Oncology Early Clinical Development

LGX818/MEK162

Clinical Trial Protocol CMEK162X2110 (C4221005)

A Phase Ib/II, multicenter, open-label, dose escalation study of LGX818 in combination with MEK162 in adult patients with BRAF V600 - dependent advanced solid tumors

STATISTICAL ANALYSIS PLAN

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List of abbreviations

ADI	Actual dose intensity
AE	Adverse Event
ALT/SGPT	Alanine transaminase/glutamic pyruvic transaminase
aPTT	Activated partial thromboplastin time
AST/SGOT	Aspartate transaminase/glutamic oxaloacetic transaminase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BCRP	Breast Cancer Resistance Protein
BID	Bis In Diem/ twice daily
BLRM	Bayesian Logistic Regression Model
BOR	Best Overall Response
BRAF	V-raf murine sarcoma viral oncogene homolog B1
BRAFi	BRAF inhibitor
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
C_{max}	Maximum plasma concentraion
CK/ CPK	Creatine kinase / Creatine phosphokinase
CR	Complete Response
CRC/ mCRC	Colorectal cancer/ metastatic CRC
CRF	Clinical Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTT	Clinical Trial Team
CV	Coefficient of Variation
CYP	Cytochrome P450
DCR	Disease Control Rate
DDS	Dose Determining Set
DLT	Dose Limiting Toxicity
DOR	Duration Of Response
ECG	Electrocardiogram
eCRF	Electronic case report/record form
EGFR	Epidermal growth factor receptor
EOT	End Of Treatment
EPT	Early Program Team
ERK	Extracellular signal Regulated Kinase
EWOC	Escalation With Overdose Control
FAS	Full Analysis Set
FU	Follow Up

HDL	High-density lipoprotein
ICF	Informed Consent Form
IHC	Immunohistochemistry
KRAS	V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LVEF	Left ventricular ejection fraction
mCRC	Metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated protein kinase
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NRAS	Neuroblastoma RAS viral oncogene homolog
OAT	Organic anion transporter
ORR	Objective Response Rate
OS	Overall Survival
PD	Pharmacodynamic / Progressive Disease
PDI	Planned dose intensity
PFS	Progression-Free Survival
P-gp	Permeability glycoprotein
PI3K	Phosphatidylinositol 3' Kinase
PIK3CA	Phosphatidylinositol 3' Kinase Catalytic Alphapolypeptide
PK	Pharmacokinetic
PR	Partial Response
PT	Prothrombin time
PTEN	Phosphatase and Tensin Homolog gene
QD	Quaque Die/ once daily
QOD	Every other day
QTcB	QT interval adjusted according to Bazett
QTcF	QT interval adjusted according to Fredericia
RAF	V-raf murine sarcoma viral oncogene
RAP	Report and Analysis Plan
RBC	Red Blood Cell
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended Phase II Dose
RT-PCR	Reverse-transcriptase polymerase chain reaction
SAE	Serious Adverse Event
SD	Stable Disease
SOD	Sum of Diameters
$t_{½}$	Terminal elimination half-life
t_{max}	Time to reach maximum plasma concentration

TSH	Thyroid-stimulating hormone
TTR	Time To (overall) Response
VAP	Validation and Analysis Planning
WBC	White Blood Cell
WHO	World Health Organization

1 Introduction

This document provides the detailed statistical methodology for the analysis of data for initial interim Clinical Study Report (CSR) of the study CMEK162X2110 (C4221005) as well as the final CSR.

An initial interim CSR will be prepared based on all Phase Ib/Phase II patient data from the dual study drug combination. The cut-off for reporting will be either LPFV + 18 months or when 80% of the patients can be assessed for progression free survival (PFS), whichever occurs first. Additional data for patients continuing to receive the MEK162 and LGX818 dual combination beyond the cutoff point for the initial reporting, as allowed by the protocol, and the Phase Ib/II data from the LGX818 and MEK162 and LEE011 triple combination will be summarized in a final CSR once all patients have discontinued the study. Although this SAP provides comprehensive detail on analyses performed throughout the lifetime of the study, only analyses included in the appendices for the final CSR (Section 4: Final Analysis Appendices) will be performed for the final analysis. For the presentation of results in the final analysis, LGX818, MEK162, and LEE011 will be referred to by their respective generic names: encorafenib, binimetinib, and ribociclib.

In this document, the dual and triple combination refers to the combination of LGX818 and MEK162, and LGX818 and MEK162 and LEE011, respectively, when not specified.

The purpose of the CSRs is to report the estimated maximum tolerated dose (MTD) and/or recommended phase II dose (RP2D), characterize the dose limiting toxicities (DLT), safety profile and efficacy of LGX818/MEK162 and LGX818/MEK162/LEE011 combinations in patients with solid tumors harboring a BRAF V600 mutation.

In addition, the CSR also report the assessment of clinical efficacy and safety of the LGX818 and MEK162 combination in patients with BRAF V600 mutant metastatic colorectal cancer (mCRC), patient with BRAF V600 mutant metastatic melanoma, who have progressed after prior selective BRAF inhibitor and patient with BRAF V600 mutant metastatic melanoma, who are naïve to prior selective BRAF inhibitor treatment.

An interim analysis is planned for the phase II part of patients with BRAF V600 mutant mCRC, when 50% of the total sample size (14 patients) have completed four cycles of treatment, to allow stopping early for futility when there is no treatment effect.

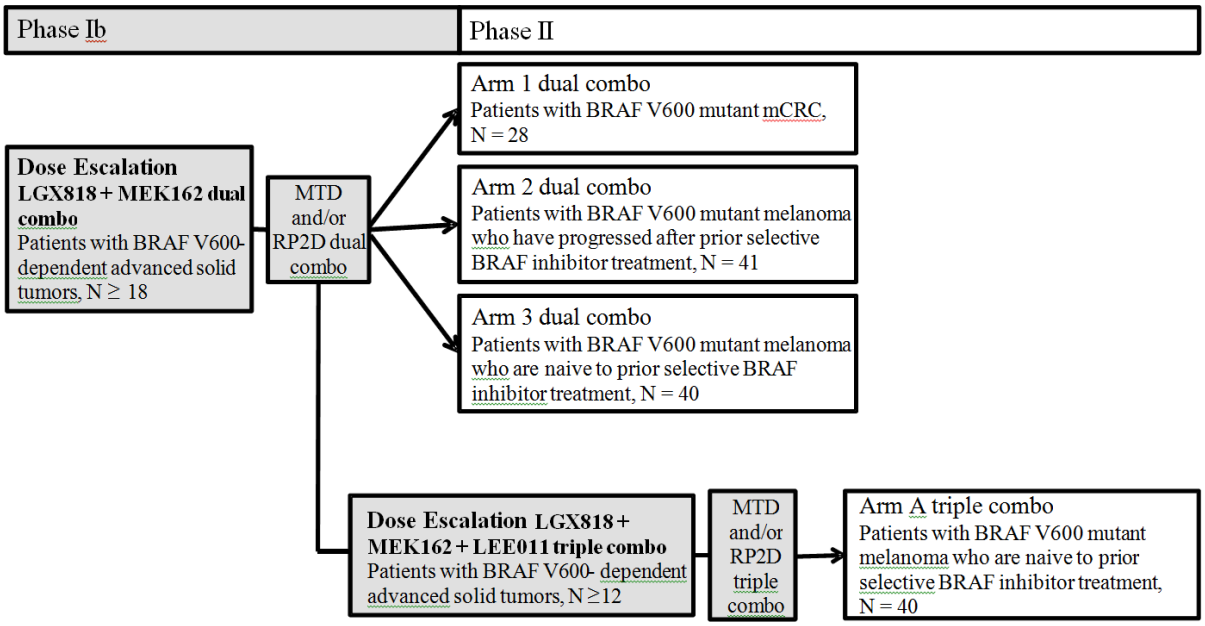
Note that obvious corrections will be made at the time of analysis to address minor formatting or spelling mistakes present in the SAP without the need to amend this document.

1.1 Study design

This is a multi-center, open-label, dose finding, Phase Ib dose escalation study to estimate the MTD(s) and/or RP2D(s) for the combination of LGX818 and MEK162 and triple combination of LGX818 and MEK162 and LEE011, followed each independently by a Phase II part to assess the clinical efficacy and to further assess the safety of the combinations in selected patient populations.

Oral LGX818 and MEK162 will be administered once daily and twice daily, respectively, on a continuous schedule. Oral LGX818 and MEK162 and LEE011 will be administered once daily on a continuous schedule (LGX818), twice daily on a continuous schedule (MEK162) and once daily three week on, one week off (LEE011), respectively. Patient will be treated until progression of disease, unacceptable toxicity develops, or withdrawal of infored consent, whichever occurs first. Continued treatment beyond progression of disease will be allowed under certain circumstances.

Figure 1-1 Study design schematic



Dose escalation (Phase Ib)

The dose escalation part of the trial will be conducted in adult patients with BRAF V600-dependent advance solid tumors. This part of the trial is expected to enroll at least 18 patients for the dual combination and at least 12 patients for the triple combination. For the purposes of the dose escalation decisions, each cohort will consist of 3 to 6 newly enrolled patients. The successive cohorts of patients will receive increasing doses of the combinations. The first cohort for the dual combination will be treated with the starting combination doses of 50 mg once daily (qd) for LGX818 and 45 mg twice daily (bid) for MEK162. The first cohort for the triple combination will be treated with the starting combination doses of 200 mg once daily (qd) for LGX818, 45 mg twice daily (bid) for MEK162 and 100 mg once daily (qd) for LEE011 (3 weeks on/1 week off regimen).

Once all patients in a dose cohort have completed 28 days (1 cycle) of treatment and an assessment of their dose limiting toxicity (DLT) status is performed, the adaptive Bayesian logistic regression model (BLRM) will be updated. At each decision time point, the adaptive BLRM provides the upper boundary for the combinations that meet the escalation with overdose control (EWOC) criteria. The clinical synthesis of the available toxicity information,

pharmacokinetic (PK), CCI and efficacy, as well as the recommendations from the adaptive BLRM are used to determine the dose combination for the next cohort(s). The Sponsor and investigators will decide on next dose levels and dosing schedule(s) to be explored at the dose escalation teleconference.

Various dose levels will be explored until the MTD is determined and/or until a consensus between the Sponsor and Investigators is reached and it is considered that there is no benefit of further increasing the dose. At this time the RP2D, a dose less than or equal to the MTD, will be estimated based on a review of the totality of the available study data. At least 6 patients eligible for the dose determining analysis set (DDS) must be treated at the dose(s) declared to be the MTD/RP2D. More than one dose-combination may be identified as a MTD, and more than one RP2D may be established for further evaluation in the phase II part of the study. In the case that all dose combinations are considered to be too toxic by the adaptive BLRM after the first cohort, no MTD/RP2D can be defined.

Phase II

Following MTD/RP2D declaration, for the dual combination patients will be enrolled in three Phase II arms.

- Phase II Arm 1 will assess the disease control rate (DCR) of the dual combination in patients with BRAF V600 mutant mCRC.
- Phase II Arm 2 will assess the objective response rate (ORR) of the dual combination in patients with BRAF V600 mutant melanoma who have progressed after prior selective BRAF inhibitor treatment.
- Phase II Arm 3 will assess the ORR of the dual combination in metastatic BRAF mutant melanoma patients who are naïve to prior treatment with a selective BRAF inhibitor.

Following MTD/RP2D declaration, for the triple combination patients will be enrolled in an additional Phase II arm.

- Phase II Arm A will assess the objective response rate (ORR) of the triple combination in patients with locally advanced or metastatic BRAF V600 mutant melanoma who are naïve to previous treatment with a selective BRAF inhibitor.

Phase II arms will also assess the safety of the combinations.

If more than one dose combination or dosing schedule has been defined as MTD/RP2D, The Sponsor may decide to open the Phase II arms for more than one MTD/RP2D and/or start the Phase II arms with different dose combinations or schedules.

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	
Phase Ib: To estimate the MTD(s) and/or RP2D(s) of oral LGX818 in combination with oral MEK162, and of oral LGX818 in combination with oral MEK162 and oral LEE011 in patients with BRAF V600-dependent advanced solid tumors	Phase Ib: Incidence of Dose Limiting Toxicities
Phase II: To assess clinical efficacy of the LGX818 and MEK162 dual combination and LGX818 and MEK162 and LEE011 triple combination in the respective Phase II populations: Arm 1: metastatic BRAF V600 mutant mCRC patients (dual combination) Arm 2: metastatic BRAF V600 mutant melanoma patients who have progressed after prior selective BRAFi treatment (dual combination) Arm 3/ Arm A: metastatic BRAF V600 mutant melanoma patients who are naïve to prior selective BRAFi treatment (dual and triple combination).	Phase II arm 1: Disease control rate (DCR) as per RECIST v1.1 Phase II arms 2 and 3 / Phase II arm A: Objective Response Rate (ORR) as per RECIST v1.1
Secondary	
Phase Ib + II: To characterize the safety and tolerability of LGX818 and MEK162 in combination, and LGX818 and MEK162 and LEE011 in combination	Phase Ib + II Incidence and severity of AE
Phase Ib To determine the single and multiple dose PK profile of the LGX818 and MEK162 combination, and of the LGX818 and MEK162 and LEE011 combination	Phase Ib Time vs. plasma concentration, basic PK parameters of LGX818 and MEK162 and LEE011 and known active metabolite(s)
To assess preliminary clinical anti-tumor activity of the LGX818 and MEK162 combination, and of the LGX818 and MEK162 and LEE011 combination	ORR as per RECIST v1.1
Phase II To further assess clinical efficacy of the LGX818 and MEK162 dual combination and of the LGX818 and MEK162 and LEE011 triple combination in the Phase II populations	Phase II Progression free survival (PFS), time to response (TTR), duration of response (DOR) as per RECIST v1.1, and Overall Survival (OS)

To characterize baseline molecular status of molecules relevant to RAF/MEK/ERK and EFGR/ PI3K/AKT signaling in tumor tissue	Baseline molecular status (mutation/amplification/expression) in tumor tissue of potential predictive markers of tumor response or resistance (BRAF, HRAS, KRAS, NRAS, PTEN, cKIT, PIK3CA, MAP2K1, MAP2K2, ARAF, c-MET, RAF1, EGFR)
[redacted]	[redacted]

1.3 Data Analysis

Data will be analyzed by the Sponsor and/or designated CRO according to the data analysis section 10 of the clinical study protocol [CMEK162X2110] and will be available in CSR Appendix 16.1. Impo1tant info1mation will be given in the following sections and details are provided as applicable in CSR Appendix 16.1.9.

The Bayesian modelling of the analysis will be nm using R version 2-13.2 and WinBUGS Version 1.4.3 in the MODESIM (production) and GPS II environments. Other statistical analysis will be perfo1med using SAS® version 9.2 or higher.

The following rnles will be followed for reporting results unless stated othe1wise:

Phase lb dose escalation data: Coho1ts 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 display/perfo1med by treatment group unless othe1wise specified.

Phase II data: Data will be summarized and listed by arm (See Section 2.1.1).

Phase lb/II combined data: Data will be summarized and listed by ann and treatment group (See Section 2.1.1).

Screen failure patients are those who signed the info1med consent, but never staited the study treatment for any reason. For these patients, the only info1mation collected on the eCRF will be the screening log and the demography pages. These will not be included in any analysis, but will be reported in the CSR as sepai·ate listings.

1.4 Analysis not according to the protocol

The protocol lists the primaiy vai·iable of Phase 2 data as the estimation of trne DCR and ORR by ann using a Bayesian design. Instead a frequentist approach will be used for the analysis of DCR and ORR of the Phase 2 data presenting the observed value and exact confidence interval.

1.5 CSR related reporting events

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

- The initial interim CSR (refened to as the initial CSR in protocol) includes all outputs described for the dual combination, with the data cut-off of August 31, 2015. This SAP describes the analysis for the initial interim CSR.
- The final CSR includes all outputs described for the triple combination and listing for the dual combination, with the data cut-off on or after all patients have completed or discontinued from the study.
- CCI [redacted]

2 Definitions and general methodology

2.1 General definitions

2.1.1 Study drug and study treatment

2.1.1.1 Naming conventions

Study drug refers to any investigational drug(s) being used for an unapproved indication. Study treatment refers to any combination of study drugs(s).

Study treatment:

- Dual combination = LGX818 + MEK162
- Triple combination = LGX818 + MEK162 + LEE011

Other naming conventions

"Study parts" or "Study phase": refers to the sequential parts of the study:

- Phase Ib (dose escalation)
- Phase II

Phase Ib for the dual and triple combination

- "Cohort" or "Dose Cohort": group of typically 3 to 6 patients enrolled sequentially at once during the dose escalation and intended to receive the same dose of study treatment.
- "Treatment group": group of patients intended to receive the same study treatment, for instance same dose level of study treatment. A treatment group can include several cohorts of patients who have received the same dose level but were recruited at different point in the study.

  For example, for dual combination subjects:

  Treat. A = LGX818 50 mg qd and MEK162 45 mg bid

  Treat. B = LGX818 100 mg qd and MEK162 45 mg bid

  …

  All dual combo patients = All dual combination patients

  For example, for triple combination subjects:

  Treat. A = MEK162 45 mg BID and LGX818 200 mg QD and LEE011 100 mg QD

  Treat. B = MEK162 45 mg BID and LGX818 200 mg QD and LEE011 200 mg QD

  …

  All triplet combo patients = All triple combination patients

Phase II for the dual and triple combination

- "Phase II arm": refer to separate groups of patients to be displayed separately according to study design even if receiving the same treatment.

  For example, for dual combination subjects:

Phase II arm 1, refer to patients with BRAF V600 mCRC

Phase II arm 2, refer to patients with BRAF V600 mutant melanoma who have progressed after prior selective BRAF inhibitor treatment

Phase II arm 3, refer to patients with BRAF V600 mutant melanoma who are naïve to prior selective BRAF inhibitor treatment

All dual combo patients = All dual combination patients

For example, for triple combination subjects:

BRAF mutant melanoma no prior BRAF inhibitor

All triple combo patients = All triple combination patients

Phase 1b/II combined for the dual combination

- The Phase Ib patients in the LGX818 400/450/600 mg treatment groups whose disease matches one of the Phase II arms will be combined with Phase II data in the by arm and treatment group.

  Arm 1, refers to BRAF V600 mutant mCRC

  Treat. A, refers to LGX818 400/450 mg qd and MEK162 45 mg bid

  Treat. B, refers to LGX818 600 mg qd and MEK162 45 mg bid

  Arm 2, refers to BRAF V600 mutant melanoma who have progressed after prior selective BRAF inhibitor treatment

  Treat. A, refers to LGX818 400/450 mg qd and MEK162 45 mg bid

  Treat. B, refers to LGX818 600 mg qd and MEK162 45 mg bid

  Arm 3, refers to BRAF V600 mutant melanoma who are naïve to prior selective BRAF inhibitor treatment

  Treat. A, refers to LGX818 400/450 mg qd and MEK162 45 mg bid

  Treat. B, refers to LGX818 600 mg qd and MEK162 45 mg bid

Phase 1b/II combined for the triple combination

- The Phase Ib patients in the LEE011 100/200/400/600 mg treatment groups whose disease matches the Phase II arm will be combined with Phase II data in the by treatment group/arm analyses.

  Arm 1, refers to BRAF mutant melanoma no prior BRAF inhibitor

  Treat. A, refers to LGX818 200 mg QD and MEK162 45 mg BID and LEE011 100 mg QD

  Treat. B, refers to LGX818 200 mg QD and MEK162 45 mg BID and LEE011 200 mg QD

  Treat. C, refers to LGX818 200 mg QD and MEK162 45 mg BID and LEE011 400 mg QD

  Treat. D, refers to LGX818 200 mg QD and MEK162 45 mg BID and LEE011 600 mg QD

2.1.1.2 Planned/received treatment

- Intended/planned treatment is the first planned treatment reported in the DAR (e)CRF. For combination trial it is the combination of the first planned treatment reported in the DAR (e)CRF of each component of the combination.
- Treatment received is defined as:

  (i) the treatment assigned if it was received at least once, or

  (ii) the first treatment received when starting therapy with study treatment if the assigned treatment was never received.

Each patient will be classified into and analyzed consistently within one (and only one) treatment group/arm.

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

2.1.2.1 Date of first administration of study drug

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 DAR (e)CRF. For the sake of simplicity, 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

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 Date of first administration of study treatment

The date of first administration of study treatment is derived as the first date when a nonzero dose of any component of study treatment was administered and recorded on DAR (e)CRF (i.e. earliest date between first LGX818 dose and first MEK162 dose for the dual combination and earliest date among first LGX818 dose, first MEK162 dose and first LEE011 dose for the triple combination). For the sake of simplicity, the date of first administration of study treatment will also be referred as ***start of study treatment***.

2.1.2.4 Date of last administration of study treatment

The date of last administration of study treatment is derived as the last date when a nonzero dose of any component of study treatment (i.e. latest date between last LGX818 dose and last MEK162 dose for the dual combination and latest date among last LGX818 dose, last MEK162 dose and last LEE011 dose for the triple combination).

2.1.2.5 Last date of exposure to study treatment

Exposure to study treatment includes the exposure to any of the treatment component including any planned rest period between two administrations. As a consequence the last date

of exposure to a component of study treatment is the day before the first missed dose of any of the component:

- LGX818 once or twice daily (qd or bid) administration*: last date of exposure = last date of administration LGX818
- MEK162 twice daily (bid) administration: last date of exposure = last date of administration MEK162
- LEE011 once daily (3 weeks on, 1 week off schedule) administration: last date of exposure = last date of administration LEE011 + (number of last consecutive days of non 0 dose /planned consecutive days the patient should have taken the drug)*7

The last date of exposure to study treatment is the latest of the dates of last exposure of components of the combination or death date if earlier.

* LGX818 every other day (qod) administration: last date of administration LGX818 + 1 day.

2.1.2.6 Study day

The study day for all assessments **post**-treatment is calculated as the difference between the date of the event (e.g., visit date, onset date of an event, assessment date, disease progression, etc.) and the start of study treatment, plus one day. The first day of study treatment administration is therefore Study **Day 1**.

The study day for assessments **pre**-treatment is calculated as the difference between the date of the event (e.g., visit date, onset date of an event, assessment date, disease progression, etc.) and the start of study treatment. The day before start of study treatment administration is therefore Study **Day -1**. For the particular case of pre-treatment assessments performed on the day of first administration study day will be set to **Day 1**.

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

Cycle definition

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.

2.1.2.7 Baseline

Baseline is the last available and valid assessment performed or value measured within 14 days before the first administration of study treatment, unless otherwise stated under the related assessment section. Baseline can 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, samples for biomarkers).

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.

2.1.2.8 On-treatment assessment/event

An on-treatment assessment/event is defined as any assessment/event obtained in the time interval from the date of first administration of study treatment until the date of last administration of study treatment (i.e., including combination partner) + 30 days inclusive.

2.1.2.9 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.

Table 2-1 **Time windows**

Assessment	Visit	Time Window	Planned Visit Timing	Time Window Definition
Efficacy Assessments				
Tumor response for imaging assessments	Screening	Baseline	Pre-treatment	D-42 to D-1 for whole body bone scans D-21 to D-1 for all other image scans
	C1D28	Between week 3 and week 4 ± 3 days	C1D28	D18 to D31
	C2D28	C2D28 ± 7 days	D56	D49 to D63
	C4D28	C4D28 ± 7 days	D112	D105 to D119
	every 8 weeks (2 cycles) until disease progression, i.e. C6D28, C8D28 ...			
	EOT	EOT + 14 days± 3 days		
Biomarkers				
Tumor Biopsy Samples				
Fresh tumor biopsy	Screening	Baseline	Pre-treatment	D-14 to D-1
	C1D8 or C1D16	C1D8 ± 3 days or C1D16 + 5 days± 3 days	D8 or D16	D5 to D11 or D13 to D24
	relapse			
CCI [redacted]				

Notes:
C = cycle, D = Day, 01 = start of study treatment
All other assessments *(i.e. laboratory evaluations etc.) the reported visit will be used*

Table 2-2 Time windows for PK analyses

Assessment	Visit	Time Window	PK assessment time point	Time Window Definition
Phase Ib (Dose escalation)	C1D1	-03:00	< 00:00 pre-dose	C1D1, [-03:00, 00:00]
	C1D1	± 00:05	00:30 post-dose	C1D1, [00:25, 00:35]
	C1D1	± 00:15	01:30 post-dose	C1D1, [01:15, 01:45]
	C1D1	± 00:30	02:30 post-dose	C1D1, [02:00, 03:00]
	C1D1	± 00:30	04:00 post-dose	C1D1, [03:30, 04:30]
	C1D1	± 01:00	06:00 post-dose	C1D1, [05:00, 07:00]
	C1D1	± 01:00	08:00 post-dose	C1D1, [07:00, 09:00]
	C1D2	-03:00	< 00:00 pre-dose	C1D2, [-03:00, 00:00]
	C1D15	-03:00	< 00:00 pre-dose	C1D15, [-03:00, 00:00]
	C1D15	± 00:05	00:30 post-dose	C1D15, [0:25, 00:35]
	C1D15	± 00:15	01:30 post-dose	C1D15, [01:15, 01:45]
	C1D15	± 00:30	02:30 post-dose	C1D15, [02:00, 03:00]
	C1D15	± 00:30	04:00 post-dose	C1D15, [03:30, 04:30]
	C1D15	± 01:00	06:00 post-dose	C1D15, [05:00, 07:00]
	C1D15	± 01:00	08:00 post-dose	C1D15, [07:00, 09:00]
	C1D16	-03:00	< 00:00 pre-dose	C1D16, [-03:00, 00:00]
	C2D1	-03:00	< 00:00 pre-dose	C2D1, [-03:00, 0:00]
	every cycle Day 1 (pre-dose), up to Cycle 10, i.e. C3D1, C4D1, …, C10D1			
Phase II arm 2 + Phase II arm 3 (Phase II arm 1, if required)*** / Phase II arm A	C1D1	-03:00	< 00:00 pre-dose	C1D1, [-3:00, 000:00]
	C1D1	± 00:05	00:30 post-dose	C1D1, [0:25, 000:35]
	C1D1	± 00:15	01:30 post-dose	C1D1, [01:15, 01:45]
	C1D1	± 00:30	02:30 post-dose	C1D1, [02:00, 03:00]
	C1D1	± 01:00	05:00 post-dose	C1D1, [04:00, 06:00]
	C1D1	± 01:00	08:00 post-dose	C1D1, [07:00, 09:00]
	C1D2	-03:00	< 00:00 pre-dose	C1D2, [-03:00, 00:00]
	C1D15	-03:00	< 00:00 pre-dose	C1D15, [-03:00, 00:00]
	C1D15	± 00:05	00:30 post-dose	C1D15, [00:25, 00:35]
	C1D15	± 00:15	01:30 post-dose	C1D15, [01:15, 01:45]
	C1D15	± 00:30	02:30 post-dose	C1D15, [02:00, 03:00]
	C1D15	± 01:00	05:00 post-dose	C1D15, [04:00, 06:00]
	C1D15	± 01:00	08:00 post-dose	C1D15, [07:00, 09:00]
	C1D16	- 03:00	< 00:00 pre-dose	C1D16, [-03:00, 00:00]
	C2D1	-03:00	< 00:00 pre-dose	C2D1, [-03:00, 0:00]
	every cycle Day 1 (pre-dose), up to Cycle 10, i.e. C3D1, C4D1, …, C10D1			

Notes:

C = cycle, D = Day, hh:mm = hours and minutes

00:00 = time of study treatment intake

Assessment	Visit	Time Window	PK assessment time point	Time Window Definition
**** first 10 patients in each arm only.*				

2.1.2.10 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. Rules for imputing dates for adverse events (AEs), concomitant medications, and anti-neoplastic therapies are described separately in this section.

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)
- PK and biomarker data, 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.

AE data imputation

Missing and partial date for AE 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 partial AE start date, the date imputation will be based on the temporal relation between the partial date and start of treatment date.

For partial AE end date or completely missing end date (AE is ongoing), the date imputation will be based on the temporal relation between the partial date, the last contact date and the 30-day follow date. If the minimum date of the last contact date and 30-day FU date is before the AE start date (imputed or not), the imputed AE end date will be set to the AE start date.

Table 4-11 provides examples of the different considered imputations for AE start date.

Table 4-12 provides examples of the different considered imputations for AE end date.

Table 2-3 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 2-4 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	31DEC2001
ddmmm2001	20OCT2001	Yes	20OCT2001
ddSEP2001	20OCT2001	No	30SEP2001
ddOCT2001	20OCT2001	No	31OCT2001
ddOCT2001	20OCT2001	Yes	20OCT2001

Concomitant medication date imputation

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

Incomplete date for anti-neoplastic therapies

Prior therapies

Start date:

The same rule which is applied to the imputation of AE/concomitant medication start date.

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.

Date of progression:

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.

If the end date or the date of progression is not missing and the imputed start date is after the end date or after the date of progression, use the min(end date, date of progression) as the imputed start date.

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.

End date: No imputation.

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 FAS includes all patients who received at least one dose of LGX818 or MEK162 or LEE011. Patients will be classified according to the planned treatment regimen (dose, schedule, tablet variant). 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.

Note that patients who were screened and are eligible but never started treatment will not be included in the FAS. This is considered as an acceptable deviation from the ITT principle in the context of the Phase I study in which safety is considered as a primary objective.

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. Patients will be analyzed according to the planned treatment regimen.

Safety Set

The safety set includes all patients who received at least one dose of LGX818 or MEK162 or LEE011, 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 (See Section 2.1.1.2).

Dose Determining Set (DDS)

The dose-determining set (DDS) includes all Phase Ib patients from the safety set who either completed a minimum exposure requirement and have sufficient safety evaluations or discontinued prematurely due to a dose limiting toxicity (DLT).

A patient is considered to have met the minimum exposure requirement if having received at least 75% of the planned combination doses (i.e. 21 out of 28 planned daily doses for QD or BID, 11 out of 14 planned doses for an every other day dosing schedule, and 16 days out of 21 days for 3 week on, 1 week off dosing schedule) of study treatment within the first Cycle of dosing. The length of a cycle is 28 days.

Patients who do not experience DLT during the first cycle will be considered to have sufficient safety evaluations if they have been observed for ≥ 28 days following the first dose, and are considered by both the Sponsor and Investigators to have enough safety data to conclude that a DLT did not occur.

Patients excluded from this analysis set will be identified through a manual protocol deviation (PD) with severity code 18 (“exclude from MTD determining analysis set”)

Below is a summary of protocol deviations leading to exclusion from analysis sets. Severity codes are defined in the Novartis Validation and Analysis Planning (VAP) Module 3. This study was previously under the sponsorship of Novartis and transitioned to Pfizer sponsorship with PPD oversite, but protocol deviations are still coded according to the Novartis VAP Module 3. Patients were excluded from the analysis sets defined above based on the protocol deviations entered in the database.

Analysis set	**Protocol deviations [severity codes leading to exclusion]**
Full analysis set	Patient not correctly consented [8]
Safety set	Patient not correctly consented [8] Patient has no adverse event record (including no record that no event occurred) [5]
Dose determining set	Patient not correctly consented [8] Patient did not have sufficient safety evaluations for the investigator to be able to complete the end of cycle 1 DLT

	assessment and did not have a DLT [18] Minimum exposure requirements not met and did not have a DLT [18]

[8] (exclude from all analysis) / [5] (exclude from all safety analyses) / [18] (exclude from MTD determining analysis set)

2.3 Interim analyses

Since Phase II Arm 1 was terminated before the planned number of patients was reached, this part of the analysis will not be conducted.

3 Statistical methods used in reporting

The data will be summarized by treatment group and overall (when appropriate) with respect to demographic and baseline characteristics, preliminary efficacy and safety observations and measurements, and all relevant PK and PD measurements using descriptive statistics (quantitative data) and contingency tables (qualitative data).

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.

Data from participating centers will be combined. Unless otherwise specified, patients of the escalation part treated at the MTD with the same dose level but were recruited at different point in the study will be pooled into a single treatment group.

Listings of all raw data will be produced and ordered by treatment group (in Phase Ib) or patient group (in Phase II), 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.

3.1 Intra-patient dose escalation

For patients undergoing intra-patient dose escalation, all data will be summarized and listed by initial treatment group they were assigned to.

3.2 Patient disposition, background and demographic characteristics

Demographic and other baseline data, including disease characteristics, will be summarized descriptively by treatment group in Phase Ib and patient group in Phase II using the FAS.

3.2.1 Patient disposition

The number of patients who were enrolled and treated, as well as those who completed or discontinued treatment or the study (along with their reasons for premature discontinuation), or were still ongoing at the time of the analysis will be summarized. If treatment discontinuation or study evaluation completion due to COVID-19 is reported for any patients,

this will also be included in the summary. 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).

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

3.2.2 Protocol deviations

All protocol deviations will be finalized before database lock. This study was previously under the sponsorship of Novartis and transitioned to Pfizer sponsorship with PPD oversite, but protocol deviations are still coded according to the Novartis VAP Module 3. Protocol deviations and reasons for exclusion from populations will be tabulated. The number and percentage of patients in the FAS with any protocol deviations will be tabulated by the deviation category (as specified in the Novartis VAP Module 3 documents) and within each deviation category, deviations due to COVID-19 will also be summarized. All protocol deviations will be listed.

3.2.3 Background and demographic characteristics

Background and demographic characteristics including age, gender, race, ethnicity, height, weight, WHO performance status, tumor type, medical conditions, BRAF mutation status, geographic region and LDH, etc. will be listed and summarized using descriptive statistics. The summaries will be based on the assessments from the screening visit (baseline).

In addition, the following derived variables derived from the demographic (e)CRF will be described:

- age groups summarized by class (<65, ≥65 years)
- weight summarized by class (<55, 55-75, ≥75 kg)
- Body mass index (BMI) calculated as weight/(height**2) (kg/m^2) where weight is measured in kg and height in m
- The body surface area (BSA) is calculated using Gehan and George formulae:
  BSA [m^2] = 234.94*(height[cm]**0.422)*(weight[kg]**0.515)/10000

3.2.4 Medical History

Past and current medical history will be summarized and listed. Separate summaries will be presented for current and past historical medical conditions; these summaries will be presented by primary system organ class and preferred term. Medical history/current medical conditions will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 18.1.

3.2.5 Prior antineoplastic therapy

Prior anti-neoplastic therapies will be listed, and the latest therapy will be summarized in three separate tables for surgery (procedure, residual disease for non-biopsy surgery), radiotherapy (location, setting and best overall response) and medications (therapy type,

setting, previous treatment with selective BRAF inhibitor and best overall response). In addition, the time between end of last therapy and start of treatment will be summarized.

Last surgery is derived based on procedure date. Last radiotherapy is derived based on end date. Last treatment is derived based on the last end date of any of the components of the regimen.

The summary of prior anti-neoplastic medications will be presented by Anatomical Therapeutic Chemical (ATC).

3.2.6 Diagnosis and extent of cancer

Diagnosis and extent of cancer will be listed and the summarized by number (%) of patients in each of the categories for the following variables: primary site of cancer (includes melanoma type and subtype), details of tumor histology/cytology, histological grade, stage at initial diagnosis, current stage of cancer, current extent of disease (metastatic sites), and types of lesions at baseline.

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

- Time since initial diagnosis to first dose of study drug, calculated as (date of study treatment start – date of initial diagnosis of primary site + 1)/30.4375. The following categories will be used: <6 months, ≥6 to <12 months, ≥12 to <24 months, ≥24 months
- Time since initial diagnosis to first relapse, calculated as (date of first relapse – date of initial diagnosis of primary site + 1)/30.4375. The following categories will be used: <6 months, ≥6 to <12 months, ≥12 to <24 months, ≥24 months
- Time since initial diagnosis to most recent recurrence/relapse, calculated as (date of most recent recurrence/relapse – date of initial diagnosis of primary site + 1)/30.4375. The following categories will be used: <6 months, ≥6 to <12 months, ≥12 to <24 months, ≥24
- Time since most recent recurrence/relapse to first dose of drug, calculated as (date of study treatment start - date of most recent recurrence/relapse + 1)/30.4375. The following categories will be used: <1 month, ≥1 to <2 months, ≥2 to <3 months, ≥3 months

See Section 2.1.2.10 for handling partial missing dates for the intervals.

3.2.7 Other baseline characteristics

All data collected during the baseline evaluation, including child bearing potential, pregnancy test results, and exploratory biomarker informed consent will be listed.

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

3.3.1 Study medication

Exposure will be summarized overall in terms of:

- The duration of study treatment exposure,

- The cumulative dose,
- The dose intensity (DI) and/or relative dose intensity (RDI)
- The percentage of actual days dosed during the treatment period for daily dosed compounds
- The percentage of days received planned doses during the treatment period for daily dosed compounds (calculated for Phase II subjects only)

Exposure will be summarized on the Safety Set. For bid regimen, note that if interruption is after a one day reduction, this one day reduction will be considered as start of interruption and not as reduction.

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 2.1.2.3 and Section 2.1.2.5, respectively.

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

3.3.1.2 Cumulative dose

The actual cumulative dose for each study drug is defined as the total dose for this study drug given during the study drug exposure and is expressed in mg. For patients who did not take any of the drug, the actual cumulative dose is by definition equal to zero.

The planned cumulative dose is defined as the total dose planned to be given during the study treatment exposure and is expressed in mg.

3.3.1.3 Dose intensity and relative dose intensity

The dose intensity (DI) for patients with non-zero duration of exposure is defined as follows:

Planned dose intensity (PDI) (mg/day) = planned cumulative dose (mg) / planned number of days patient should have taken the drug (days)

Actual dose intensity (ADI) (mg/day) = actual cumulative dose (mg) / planned number of days patient should have taken the drug (days)

For patients who did not take any drug the ADI is (by definition) equal to zero.

ADI and PDI will be expressed in mg/day for LGX818, MEK162 and LEE011.

Relative dose intensity (RDI) = ADI (mg/day) / PDI (mg /day).

For patients who did not take any drug the actual RDI is (by definition) equal to zero.

The ADI and RDI will be summarized separately for each of the study treatment components by using the duration of the study treatment exposure, not the duration of each of the components.

The RDI for each of the study treatment components will be presented also with the following categories: <0.5, ≥ 0.5 to < 0.75, ≥ 0.75 to < 0.9, ≥ 0.9 to < 1.1 and ≥ 1.1.

Dose intensity for the first cycle or by cycle can be computed using cycle length definition (see Section 2.1.2.6) as exposure periods.

3.3.1.4 Dose change

Dose delay/interruption: any dose change/delay flagged in the DAR CRF page, satisfying the following criteria:

- a reason other than "as per protocol",
- a zero actual dose,
- occurs between the first and last non-zero doses,
- follows a non-zero actual dose.

Dose reduction: any dose change/delay flagged in the DAR CRF page, satisfying the following criteria:

- a reason other than "as per protocol",
- a non-zero actual dose below the immediate previous non-zero actual dose
- a non-zero actual dose below the treatment assigned as per safety set

Dose increment: any dose change/delay flagged in the DAR CRF page, satisfying the following criteria:

- a reason other than "as per protocol",
- a non-zero actual dose above any previous non-zero actual dose
- a non-zero actual dose above the treatment assigned as per safety set

The following criteria are used to identify an intra-patient dose escalation:

- dose change flag checked with reason "as per protocol"
- planned dose above any previous planned dose.

3.3.2 Concomitant medication

The Safety set will be used for all below mentioned concomitant medication tables.

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) besides the study treatment that were administered to a patient preceding or coinciding with the study assessment period.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List (WHODRUG 19SEP2014, version 4.3) to allow for categorization by

preferred term and by ATC class (note that a medication/therapy can appear with more than one ATC class).

Concomitant medications and significant non-drug therapies taken concurrently with the study treatment will be listed and summarized by ATC class, preferred term by contingency tables. These summaries will include medications starting on or after the start of study treatment or medications starting prior to the start of study treatment and continuing after the start of study treatment.

Any prior concomitant medications or significant non-drug therapies starting and ending prior to the start of study treatment will be listed.

Further anti-neoplastic therapies administered concomitantly with study treatment will be listed based on their identification (by the method given in Section 3.2.5) by the protocol deviation process.

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

Concomitant medications with a possible PK interaction with LGX818, MEK162 and LEE011 will be identified prior to database lock and listed:

- Inhibitors, inducers and/or substrates of CYP2B6, CYP2C9, CYP3A4, UGT1A1, P-gp, BCRP, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, CYP1A2 and CYP2C19 will be identified, classified and listed.

See [CMEK162X2110 Protocol Appendix 14-.4] for complete list of inhibitors, inducers and substrates which might interact with LGX818 and MEK162 and LEE011.

3.4 Analysis of the primary variable(s)

3.4.1 Primary variable(s)

3.4.1.1 Phase Ib

Estimation of the MTD of the combination treatment will be based upon the estimation of the probability of DLT in Cycle 1 for patients in the DDS. This probability is estimated by the model in Section 3.4.2.1. Note that more than one dose-combination of dual combination (LGX818 and MEK162) or triple combination (LGX818 and MEK162 and LEE011) may be identified as a MTD, and more than one RP2D may be established for further evaluation in the phase II part of the study.

The dose determining set (DDS) will be used for all dose determining analyses.

3.4.1.2 Phase II

Dual combination (LGX818 and MEK162)

For arm 1, the primary variable is the Disease Control Rate (DCR) at week 16. Estimation of the true DCR using a Bayesian design as described in the protocol will not be performed for

the CSR. Instead, the observed DCR for patients in the FAS will be presented. The primary analysis of the DCR will be based on the local review of overall lesion responses.

For arms 2 + 3, the primary variable is the Objective Response Rate (ORR), defined as the proportion of patients with a best overall response of complete response (CR) or partial response (PR). Estimation of the true ORR using a Bayesian design as described in the protocol will not be performed for the CSR. Instead, the observed ORR for patients in the FAS will be presented. The primary analysis of the ORR will be based on the local review of overall lesion responses.

Triple combination (LGX818 and MEK162 and LEE011)

For arm A, the primary variable is the Objective Response Rate (ORR). Estimation of the true ORR using a Bayesian design as described in the protocol will not be performed for the CSR. Instead, the observed ORR for patients in the FAS will be presented. The primary analysis of the ORR will be based on the local review of overall lesion responses.

3.4.2 Statistical model

3.4.2.1 Phase Ib

An adaptive BLRM guided by the EWOC principle will guide the dose escalation of the combination treatment to its MTD(s)/RP2D(s). A 5-parameter BLRM for combination treatment will be fitted on the dose-limiting toxicity data (i.e. absence or presence of DLT) accumulated throughout the dose escalation, for modeling the dose-DLT relationship of LGX818 (capsule formulation) and MEK162 when given in combination.

The 5 parameter BLRM will be extended to a 10-parameter BLRM to model the dose-DLT relationship of LGX818 (capsule formulation) and MEK162 and LEE011 when given in combination.

Summaries of the posterior distribution of model parameters and posterior distribution of DLT rates based on the DLT data from all patients enrolled in the study and included in the DDS will be produced.

The 5-parameter BLRM (LGX818 and MEK162 original tablet)

The 5-parameter BLRM is formulated in the following way:
Let $\pi_1(d_1)$ be the probability of a DLT if LGX818 is given as a single agent at dose d_1, and $\pi_2(d_2)$ be the probability of a DLT if MEK162 is given as a single agent at dose d_2. Both drugs administered to non-fasted patients.
The dose-response relationship is then modeled as:

$$\text{logit}(\pi_1(d_1)) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*)$$

$$\text{logit}(\pi_2(d_2)) = \log(\alpha_2) + \beta_2 \log(d_2/d_2^*)$$

$$Odds(\pi_{12}(d_1, d_2)) = \frac{\pi_{12}(d_1, d_2)}{1 - \pi_{12}(d_1, d_2)} = \exp(\eta_{12} \frac{d_1}{d_1^*} \frac{d_2}{d_2^*}) \frac{\pi_1(d_1) + \pi_2(d_2) - \pi_1(d_1)\pi_2(d_2)}{(1 - \pi_1(d_1))(1 - \pi_2(d_2))}$$

where

- logit(π.(d.)) = log[π.(d.)/{1- π.(d.)}], π(d) is the probability of a DLT at dose d.
- $\pi_{12}(d_1,d_2)$ is the probability of a DLT given the combination doses.
- d_1^* = 100 mg and d_2^*= 60 mg are the reference doses of LGX818 and MEK162 respectively.
- $\alpha_1, \alpha_2, \beta_1, \beta_2 > 0$ and $-\infty < \eta_{12} < \infty$, with η_{12} is the interaction term.

Note that all five parameters α_1, α_2, β_1, β_2 and η_{12} correspond to the effect of the drugs when administered to non-fasted patients.

The 5-parameter BLRM (LGX818 and MEK162 smaller tablet / new tablet variant)

The 5-parameter BLRM is formulated in the following way:

Let $\pi_1(d_1)$ be the probability of a DLT if LGX818 is given as a single agent at dose d_1, and $\pi_3(d_3)$ be the probability of a DLT if MEK162 is given as a single agent at dose d_3.

The dose-response relationship is then modeled as:

$$\text{logit}(\pi_1(d_1)) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*)$$

$$\text{logit}(\pi_3(d_3)) = \log(\alpha_3) + \beta_3 \log(d_3/d_3^*)$$

$$Odds(\pi_{13}(d_1,d_3)) = \frac{\pi_{13}(d_1,d_3)}{1-\pi_{13}(d_1,d_3)} = \exp(\eta_{13}\frac{d_1}{d_1^*}\frac{d_3}{d_3^*})\frac{\pi_1(d_1)+\pi_3(d_3)-\pi_1(d_1)\pi_3(d_3)}{(1-\pi_1(d_1))(1-\pi_3(d_3))}$$

where

- logit(π.(d.)) = log[π.(d.)/{1- π.(d.)}], π(d) is the probability of a DLT at dose d.
- $\pi_{13}(d_1,d_3)$ is the probability of a DLT given the combination doses.
- d_1^* = 100 mg and d_3^*= 60 mg are the reference doses of LGX818 and MEK162 respectively.
- $\alpha_1, \alpha_3, \beta_1, \beta_3 > 0$ and $-\infty < \eta_{13} < \infty$, with η_{13} is the interaction term.

Note that all five parameters α_1, α_3, β_1, β_3 and η_{13} correspond to the effect of the drugs when administered to non-fasted patients.

The 10-parameter BLRM (LGX818 and MEK162 and LEE011)

The 10-parameter BLRM is formulated in the following way:

Let $\pi_1(d_1)$ be the probability of DLT if LGX818 is given as a single agent at QD dose d_1,

$\pi_2(d_2)$ the probability of DLT if MEK162 is given as a single agent at BID dose d_2, and

$\pi_4(d_4)$ the probability of DLT if LEE011 is given as a single agent at 3 weeks on, 1 week off dose d_4.

The single agent dose-DLT relationships are then modeled as:

LGX818:

$$\text{logit}(\pi_1(d_1)) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*)$$

MEK162:

$$\text{logit}(\pi_2(d_2)) = \log(\alpha_2) + \beta_2 \log(d_2/d_2^*)$$

LEE011:

$$\text{logit}(\pi_4(d_4)) = \log(\alpha_4) + \beta_4 \log(d_4/d_4^*)$$

The dose-DLT relationships of the dual combinations of LGX818 + MEK162, LGX818 + LEE011 and MEK162 + LEE011 are modeled as:

$$Odds(\pi_{12}(d_1,d_2)) = \frac{\pi_{12}(d_1,d_2)}{1-\pi_{12}(d_1,d_2)} = \exp(\eta_{12}\frac{d_1}{d_1^*}\frac{d_2}{d_2^*})\frac{\pi_1(d_1)+\pi_2(d_2)-\pi_1(d_1)\pi_2(d_2)}{(1-\pi_1(d_1))(1-\pi_2(d_2))}$$

$$Odds(\pi_{14}(d_1,d_4)) = \frac{\pi_{14}(d_1,d_4)}{1-\pi_{14}(d_1,d_4)} = \exp(\eta_{14}\frac{d_1}{d_1^*}\frac{d_4}{d_4^*})\frac{\pi_1(d_1)+\pi_4(d_4)-\pi_1(d_1)\pi_4(d_4)}{(1-\pi_1(d_1))(1-\pi_4(d_4))}$$

$$Odds(\pi_{24}(d_2,d_4)) = \frac{\pi_{24}(d_2,d_4)}{1-\pi_{24}(d_2,d_4)} = \exp(\eta_{24}\frac{d_2}{d_2^*}\frac{d_4}{d_4^*})\frac{\pi_2(d_2)+\pi_4(d_4)-\pi_2(d_2)\pi_4(d_4)}{(1-\pi_2(d_2))(1-\pi_4(d_4))}$$

The dose-DLT relationship of the triple combination is subsequently modeled as:

$$Odds(\pi_{124}(d_1,d_2,d_4)) = \frac{\pi_{124}(d_1,d_2,d_4)}{1-\pi_{124}(d_1,d_2,d_4)}$$

$$= \exp\left(\eta_{124}\frac{d_1}{d_1^*}\frac{d_2}{d_2^*}\frac{d_4}{d_4^*} + \eta_{12}\frac{d_1}{d_1^*}\frac{d_2}{d_2^*} + \eta_{14}\frac{d_1}{d_1^*}\frac{d_4}{d_4^*} + \eta_{24}\frac{d_2}{d_2^*}\frac{d_4}{d_4^*}\right)$$

$$\times\left[\frac{\pi_1(d_1)+\pi_2(d_2)+\pi_4(d_4)-\pi_1(d_1)\pi_2(d_2)-\pi_1(d_1)\pi_4(d_4)-\pi_2(d_2)\pi_4(d_4)+\pi_1(d_1)\pi_2(d_2)\pi_4(d_4)}{(1-\pi_1(d_1))(1-\pi_2(d_2))(1-\pi_4(d_4))}\right]$$

where logit(π.(d.)) = log[π.(d.)/{1- π.(d.)}], d_1^* = 100mg (QD), d_2^* = 60mg (BID) and d_4^* = 400mg (3 weeks on, 1 week off) are the reference doses of LGX818, MEK162 and LEE011, respectively, α_1, α_2, α_4, β_1, β_2, $\beta_4 > 0$ and $-\infty < \eta_{12}, \eta_{14}, \eta_{24}, \eta_{124} < \infty$ are the interaction terms.

Starting dose reassessment

As per [CMEK162X2110-Protocol Amendment 5-Section 6.2.2 Starting dose rationale] for LGX818 and MEK162 and LEE011 triple combination, the Bayesian model will be updated with the most recent data from the ongoing LEE011 single agent trial [CLEE011X2101] and the LGX818 and MEK126 dual combination study [CMEK162X2110], to confirm that the proposed starting dose combination is still appropriate (i.e. satisfies the EWOC criterion) before the first patient is dosed with the triple combination.

[CMEK162X2110-Protocol Amendment 5] did not state information for the dual combinations of MEK162 and LEE011 or LGX818 and LEE011 will be included. However, since these additional studies will provide information on the dose-DLT relationship of the dual combinations, the data for MEK162 and LEE011 under on-going study [CMEK162X2114] and LGX818 and LEE011 under on-going study [CLEE011X2105] have been incorporated. Table 3-1 shows summary of DLT data by study.

The information from the on-going studies [CMEK162X2114] and [CLEE011X2105] were incorporated through discounting the data directly using the following weight function, *w* [Neuenschwander (2010)].

$$w = \frac{1}{1 + 2n\tau^2/\sigma^2} = \frac{1}{1 + 2n/n^{\star}_{\infty}}$$

where *n* is the sample size of historical data, σ^2 and τ^2 are the within-trial and between-trial variance. The parameters σ and τ for both of the studies, were set at 2 and 0.5 (correspond to substantial heterogeneity between trials, i.e. $n^*_\infty = 16$), respectively. Thus, the weights (*w*) for studies [CMEK162X2114] and [CLEE011X2105] were 0.421 and 0.615, respectively. Table 3-1 shows Prior used for the triple combo.

Table 3-1 Prior used for CMEK162X2110 triple combo (LGX818 + MEK162 + LEE011)

Parameter	Means	Standard deviations	Correlation
$\log(\alpha_1), \log(\beta_1)$	-2.917, -1.820	0.986, 1.041	0.233
$\log(\alpha_2), \log(\beta_2)$	-2.326, 1.564	1.107, 1.368	-0.535
$\log(\alpha_4), \log(\beta_4)$	-2.027, -0.706	0.508, 0.511	-0.149
η_{12}	0	1.528	NA
η_{14}	0.095	0.512	NA
η_{24}	0.020	0.392	NA
η_{124}	0.020	0.392	NA

3.4.2.2 Phase II

Efficacy will be assessed using the local CT/MRI assessments evaluated under RECIST v1.1. The Best Overall Response (BOR) for each patient and individual lesion measurements will be listed. The BOR will be summarized using the Disease Control Rate (DCR) for Phase II arm 1 and the Objective Response Rate (ORR) for Phase II arms 2 + 3 and Phase II arm A.

- The ORR is defined as the proportion of patients with a BOR of CR or PR.
- The DCR is defined as proportion of patients with a BOR of CR or PR or SD.

Both confirmed and unconfirmed summaries will be provided.

Patients who withdrew prematurely due to progression of disease without having any post-dose tumor assessment will be classified as treatment failures. Similarly, patients who died due to their disease without having any post-dose tumor assessment will be classified as treatment failures.

ORR and DCR will be provided with their corresponding 95% exact confidence interval according to Clopper-Pearson method [Clopper and Pearson 1934].

3.5 Efficacy evaluation (Secondary Objectives)

Phase Ib

Preliminary clinical anti-tumor activity of the combination in patients with BRAF V600 dependent advanced solid tumors will be assessed using the Investigator read CT/MRI assessments evaluated.

ORR will be summarized as point estimate and corresponding 95% exact confidence interval according to Clopper-Pearson method by treatment group. The BOR for each patient and individual lesion measurements will be listed.

Phase II

Local read of CT/MRI assessment will be used for all Phase II efficacy assessments of tumor activity.

Progression-free survival (PFS) will be analyzed using Kaplan-Meier estimates [Kaplan and Meier 1958] (including graphical representation) with 95% confidence interval for median survival.

Overall survival (OS) will be analyzed using Kaplan-Meier estimates with 95% confidence intervals for median survival and survival probabilities for specific time-points (3, 6, 9, 12, 15 and 18 months) will be presented.

Time to response (TTR) and duration of overall response (DOR) will be analyzed using Kaplan-Meier estimate with 95% confidence interval for median survival.

If deem necessary, PFS between the Phase II arm 3 and Phase II arm A may be described in separate analysis plan documentation and displayed external to the main study CSR.

The FAS will be used for all efficacy analyses.

3.5.1 RECIST related endpoints

Response and progression evaluation will be performed according to the RECIST guideline version 1.1 (as described in detail in [CMEK162X2110 Protocol Appendix 14.1]) whenever it applies.

3.5.1.1 Best overall response and other binary endpoints

Best overall response

The Best overall response (BOR) is the best response recorded from the start of the treatment until disease progression/recurrence.

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 who are of unknown clinical response will be treated as non-responders.

3.5.1.2 Computation of time to event endpoints

Overall survival

Overall survival (OS) is defined as the time from start of treatment to date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last contact.

As of protocol amendment 10, survival follow-up is no longer performed for patients who have discontinued study treatment in the Phase II part of the study.

Progression free survival

Progression-free survival (PFS) is defined as the time from the date of first study treatment intake to the date of the first documented disease progression or death due to any cause.

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 or death 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. Patients who begin a new antineoplastic therapy prior to disease progression or death will be censored at the last adequate tumor evaluation prior to the start of the new antineoplastic therapy.

As of protocol amendment 10, post-treatment disease progression follow-up is no longer performed for patients who have discontinued study treatment in the Phase II part of the study.

Time to (overall) response

Time to (overall) response (TTR) will be based on “responders” only and is the time between the date of first treatment administration and the first documented response (CR or PR).

Duration of overall response

Duration of overall response (DOR) will be based on “responders” only and is the time between the date of first documented response (CR or PR) and the date of first documented progression or death due to underlying cancer. If progression or death due to underlying cancer has not occurred, then the patient is censored at the date of last adequate tumor assessment.

3.5.1.3 Handling of missing data and special cases

No measurable lesion at baseline

Evaluation using RECIST criteria implies that patients have measurable lesion at baseline.

According to RECIST guidelines, the overall Response should be UNK or PD. In Phase I studies when the presence of target lesions is not mandatory for enrollment, in order 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. CR and SD will be assigned if the non-target lesion responses are respectively CR, non CR-non PD, respectively, without the appearance of a new lesion.

Analysis of other progression screening methods

In the efficacy analysis, additional screening methods (e.g., bone scans) are handled differently than the regular tumor assessments.

In addition, if the screening method is not available at a given assessment this does not automatically make the overall lesion response "Unknown" at that assessment.

Change in imaging modality

As per RECIST, the same imaging method used at baseline should also be used at all subsequent assessments. However, for various reasons such as site error (e.g., switch from MRI to CT) or renal dysfunction (making contrast a risk), this is not always done. The strict implementation of RECIST would mean that any change in the imaging method apart from that used at baseline would lead to an overall response of "unknown" at that assessment.

However, the presence or absence of contrast does not necessarily change the precision of the image. To cover that possibility, the following imaging modalities listed under the same bullet point below were considered the same for the calculation of change from baseline of the sum of diameters of target lesions (SOD):

- 'CT with contrast' and 'CT without contrast'
- 'Spiral CT with contrast' and 'Spiral CT without contrast'
- 'MRI with contrast', 'MRI without contrast', 'Dynamic contrast – enhanced MRI' and 'Gadolinium-MRI'.

For other efficacy endpoints, investigator judgment only is considered even if overruling the computed response.

3.5.2 Non RECIST related endpoints

Not applicable.

3.5.3 Models and method of analysis

3.5.3.1 Analyses of time-to-event data

The following section presents the general methodology used to analyze time-to-event variables (e.g., PFS, OS, TTR and DOR) for Phase II efficacy assessments of tumor activity.

OS will be analyzed using Kaplan-Meier estimates with confidence intervals for median survival and survival probabilities for specific time-points (3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, and 48 months).

PFS will be analyzed using Kaplan-Meier estimates (including plots) with 95% confidence interval for median survival and survival probabilities for specific time-points (3, 6, 9, 12, 15, 18, 21, 24, 27 and 30 months). PFS will be calculated at the MTD/RP2D for Phase II Arm 3 and Phase II Arm A. In addition, for the purposes of the PFS figure, PFS will be calculated for Phase Ib treatment arms as well.

Kaplan-Meier estimates based on all responders with 95% confidence intervals will be presented for TTR and DOR. These two analyses based on responders will be used as a descriptive analysis. Kaplan-Meier estimates with 95% confidence intervals for median TTR and median DOR will be presented. Survival probabilities for specific time-points will include 3, 6, 9, 12, 15 and 18 months for TTR and 3, 6, 9, 12, 15, 18, 21, 24, 27 and 30 months for DOR.

Details on Kaplan-Meier estimates

An estimate of the survival function can be constructed using the Kaplan-Meier (product-limit) method 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 can 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.

Hypotheses and test statistics

Not applicable.

Hazard ratio

Not applicable.

3.5.3.2 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 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 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.

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

Waterfall plots will show the cut-off limits for target lesions for PD (+20%) and PR (-30%) as dotted lines.

On the top of the waterfall plot a heatmap will be added in order to display per patient (matching with the bar on the waterfall plot) the information regarding BRAF local mutational status.

3.5.3.3 Construction of swimmer plots

The plot will show duration of exposure (without display of dose interruption and dose change information), BOR status and on-going status or primary reasons for discontinuation by patient.

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). Other safety data includes electrocardiogram, vital signs and Ocular.

The Safety set will be used for summaries and listings of all safety data in Section 14 of the CSR with the exception of dose limiting toxicities (DLT) for which the DDS will be used. 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.

3.6.1 Adverse event

Adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 18.1) 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, serious AEs (SAEs) and death recorded during the study will be provided. Deaths will also be summarized by primary reason. Additional summaries and listings events suspected to be related to study drug by treatment, events leading to study drug discontinuation, and events 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 one of the following methods: by presenting the number and percentage of patients having at least one AE, having at least one AE in each primary system organ class, and having at least one AE for each preferred term or by presenting the number and percentage of patients having at least one AE and having at least one AE for each preferred term. Within each type of summary, AEs will be sorted by descending frequency or alphabetically (system organ class [SOC] and preferred term [PT] or PT for summaries that do not include SOC information).
- Specific groupings of clinically notable adverse events will be considered and the number of patients with at least one event in each grouping will be reported. The case retrieval sheet for each of study drug (if available) will be used to identify risks of special interest. Adverse events of special interest (All and Grade 3/4) will be tabulated by groups of special interest and preferred term for each study drug separately. In addition, separate listing will be provided for each study drug.
- AEs with incidence thresholds of ≥20% in the summarized population will be tabulated by preferred term. Grade 3/4 AEs with incidence ≥5% will be summarized similarly. Treatment-related AEs with an incidence of ≥10% will be summarized distinctly for all AE grades and for Grade 3/4.

3.6.2 Dermatologic examination

All dermatological examination data will be listed.

3.6.3 Ophthalmic examination

All ophthalmic examinations (i.e., Tonometry, Visual acuity, Visual field, Fundoscopy, Slit lamp, Optical Coherence Tomography (OCT), Fluorescein Angiography (FA), Electroretinogram (ERG)) will be listed.

3.6.4 Laboratory data

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

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

- Shift tables to the worst post-baseline value from baseline value (both expressed in CTC grades) will be produced.
- Tables of worst post-baseline value by CTC grade.

- For laboratory parameters where CTC grades are not defined, shift tables to the worst post-baseline value will be produced using the low/normal/high classifications based on laboratory reference ranges.

The following listings will be produced for the laboratory data:

- Listing of patients with laboratory abnormalities of CTC grade 3 and 4 by parameter, cycle and treatment group
- Listing of laboratory normal ranges by laboratory identification number and laboratory group
- Listing of 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))

Table 3-2 lists all those laboratory parameters for which CTCAE grades are defined, Table 3-3 lists the remaining laboratory parameters.

3.6.4.1 Hematology

Differential counts will be converted to absolute values for CTC grade classification. For all the differential counts, % will be converted to absolute values, if necessary:

e.g. Absolute WBCdiff (Wunit) = Absolute WBC (Wunit)*Relative WBCdiff(%)/100

Normal ranges should not be converted to obtain absolute normal ranges. Absolute normal ranges should be provided within lab ranges. If both are reported, absolute values will be left unchanged. Grading will be applied to absolute values.

Table 3-2 Laboratory parameters to be presented in grade shift tables based on CTC grade

Hematology and coagulation		Biochemistry		Urinalysis	
White Blood Cells (WBC)	↑↓	Creatinine	↑	Urine Protein Dipstick test	↑
Hemoglobin	↑↓	Sodium (hyper & hypo)	↑↓		
Platelets counts	↓	Potassium (hyper & hypo)	↑↓		
Absolute Neutrophils	↓	Glucose (hyper & hypo)	↑↓		
Absolute Lymphocytes	↑↓	Magnesium (hyper & hypo)	↑↓		
aPTT	↑	Uric acid	↑		
Fibrinogen	↓	Albumin	↓		
INR	↑	AST (SGOT)	↑		
		ALT (SGPT)	↑		
		Alkaline Phosphatase	↑		
		Total Bilirubin	↑		

Amylase	↑
Lipase	↑
Total cholesterol	↑
Triglycerides	↑
CPK	↑
Phosphate (Inorganic Phosphorus)	↓

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

Hematology and coagulation	Biochemistry	Urinalysis
Red blood cell count (RBC)	Urea	Specific gravity
Absolute eosinophils	Total protein	Glucose
Absolute basophils	Indirect bilirubin	Blood
Absolute monocytes	Direct bilirubin	Bilirubin
Prothrombin time	HDL	Ketones
Hematocrit	LDH	Leukocytes
	Chloride	Myoglobin
	Bicarbonate	
	LDL	
	TSH	
	Free T3	
	Free T4	
	Total Calcium	

3.6.5 Vital signs, weight and physical examinations

All vital signs measures (e.g., oral temperature, respiratory rate, sitting blood pressure, and sitting pulse) and weight will be listed by parameter, treatment group, patient and time point (cycle) for each patient with at least one notable vital sign abnormality on record. Vital sign abnormalities as defined in Table 3-4 will be derived 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 tabulated.

Table 3-4 Notable vital signs ranges

Vital sign	Criteria for clinically notable ranges
Systolic blood pressure	≥180 mmHg/≤90 mmHg with increase/decrease from baseline of ≥20

[mmHg]	mmHg
Diastolic blood pressure [mmHg]	≥105 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
Oral body Temperature [°C]	Body temperature: ≤ 35, ≥ 39
Weight [kg]	≥10% decrease/increase from baseline

3.6.6 WHO/ECOG performance status

Frequencies and percentages for the categories of the WHO performance scale will be summarized by visit.

3.6.7 Electrocardiograms

3.6.7.1 ECG data descriptive statistics

- Data from electrocardiogram will be listed, notable values will be flagged, and any other information collected will be listed. The frequency and percentage of patients with newly occurring qualitative ECG abnormalities will be tabulated. Shift table baseline to worst on-treatment result for overall assessments will also be summarized.

- Post-baseline values will also be categorized and tabulated to flag notable values according to the following rules:

Parameters	Criteria for ECG notable values
QTcF (ms), QTcB (ms) and QT (ms)	New: > 450, > 480, > 500 ms Increase from baseline > 30 Increase from baseline > 60
HR (bpm)	Increase from baseline > 25% & to a value > 100 Decrease from baseline < 25% & to a value < 50
PR (ms)	Increase > 25% to a value > 200
QRS (ms)	Increase > 25% to a value > 110

3.6.7.2 PK/QT analyses

Not applicable.

3.6.8 Other safety analyses

Cardiac imaging with decreased left ventricular ejection fraction (LVEF) will be summarized based on worst CTC grade and listed.

Any other safety information collected will be listed and notable values will be flagged.

3.6.9 Tolerability

Tolerability of study drug treatment will be assessed by summarizing the number of treatment dose interruptions and dose reductions. Reasons for dose interruption and dose reductions will be listed by patient and summarized. Dose interruption occurs when patient receives 0 mg of the study drug.

Cumulative dose, dose intensity and relative dose intensity of MEK162, LGX818 and LEE011 will be summarized. Categories for relative dose intensity of each study drug will be specified as < 0.5, ≥ 0.5 to < 0.75, ≥ 0.75 to < 0.9, ≥ 0.9 to < 1.1 and ≥ 1.1. The number and proportion of patients within each category will be presented.

3.6.10 COVID-19 Study disruptions

The following data will be summarized in relevant disposition analyses and will also be listed to indicate the extent of COVID-19 study disruptions on the trial participants and study data.

- Protocol deviations related to COVID-19
- COVID-19 related AEs
- COVID-19 related deaths
- Study drug discontinuation due to COVID-19
- Study discontinuation due to COVID-19

3.7 Pharmacokinetic data

3.7.1 Descriptive statistics

PK concentration data will be listed and summarized in the interim CSR. PK concentration data will be summarized in the final CSR but not listed.

Plasma concentrations that were excluded for the derivation of PK parameters and labeled as such in the listings will also excluded from the summary statistics.

The PK parameters defined in Table 3-5 will be calculated as appropriate. Steady state (SS) is assumed to be reached on Day 15 and the patient should have taken all scheduled doses for at least 2 consecutive days prior to Day 15. The PK parameters will be listed and summarized using relevant statistics in the interim CSR. The PK parameters will be summarized in the final CSR but not listed. Median, minimum, and maximum will be calculated for tmax and tlast. For other PK parameters, mean, standard deviation, CV% mean, geometric mean, CV% geo-mean, median, minimum, and maximum will be calculated. In addition, in case drug accumulation is observed upon multiple dosing, additional PK parameters describing drug accumulation will be added to the analysis (i.e. effective half-life).

Only PK blood samples with date and time and for which at last prior dose dates and times are adequately recorded will be included in the PK analyses. Samples taken from patients who vomited within 4 hours of dosing will be excluded from the analysis. The FAS will be used.

Table 3-5 Definition of PK parameters

Parameter	Definition
Cmax	Maximum observed plasma concentration after drug administration [mass x volume-1]
Tmax	Time to reach Cmax [time]
Ctrough	Predose plasma concentration before drug administration [mass x volume-1]

AUClast	Area under the concentration-time curve from time zero to the last measurable concentration sampling time (tlast) [mass x time x volume-1]
Tlast	Time at which the last measurable concentration was observed [time]
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 from time zero to tau after first dose [mass x time x volume-1]
AUC(0-t)	Area under the concentration-time curve from time zero to time t after first dose [mass x time x volume-1]
AUC(0-t), ss	Area under the concentration-time curve from time zero to time t after drug administration at steady state [mass x time x volume-1]
t1/2	Elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve [time]
CL/F	Apparent total plasma clearance of drug after oral administration [volume x time-1]
Vz/F	Apparent volume of Distribution at the terminal elimination phase [volume]
Cmax,ss	Maximum observed plasma concentration after drug administration at steady state [mass x volume-1]
Tmax,ss	Time to reach Cmax at steady state [time]
Ctrough,ss	Predose plasma concentration before drug administration at steady state [mass x volume-1]
AUCtau,ss	Area under the concentration-time curve from time zero to tau at steady state [mass x time x volume-1]
t1/2, ss	Elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve at steady state [time]
CL,ss/F	Apparent total plasma clearance of drug after oral administration at steady state [volume x time-1]
Vz,ss/F	Apparent volume of Distribution at the terminal elimination phase at steady state [volume]
RA*	Accumulation ratio calculated as AUCtau,ss/AUCtau

* Steady state is assumed to be reached by Cycle 1 Day 15.

3.7.2 Modeling of PK data

Selected primary PK parameters will be analyzed using mixed model to assess the dose proportionality, inter- and intra-individual variability, and steady-state attainment. If relevant, some of the analyses described below could be repeated by excluding patients receiving treatment in an inappropriate dosage or regimen as well as patients receiving concomitant therapies that may interact with LGX818 and MEK162 combination.

These analyses will be documented in separate reports.

Dose proportionality

Dose proportionality for LGX818 and MEK162 (and LEE011 if applicable) will be assessed for $AUC_{\tau,ss}$ and $C_{max,ss}$. An analysis of variance is performed on log-transformed parameters by using a mixed-effect model with patient as random effect and log(dose) as continuous fixed effect.

Dose prop01tionality will be assessed by estimating the model parameter for log(dose) as well as its 90% confidence interval, using the SOLUTION statement in SAS PROC MIXED.

The general SAS code for the model is the following:

```
PROC MIXED DATA=dataset METHOD=reml;
   CLASS Patient ID;
   MODEL log_PK_parameter = log_dose / ddfm=kr solution
                                       alpha=0.1 cl;
   RANDOM intercept/ patient= Patient ID;
RUN;
```

These analyses will be documented in separate repo1ts.

3.7.3 PK/efficacy analyses

Not applicable.

3.8 Biomarker assessments

3.8.1 Introduction

There may be circumstances when a decision is made to stop sample collection, or not peifonn or discontinue the analysis of blood/ archival tumor samples / fresh tumor biopsies / fine needle aspirates due to either practical or strategic reasons (e.g. issues related to the quality and/or quantity of the samples or issues related to the assay). Under such circumstances, the number of samples may be inadequate to perfonn a rigorous data analysis and the available data will only be listed and potentially summarized.

3.8.2 Outline of the data analysis

Biomarker analyses may be perfo1med after the completion of the end-of-study CSR and will be documented in separate repo1ts. These analyses may include but are not limited to the meta-analysis of data from this study combined with data from other studies or the analysis of biomarkers generated from samples collected during the study but analyzed after the database lock and completion of the CSR. The data analysis will be described in an addendum of the SAP or in a stand-alone analysis plan document, as appropriate.

3.8.3 Biomarker objectives

See Table 1-1.

3.8.4 Biomarker analysis data set

The Full Analysis Set will be used for all biomarker analysis. Unless othe1wise specified, all statistical analyses ofbiomarker data will be perfo1med on patients with biomarker data.

CCI

Definition of baseline and summarizing replicate data values

The Cycle 1 Day 1 assessment (pre-dose) will be used as the baseline value.

For assessments perfonned in tumor biopsies, fresh biopsy results will be used for baseline when both archived and fresh tumor samples are available.

When more than one biomarker data value are available for a patient at any time point, the mean of the replicate values will be used for all statistical analyses.

CCI [redacted]

CCI [redacted]

[redacted]

Table 3-7 Coding of compartment and staining level for IHC

Compartment	CELLOC1C	Staining level
cytoplasm	1	1+
	2	2+
	3	3+
membrane	4	1+
	5	2+
	6	3+
nucleus	7	1+
	8	2+
	9	3+

Derivation of Change and Percent Change Variables

Absolute and relative change (percent change) and fold change from baseline will be calculated for each patient and or treatment group.

Percent change is computed as ((visit i - baseline)/ baseline) * 100. To compute the average percent change from baseline is to compute the average expression level at each time point and then compute the percent change using the average values. Please note the number of patients for the average of percent change from baseline might vaiy due to potential missing values at respective time points.

3.8.5.2 IHC Summary statistics

For each IHC assay, the mean, standard deviation, %CV, median, minimum, maximum, inter-quaiiile range, number, and percent of the H-score values for each treatment group at each time point will be reported. Interquaiiile range is the number of data points between the 25th and 75th percentile.

The summa1y statistics will be repo1ied for each subcellular localization separately for the IHC assays where the H-score data is repo1ied by subcellular localization.

Summary statistics (mean, standard deviation, median, minimum, maximum) for change from baseline and/or percent change from baseline and the frequency and associated percentage of data points in each treatment group will be repo1ied.

The derived IHC H-scores and the individual components of the H-scores will be listed for each patient for all time points and ordered by the treatment group.

Table 3-8 Compartment and statistic for IHC

[redacted]

3.8.6.1 Handling of RT-PCR data

RT-PCR data will be repo1ied as PCR cycle (CT) values, which refer to the cycle number at which the amount of amplified target reaches a fixed threshold, or the threshold cycle for linear amplification. The higher the raw CT for a target gene, the weaker the level of expression for this gene. Raw CT (threshold cycle) results will be nonnalized. Nonnalization of the CT value, or .6.CT, is generally the average CT of the control genes minus the raw CT of the target gene. .6.CT is, by definition, on the log2 scale. No transformation will be applied to these data. Each raw CT value should be checked and if it exceeds the maximum reliable CT, then impute those values with the value of the maximum reliable CT.

Deriving change and percent change variables

For RT-PCR data, the fold change from baseline is calculated using the fo1mula 2Mcr, where .6..6.CT= post.6.CT- pre.6.CT.

3.8.6.2 RT-PCR Summary Statistics

Absolute and/or relative (% and/or fold) changes from baseline will be listed by patient and summarized using descriptive statistics by treatment group for baseline and all available post baseline visits for each biomarker. The descriptive statistics will include the mean, standard deviation, %CV, median, minimum, and maximum for each treatment group at each time point.

The raw CT values will also be listed by patient ordered by time point within treatment groups.

Table 3-9 CCI [redacted]

[redacted]

Terminology and definitions:

- Exon - The coding region of DNA
- Intron - The noncoding region of DNA
- Synonymous mutation - A change in an exon of DNA that does not cause a change to the resultant amino acid sequence.
- Nonsynonymous - A change in an exon of DNA that causes a change to the resultant amino acid sequence. Mutations may or may not produce discemable changes in the observable characteristics (phenotype) of an organism. Mutations play a pait in both nonnal and abnonnal biological processes, including evolution, cancer, and the development of the immune system.
- Mutation - a change in the genetic material of an individual
  - Point mutations - often caused by malfunction of DNA replication, exchange a single nucleotide for another.
    - Silent mutations - code for the same amino acid
    - Missense mutations - code for a different amino acid (nonsynonymous)
    - Nonsense - code for a "stop" and trnncate the resultant protein
  - Inse1tions - add one or more extra nucleotides into the DNA
  - Deletion - remove one or more nucleotides from the DNA
  - Fraineshift mutation - a mutation caused by an inse1tion or a deletion of a number of nucleotides not evenly divisible by 3 from a DNA sequence. This causes a completely different sequence of amino acids to be produced, rendering the original protein non-functional
- Amplifications - also known as gene duplications, lead to multiple copies of all chromosomal regions, increasing the dosage of the genes located within them
- Deletions - when lai·ge chromosomal regions are removed, leading to loss of the genes within those regions
- Translocations - interchange of genetic paits of different chromosomes

CCI [redacted]

3.8.7.2 Somatic Mutation summary statistics

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Results will be fmther categorized and summai·ized by the type of variant(s) present for each biomai·ker (copy number vai·iant, reaiTangement, sequence vai·iant). Exon mutations occuning

due to sequence variation will also be categorically summarized for each biomarker.If somatic mutations are analyzed in multiple samples from a patient (e.g. biopsy) fresh and/or frozen sample, the patient may be considered having a mutation if a mutation is observed in at least one of the samples.

All the mutation data will be listed for each patient ordered by treatment group.

3.8.8 Next Generation Sequencing

NGS data, also known as deep sequencing data will be generated on a panel of ~200 genes. As these data are extensive, complex and not fully understood, only the following markers of the panel will be shown, if the variant exists at a frequency of> 15% in the trial population. Note that a gene will be considered as amplified if six (6) or greater copies of a given gene are present in the sample. Loss will be defined if zero (0) copies of a given gene are present in the sample. Additional markers assessed using this technology may be described in separate analysis plan documentation and displayed external to the main study CSR.

CCI [redacted]

3.8.1O Relationship between biomarkers and PK parameters

If deem necessaiy, this paii of analysis may be described in sepai·ate analysis plan documentation and displayed external to the main study CSR.

3.8.11 Association between biomarkers and clinical outcome

If deem necessaiy, this paii of analysis may be described in separate analysis plan documentation and displayed external to the main study CSR.

4 Final Analysis Appendices

The appendices include a comprehensive list of tables listings, and figures to support the final CSR.

4.1.1 Tables

Table Number	Title	Analysis Set	Subset
Table 14.1.1.1.ld	Analysis set by treatment group/arm	Full Analysis Set	Phase lb/11, Triple Combination
Table 14.l.1.1.2d	Significant protocol deviations by treatment group/arm	Full Analysis Set	Phase lb/11, Triple Combination
Table 14.1.1.2.la	Patient disposition by treatment group	Full Analysis Set	Phase lb, Dual Combination

Table 14.1.1.2.1b	Patient disposition by arm	Full Analysis Set	Phase II, Dual Combination
Table 14.1.1.2.1d	Patient disposition by treatment group/arm	Full Analysis Set	Phase Ib/II, Triple Combination
Table 14.1.1.2.2a	Demographics and baseline characteristics by treatment group	Full Analysis Set	Phase Ib, Dual Combination
Table 14.1.1.2.2b	Demographics and baseline characteristics by arm	Full Analysis Set	Phase II, Dual Combination
Table 14.1.1.2.2d	Demographics and baseline characteristics by treatment group/arm	Full Analysis Set	Phase Ib/II, Triple Combination
Table 14.1.1.2.3d	Disease history by treatment group/arm	Full Analysis Set	Phase Ib/II, Triple Combination
Table 14.1.3.1d	Relevant medical histories, by primary system organ class, preferred term and treatment group/arm	Full Analysis Set	Phase Ib/II, Triple Combination
Table 14.1.3.2d	Current medical conditions, by primary system organ class, preferred term and treatment group/arm	Full Analysis Set	Phase Ib/II, Triple Combination
Table 14.1.4.1d	Prior antineoplastic therapy – Surgery, by treatment group/arm	Full Analysis Set	Phase Ib/II, Triple Combination
Table 14.1.4.2d	Prior antineoplastic therapy – Radiotherapy, by treatment group/arm	Full Analysis Set	Phase Ib/II, Triple Combination
Table 14.1.4.3d	Prior antineoplastic therapy – Medication, by treatment group/arm	Full Analysis Set	Phase Ib/II, Triple Combination
Table 14.1.4.4d	Prior antineoplastic therapy – Medication, by preferred term and treatment group/arm	Full Analysis Set	Phase Ib/II, Triple Combination
Table 14.1.4.5d	Prior Medications stopped prior to the start of study drug by preferred term, and treatment group/arm	Safety Set	Phase Ib/II, Triple Combination
Table 14.2.1.1d	Summary of best overall response as per local assessment by treatment group/arm	Full Analysis Set	Phase Ib/II, Triple Combination
Table 14.2.2.1b	Analysis of overall survival using Kaplan-Meier method by arm	Full Analysis Set	Phase II, Dual Combination
Table 14.2.2.1d	Analysis of overall survival using Kaplan-Meier method by arm	Full Analysis Set	Phase II, Triple Combination
Table 14.2.3.1b	Analysis of progression free survival as per local assessment using Kaplan-Meier method by arm	Full Analysis Set	Phase II, Dual Combination
Table 14.2.3.1d	Analysis of progression free survival as per local assessment using Kaplan-Meier method by arm	Full Analysis Set	Phase II, Triple Combination

Table 14.2.4.1d	Analysis of time to response as per local assessment using Kaplan-Meier method by arm	Full Analysis Set	Phase II, Triple Combination, Confirmed Responders
Table 14.2.5.1b	Analysis of duration of response as per local assessment using Kaplan-Meier method by arm	Full Analysis Set	Phase II, Dual Combination, Confirmed Responders
Table 14.2.5.1d	Analysis of duration of response as per local assessment using Kaplan-Meier method arm	Full Analysis Set	Phase II, Triple Combination, Confirmed Responders
Table 14.3.1.1.1d	Dose limiting toxicities occurring during the first 28 days by primary system organ class, preferred term and treatment group	Dose Determining Set	Phase Ib, Triple Combination
Table 14.3.1.2.1d	Treatment-emergent adverse events (all causality) by preferred term, maximum grade (grades 1-4) and treatment group/arm	Safety Set	Phase Ib/II, Triple Combination
Table 14.3.1.2.2a	Treatment-emergent adverse events (all causality) by preferred term, maximum grade (overall and grade 3/4) and treatment group	Safety Set	Phase Ib, Dual Combination
Table 14.3.1.2.2b	Treatment-emergent adverse events (all causality) by preferred term, maximum grade (overall and grade 3/4) and arm	Safety Set	Phase II, Dual Combination
Table 14.3.1.2.2d	Treatment-emergent adverse events (all causality by preferred term, maximum grade (overall and grade 3/4), and treatment group/arm	Safety Set	Phase Ib/II, Triple Combination
Table 14.3.1.2.3d	Serious adverse events (all causality) by preferred term, maximum grade (overall and grade 3/4), and treatment group/arm	Safety Set	Phase Ib/II, Triple Combination
Table 14.3.1.2.4a	Treatment-emergent adverse events leading to permanent study drug discontinuation (all causality) by preferred term, maximum grade (grades 1-4) and treatment group	Safety Set	Phase Ib, Dual Combination
Table 14.3.1.2.4b	Treatment-emergent adverse events leading to permanent study drug discontinuation (all causality) by preferred term, maximum grade	Safety Set	Phase II, Dual Combination

	(grades 1-4) and arm		
Table 14.3.1.2.4d	Treatment-emergent adverse events leading to permanent study drug discontinuation (all causality)by class, preferred term, maximum grade (grades 1-4) and treatment group/arm	Safety Set	Phase Ib/II, Triple Combination
Table 14.3.1.2.5d	Treatment-emergent adverse events requiring dose adjustment or delay (all causality) by preferred term, maximum grade (grades 1-4) and treatment group/arm	Safety Set	Phase Ib/II, Triple Combination
Table 14.3.1.2.6a	Treatment-emergent adverse events (all causality) occurring in >= 20% of patients by preferred term and treatment group	Safety Set	Phase Ib, Dual Combination
Table 14.3.1.2.6b	Treatment-emergent adverse events (all causality) occurring in >= 20% of patients by preferred term and arm	Safety Set	Phase II, Dual Combination
Table 14.3.1.2.6d	Treatment-emergent adverse events (all causality) occurring in >= 20% of patients by preferred term and treatment group/arm	Safety Set	Phase Ib/II, Triple Combination
Table 14.3.1.2.7a	Treatment-emergent adverse events (all causality) occurring in >= 5% of patients by preferred term, grade 3/4 and treatment group	Safety Set	Phase Ib, Dual Combination
Table 14.3.1.2.7b	Treatment-emergent adverse events (all causality) occurring in >= 5% of patients by preferred term, grade 3/4 and arm	Safety Set	Phase II, Dual Combination
Table 14.3.1.2.7d	Treatment-emergent adverse events (all causality) occurring in >= 5% of patients by preferred term, grade 3/4 and treatment group/arm	Safety Set	Phase Ib/II, Triple Combination
Table 14.3.1.3.1d	Treatment-emergent adverse events (treatment-related) by primary system organ class, preferred term, maximum grade (grades 1-4) and treatment group/arm	Safety Set	Phase Ib/II, Triple Combination
Table 14.3.1.3.2a	Treatment-emergent adverse events (treatment-related) by preferred term, maximum grade (overall and grade 3/4) and treatment group	Safety Set	Phase Ib, Dual Combination
Table 14.3.1.3.2b	Treatment-emergent adverse events	Safety Set	Phase II, Dual

	(treatment-related) by preferred term, maximum grade (overall and grade 3/4) and arm		Combination
Table 14.3.1.3.2d	Treatment-emergent adverse events (treatment-related) by preferred term, maximum grade (overall and grade 3/4) and treatment group/arm	Safety Set	Phase Ib/II, Triple Combination
Table 14.3.1.3.3a	Treatment-emergent adverse events (treatment related) occurring in >= 10% of patients by preferred term, maximum grade and treatment group	Safety Set	Phase Ib, Dual Combination
Table 14.3.1.3.3b	Treatment-emergent adverse events (treatment related) occurring in >= 10% of patients by preferred term, maximum grade and arm	Safety Set	Phase II, Dual Combination
Table 14.3.1.3.3d	Treatment-emergent adverse events (treatment related) occurring in >= 10% of patients by preferred term, maximum grade and treatment group/arm	Safety Set	Phase Ib/II, Triple Combination
Table 14.3.2.2.1a	Deaths, by preferred term and treatment group	Safety Set	Phase Ib, Dual Combination
Table 14.3.2.2.1b	Deaths, by preferred term and arm	Safety Set	Phase II, Dual Combination
Table 14.3.2.2.1d	Deaths, by preferred term and treatment group/arm	Safety Set	Phase Ib/II, Triple Combination
14.3.2.2.2a	Deaths, by primary reason and treatment group	Safety Set	Phase Ib, Dual Combination
14.3.2.2.2b	Deaths, by primary reason and arm	Safety Set	Phase II, Dual Combination
14.3.2.2.2d	Deaths, by primary reason and treatment group/arm	Safety Set	Phase Ib/II, Triple Combination
Table 14.3.4.1.1d	Hematology and coagulation shift table based on CTC grade by parameter and treatment group/arm	Safety Set	Phase Ib/II, Triple Combination
Table 14.3.4.1.2d	Hematology and coagulation shift table based on normal range by parameter and treatment group/arm	Safety Set	Phase Ib/II, Triple Combination
Table 14.3.4.1.3d	Biochemistry shift table based on CTC grade by parameter and treatment group/arm	Safety Set	Phase Ib/II, Triple Combination
Table 14.3.4.1.4d	Biochemistry shift table based on normal range by parameter and treatment group/arm	Safety Set	Phase Ib/II, Triple Combination
Table 14.3.4.1.5d	Urinary shift table based on CTC	Safety Set	Phase Ib/II, Triple

	grade by parameter and treatment group/arm		Combination
Table 14.3.4.1.6d	Urinary laboratory parameters without CTC grades by visit and treatment group/arm	Safety Set	Phase Ib/II, Triple Combination
Table 14.3.4.1.7d	Notable hepatic laboratory values by parameter and treatment group/arm	Safety Set	Phase Ib/II, Triple Combination
Table 14.3.5.2d	Notably abnormal vital signs by treatment group/arm	Safety Set	Phase Ib/II, Triple Combination
Table 14.3.6.2.1d	Notable ECG values per central analysis by treatment group/arm	Safety Set	Phase Ib/II, Triple Combination
Table 14.3.6.2.2d	New clinically meaningful ECG abnormalities per central analysis, by evaluation type and treatment group/arm	Safety Set	Phase Ib/II, Triple Combination
Table 14.3.6.2.3d	ECG shift table based on notable values by treatment group/arm	Safety Set	Phase Ib/II, Triple Combination
Table 14.3.7.1d	Left ventricular ejection fraction worst CTC grade by treatment group/arm	Safety Set	Phase Ib/II, Triple Combination
Table 14.3.8.1d	WHO/ECOG performance status by treatment group/arm	Safety Set	Phase Ib/II, Triple Combination
Table 14.4.1.1a	Duration of exposure to study drug by treatment group	Safety Set	Phase Ib, Dual Combination
Table 14.4.1.1b	Duration of exposure to study drug by arm	Safety Set	Phase II, Dual Combination
Table 14.4.1.1d	Duration of exposure to study drug by treatment group/arm	Safety Set	Phase Ib/II, Triple Combination
Table 14.4.1.2d	Dose reductions of study treatment by treatment group/arm	Safety Set	Phase Ib/II, Triple Combination
Table 14.4.1.3d	Dose delays of study treatment by treatment group/arm	Safety Set	Phase Ib/II, Triple Combination
Table 14.4.1.4a	Summary statistics of exposure of study treatment by treatment group	Safety Set	Phase Ib, Dual Combination
Table 14.4.1.4b	Summary statistics of exposure of study treatment by arm	Safety Set	Phase II, Dual Combination
Table 14.4.1.4c	Summary statistics of exposure of study treatment by treatment group/arm	Safety Set	Phase Ib/II, Dual Combination
Table 14.4.1.4d	Summary statistics of exposure of study treatment by treatment group/arm	Safety Set	Phase Ib/II, Triple Combination
Table 14.4.2.1d	Concomitant medications and significant non-drug therapies started prior to the start of study drug by	Safety Set	Phase Ib/II, Triple Combination

	preferred term and treatment group/arm		
Table 14.4.2.2d	Concomitant medications and significant non-drug therapies started after the start of study drug by preferred term and treatment group/arm	Safety Set	Phase Ib/II, Triple Combination
Table 14.4.2.3a	Antineoplastic therapy since discontinuation of study drug by preferred term and treatment group	Safety Set	Phase Ib, Dual Combination
Table 14.4.2.3b	Antineoplastic therapy since discontinuation of study drug by preferred term and arm	Safety Set	Phase II, Dual Combination
Table 14.4.2.3d	Antineoplastic therapy since discontinuation of study drug by preferred term and treatment group/arm	Safety Set	Phase Ib/II, Triple Combination
Table 14.4.4.1.1	Summary of encorafenib concentrations by treatment group	Full Analysis Set	Phase Ib
Table 14.4.4.1.2	Summary of encorafenib concentrations by arm	Full Analysis Set	Phase II
Table 14.4.4.2.1	Summary of binimetinib concentrations by treatment group	Full Analysis Set	Phase Ib
Table 14.4.4.2.2	Summary of binimetinib concentrations by arm	Full Analysis Set	Phase II
Table 14.4.4.3.1	Summary of AR00426032 concentrations by treatment group	Full Analysis Set	Phase Ib
Table 14.4.4.3.2	Summary of AR00426032 concentrations by arm	Full Analysis Set	Phase II
Table 14.4.4.4.1	Summary of ribociclib concentrations by treatment group	Full Analysis Set	Phase Ib, Triple Combination
Table 14.4.4.4.2	Summary of ribociclib concentrations by arm	Full Analysis Set	Phase II, Triple Combination
Table 14.4.4.5.1	Summary of LEQ803 concentrations by treatment group	Full Analysis Set	Phase Ib, Triple Combination
Table 14.4.4.5.2	Summary of LEQ803 concentrations by arm	Full Analysis Set	Phase II, Triple Combination
Table 14.4.5.1.1	Summary of PK parameters of primary interest for encorafenib by profile day and treatment group	Full Analysis Set	Phase Ib
Table 14.4.5.1.2	Summary of PK parameters of primary interest for encorafenib by profile day and arm	Full Analysis Set	Phase II
Table 14.4.5.2.1	Summary of PK parameters of primary interest for binimetinib by	Full Analysis Set	Phase Ib

	profile day and treatment group		
Table 14.4.5.2.2	Summary of PK parameters of primary interest for binimetinib by profile day and arm	Full Analysis Set	Phase II
Table 14.4.5.3.1	Summary of PK parameters of primary interest for AR00426032 by profile day and treatment group	Full Analysis Set	Phase Ib
Table 14.4.5.3.2	Summary of PK parameters of primary interest for AR00426032 by profile day and arm	Full Analysis Set	Phase II
Table 14.4.5.4.1.1	Summary of PK parameters of primary interest for ribociclib by profile day and treatment group	Full Analysis Set	Phase Ib, Triple Combination
Table 14.4.5.4.1.2	Summary of PK parameters of primary interest for ribociclib by profile day and arm	Full Analysis Set	Phase II, Triple Combination
Table 14.4.5.4.2.1	Summary of PK parameters of primary interest for LEQ803 by profile day and treatment group	Full Analysis Set	Phase Ib, Triple Combination
Table 14.4.5.4.2.2	Summary of PK parameters of primary interest for LEQ803 by profile day and arm	Full Analysis Set	Phase II, Triple Combination
Table 14.4.5.5.1	Summary of PK parameters of secondary interest for encorafenib by profile day and treatment group	Full Analysis Set	Phase Ib
Table 14.4.5.5.2	Summary of PK parameters of secondary interest for encorafenib by profile day and arm	Full Analysis Set	Phase II
Table 14.4.5.6.1	Summary of PK parameters of secondary interest for binimetinib by profile day and treatment group	Full Analysis Set	Phase Ib
Table 14.4.5.6.2	Summary of PK parameters of secondary interest for binimetinib by profile day and arm	Full Analysis Set	Phase II
Table 14.4.5.7.1	Summary of PK parameters of secondary interest for AR00426032 by profile day and treatment group	Full Analysis Set	Phase Ib
Table 14.4.5.7.2	Summary of PK parameters of secondary interest for AR00426032 by profile day and arm	Full Analysis Set	Phase II
Table 14.4.5.8.1.1	Summary of PK parameters of secondary interest for ribociclib by profile day andv treatment group	Full Analysis Set	Phase Ib, Triple Combination
Table 14.4.5.8.1.2	Summary of PK parameters of secondary interest for ribociclib by	Full Analysis Set	Phase II, Triple Combination

	profile day and arm		
Table 14.4.5.8.2.1	Summary of PK parameters of secondary interest for LEQ803 by profile day and treatment group	Full Analysis Set	Phase Ib, Triple Combination
Table 14.4.5.8.2.2	Summary of PK parameters of secondary interest for LEQ803 by profile day and arm	Full Analysis Set	Phase II, Triple Combination
Table 14.4.5.9.1	Dose proportionality analysis	Full Analysis Set	Phase Ib/II
Table 14.4.5.10.1	Statistical Analysis of Accumulation for Encorafenib: Cycle 1	Full Analysis Set	
Table 14.4.5.10.2	Statistical Analysis of Accumulation for Binimetinib: Cycle 1	Full Analysis Set	
Table 14.4.5.10.3	Statistical Analysis of Accumulation for AR00426032: Cycle 1	Full Analysis Set	
Table 14.4.5.10.4	Statistical Analysis of Accumulation for Ribociclib: Cycle 1	Full Analysis Set	Triple Combination
Table 14.4.5.10.5	Statistical Analysis of Accumulation for LEQ803: Cycle 1	Full Analysis Set	Triple Combination
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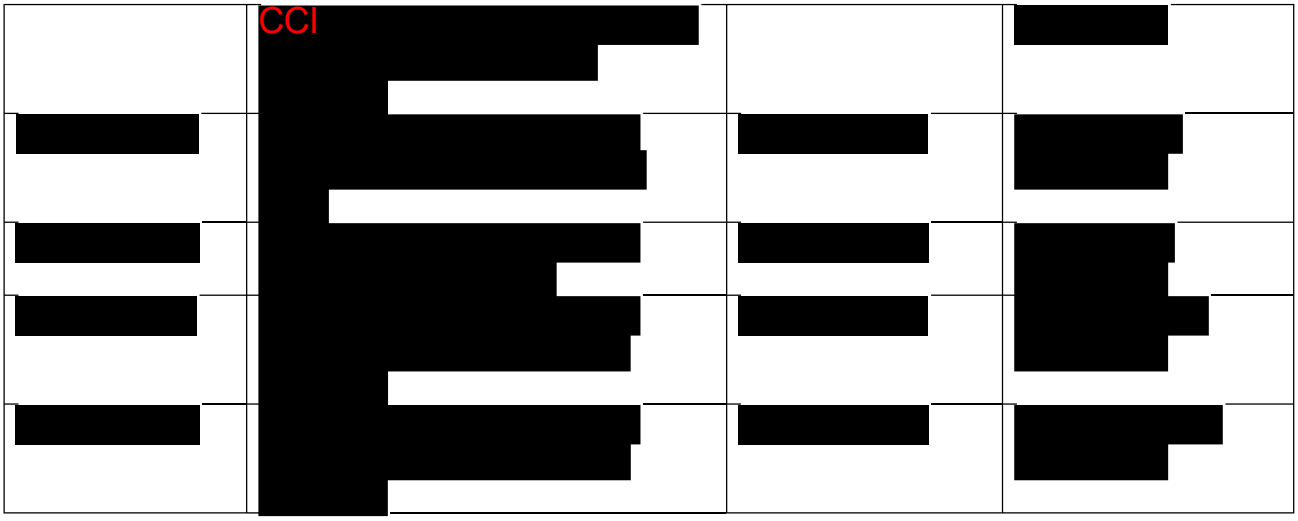

4.1.2 Listings

Listing Number	Title	Analysis Set	Subset
Listing 16.2.1.1.1	Analysis sets	Full Analysis Set	
Listing 16.2.1.1.2	Dose level and analysis sets	Full Analysis Set	
Listing 16.2.1.2	Treatment and study completion by treatment	Full Analysis Set	
Listing 16.2.2.1	Significant protocol deviations by treatment	Full Analysis Set	
Listing 16.2.2.2	Study disruption due to COVID-19	Full Analysis Set	
Listing 16.2.4.1.1	Patient baseline demographics by treatment	Full Analysis Set	
Listing 16.2.4.1.2	Baseline disease diagnosis by treatment	Full Analysis Set	
Listing 16.2.5.1.1	Dosage administration record by treatment – encorafenib	Safety Set	
Listing 16.2.5.1.2	Dosage administration record by treatment – binimetinib	Safety Set	
Listing 16.2.5.1.3	Dosage administration record by treatment – ribociclib	Safety Set	Triple Combination
Listing 16.2.6.1	Overall response per patient by assessment and treatment	Full Analysis Set	
Listing 16.2.7.1	Adverse events by treatment	Full Analysis Set	
Listing 16.2.7.2	Dose limiting toxicities (DLT) by treatment group	Full Analysis Set	Triple Combination
Listing 16.2.8.1.1	Hematology: primary hematology parameters by treatment group	Full Analysis Set	
Listing 16.2.8.1.2	Hematology: WBC and	Full Analysis Set	

	differentials by treatment		
Listing 16.2.8.1.3	Hematology: coagulation parameters by treatment	Full Analysis Set	
Listing 16.2.8.1.4	Hematology: others by treatment	Full Analysis Set	
Listing 16.2.8.1.5	Biochemistry: liver function test and related variables by treatment	Full Analysis Set	
Listing 16.2.8.1.6	Biochemistry: renal variables by treatment	Full Analysis Set	
Listing 16.2.8.1.7	Biochemistry: electrolytes by treatment group	Full Analysis Set	
Listing 16.2.8.1.8	Biochemistry: others by treatment	Safety Set	
Listing 16.2.8.1.9	Urinary: urinalysis by treatment	Full Analysis Set	
Listing 16.2.8.1.10	Thyroid function tests, by treatment group	Full Analysis Set	
Listing 16.2.8.1.11	Pregnancy test results by treatment	Full Analysis Set	
Listing 16.2.8.1.12	Patients with newly occurring notable hepatic laboratory values, by treatment	Safety Set	
Table 14.3.2.2.1	Deaths during treatment by treatment	Full Analysis Set	

4.1.3 Figures

Figure Number	Title	Analysis Set	Subset
Figure 14.2.1.1b	Best percentage change from baseline in sum of longest diameters and best overall response as per local assessment by arm	Full Analysis Set	Phase II, Dual Combination
Figure 14.2.1.1d	Best percentage change from baseline in sum of longest diameters and best overall response as per local assessment by treatment group/arm	Full Analysis Set	Phase Ib/II, Triple Combination
Figure 14.2.1.2b	Kaplan-Meier plot of progression-free survival as per local assessment by arm	Full Analysis Set	Phase II, Dual Combination
Figure 14.2.1.2d	Kaplan-Meier plot of progression-free survival as per local assessment by arm	Full Analysis Set	Phase Ib/II, Triple Combination
Figure 14.4.4.1a	Mean Plasma Concentration-time Profiles for Encorafenib: Cycle 1	Full Analysis Set	Phase Ib
Figure 14.4.4.1b	Mean Plasma Concentration-time Profiles for Encorafenib: Cycle 1	Full Analysis Set	Phase II
Figure 14.4.4.2a	Mean Plasma Concentration-time Profiles for Binimetinib: Cycle 1	Full Analysis Set	Phase Ib

Figure 14.4.4.2b	Mean Plasma Concentration-time Profiles for Binimetinib: Cycle 1	Full Analysis Set	Phase II
Figure 14.4.4.3a	Mean Plasma Concentration-time Profiles for AR00426032: Cycle 1	Full Analysis Set	Phase Ib
Figure 14.4.4.3b	Mean Plasma Concentration-time Profiles for AR00426032: Cycle 1	Full Analysis Set	Phase II
Figure 14.4.4.4a	Mean Plasma Concentration-time Profiles for Ribociclib: Cycle 1	Full Analysis Set	Phase Ib, Triple Combination
Figure 14.4.4.4b	Mean Plasma Concentration-time Profiles for Ribociclib: Cycle 1	Full Analysis Set	Phase II, Triple Combination
Figure 14.4.4.5a	Mean Plasma Concentration-time Profiles for LEQ803: Cycle 1	Full Analysis Set	Phase Ib, Triple Combination
Figure 14.4.4.5b	Mean Plasma Concentration-time Profiles for LEQ803: Cycle 1	Full Analysis Set	Phase II, Triple Combination
Figure 14.5.1	Duration of exposure and RECIST status by mutation status	Full Analysis Set	Phase Ib

5 References

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Neuenschwander, Branson and Gsponer (2008). Critical aspects of the Bayesian approach to phase I cancer trials, *Statistics in medicine* 27, 2420-2439

6. Change control

Version	Date	Change
Draft V1.0	04-JUN-13	Original version
Draft V1.1-1.7	06-JAN-14 to 18-JUN-14	Changes due to CTT review and additional minor changes
Final V2.0	01-JUN-15	Changes due to protocol amendment
Draft V2.1	20-SEP-22	Changes due to final analysis.
Draft V2.2	20-JAN-23	Changes to adverse event analyses to remove summary by primary system organ class to multiple tables and to adjust percentage thresholds