCinf With : CV% = coefficient of variation (%) = 100*sd/mean CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100	

Descriptive graphical plots of individual plasma concentration by time will be generated, as will mean concentration time profiles for MEK162, AR00426032, LEE011, and LEQ803. CCI [redacted]

Listings for PK concentration, primary PK parameters, and secondary PK parameters will be presented for plasma LEE011, LEQ803, MEK162, and AR00426032.

Only the data belonging to the time windows displayed in the Table 3-17 will be taken into account for the analysis. PK samples collected outside the below windows will be flagged in the concentration data listings and excluded from all associated tables and mean figures, but retained in the individual concentration-time plots and estimation of PK parameters. The PAS will be used for the PK analysis, figures, tables, and listings.

The data from 24-hour time point will be included in the analysis of LEE001 and LEQ803. Due to BID administration of MEK162, analysis of MEK162 and AR00426032 will exclude 24-hour time point samples; Cycle 1 Day 1 profiles will include samples up to and including 8-hour time point, and for Cycle 1 Day 14 or Day 21 profiles the concentration measured at the 24-hour time point will be assigned at 12-hours post-dose (with actual time of 24-hour time point minus 12 hours) for the purposes of PK parameter calculation only.

Table 3-17 Time windows for presentation of PK concentrations*

Scheduled time point		Window
Pre-dose	Right before dosing	Not specified
Post-dose	30 min	± 15 min
	1 hour	± 15 min
	2 hours	± 15 min
	4 hours	± 30 min
	8 hours	± 30 min
	24 hours	± 1 h

*Table 3-17 applies to both 28-day and 21-day dosing regimens for Phase Ib and Phase II. Only a subset of samples will be collected for Phase II, i.e. pre-dose, and 30 min, 2 hours, and 4 hours post-dose.

3.6.1.3 Advanced data analysis methods

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The following statistical analyses of PK data will be performed:

Dose-proportionality

An analysis of dose proportionality will be conducted for $AUC_{tau,ss}$ and $C_{max,ss}$ of LEE011 and LEQ803 using a power model on log-transformed scale, based on the data from the dose-escalation phase only (Phase Ib). The log-transformed PK parameters will each be regressed onto a fixed factor for ln(dose), as described below, for each dosing regimen separately:

$$\ln(\text{PK parameter}) = \ln(\alpha) + \beta * \ln(\text{dose})$$

The 90% confidence interval (CI) of the slope for each PK parameter will be computed from the model and presented in the summary table. Dose proportionality will be concluded if the 90% CI of the slope lies entirely within $(1 + \ln(0.8)/\ln(r), 1 + \ln(1.25)/\ln(r))$ where r is a ratio that describes the dose range and is defined as (highest dose/lowest dose).

Accumulation

For each regimen separately (Day 21 and Day 28 regimen), an assessment of accumulation ($AUC_{tau,ss}/AUC_{tau}$ and $C_{max,ss}/C_{max}$) will be performed for MEK162, AR00426032, LEE011, and LEQ803, as appropriate, using a linear mixed model on the natural logarithms of the PK metrics with day as a fixed effect and patient as a random effect. When there is more than one dose level in the data, dose and day by dose interaction will also be added in the model as fixed effects and accumulation ratios will be estimated for each dose separately. The results will be transformed back to the original scale to obtain geometric least square (LS) means. The number of observations for each day (N), geometric LS means, ratio of geometric LS means, 90% CI and intra-patient CV will be presented.

Also, PK/PD analyses may be explored to identify possible PK/PD relationships with relevant clinical markers and/or safety parameters (e.g., retinal events).

To assess drug-drug interaction potential effect on exposure as a function of dose of the other drug, the following scatter plots will be created:

- For each LEE011 dose, LEE AUC and C_{max} versus MEK162 dose
- For each LEE011 dose, LEQ803 AUC and C_{max} versus MEK162 dose
- For each MEK162 dose, MEK162 AUC and C_{max} versus LEE011 dose
- For each MEK162 dose, AR00426032 AUC and C_{max} versus LEE011 dose

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