Clinical Development & Medical Affairs

LGX818/MEK162

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

Document type	Amended Protocol Version
EUDRACT number	2011-005875-17
Version number	10
Development phase	Ib/II
Document status	Final
Release date	15-March-2021

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List of abbreviations

AE	Adverse event
AKT/PKB	See PKB
ALT/SGPT	Alanine aminotransferase/glutamic pyruvic transaminase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST/SGOT	Aspartate aminotransferase/glutamic oxaloacetic transaminase
ATP	Adenosine triphosphate
AUC	Area under the curve
AV	Atrioventricular
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
BUN	Blood urea nitrogen
CHF	Congestive heart failure
CK/CPK	Creatine kinase / Creatine phosphokinase
CL	Clearance
Cmax	Maximum plasma concentration
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CR	Complete response
CRC / mCRC	Colorectal cancer / metastatic CRC
CrCl	Creatinine clearance
CRF	Case report form
CRO	Contract research organization
CSF	Clinical service form
CSR	Central serous retinopathy / Clinical study report
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CV	Coefficient of variation
CYP	Cytochrome P450
DCR	Disease control rate
DDS	Dose determining set
DILI	Drug-induced liver injury
DLT	Dose limiting toxicity
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
DOR	Duration of response
DS&E	Drug safety and epidemiology
DTIC	Dacarbazine
EC	Ethics committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern cooperative oncology group

eCRF	Electronic case report/record form
EDC	Electronic data capture
EDP	Exposure during pregnancy
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EMEA	European Medicines Evaluation Agency
EOT	End of treatment
ErbB	Erythroblastic leukemia viral oncogene
ERG	Electroretinogram
ERK	Extracellular signal regulated kinase
EUA	Emergency use authorization
EWOC	Escalation with overdose control
FAS	Full analysis set
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose positron emission tomography
FFPE	Formalin-fixed paraffin embedded
FMI	Final market image
FU	Follow-up
GCP	Good clinical practice
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GLP	Good laboratory practice
GTPase	Guanosine-5'-triphosphatase
hCG	Human chorionic gonadotropin
HDL	High-density lipoprotein
HDPE	High-density polyethylene
hERG	Human ether-à-go-go related gene
HFSR	Hand foot skin reaction
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HR	Heart rate
hr(s)	Hour(s)
i.v.	Intravenous
IB	Investigator brochure
IC50	Inhibition concentration 50%
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Institutional ethics committee
IHC	Immunohistochemistry
ILD	Interstitial lung disease
IN	Investigator notification
INR	International normalized ratio
IOP	Intra ocular pressure
IRB	Institutional review board
IUD	Intra-uterine device
IUS	Intra-uterine system
KA	Keratoacanthomas

KRAS	V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
LC/MS/MS	Liquid chromatography tandem mass spectrometry
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LFT	Liver function test
LIMS	Laboratory information management system
LLN	Lower limit of normal
LLOQ	Lower limit of quantitation
LPLT	Last patient last treatment
LPLV	Last patient last visit
LVEF	Left ventricular ejection fraction
MAPK	Mitogen-activated protein kinase
MedDRA	Medical dictionary for regulatory activities
MEK	Mitogen-activated protein kinase kinase
MIA	Melanoma inhibitory activity
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multi-gated acquisition scan
NaF PET	Sodium fluoride positron emission tomography
NCI	National Cancer Institute
NRAS	Neuroblastoma RAS viral oncogene homolog
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
OAT	Organic anion transporter
OCT	Optical coherence tomography / organic cation transporter
ORR	Overall response rate
OS	Overall survival
PD	Pharmacodynamic / Progression of disease
PFS	Progression free survival
P-gp	Permeability glycoprotein
PHI	Protected health information
Pi	Inorganic phosphorus/phosphate
PI3K	Phosphatidylinositol 3' kinase
PIK3CA	Phosphatidylinositol 3' kinase catalytic alphapolypeptide
PK	Pharmacokinetic
PKB	Protein kinase B (also known as AKT)
PLT	Platelets
po	Per os/by mouth/orally
PPS	Per protocol set
PR	Partial response
PS	Performance status
PT	Prothrombin time
PTEN	Phosphatase and tensin homolog
PVC	Premature ventricular contraction
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 (RAP) (i.e. regulatory document which provides evidence of preplanned analyses)
RAS	Rat sarcoma viral oncogene homologue
Rb	Retinoblastoma protein
RBC	Red blood cells
REB	Research ethics board
RECIST	Response evaluation criteria in solid tumors
RP2D	Recommended Phase II dose
RT-PCR	Reverse-transcriptase polymerase chain reaction
RVO	Retinal vein occlusion
SAE	Serious adverse event
SARS-CoV2	Severe acute respiratory syndrome coronavirus 2
SCC	Squamous cell carcinoma
SD	Stable disease
SEC	Study evaluation completion
SUSAR	Suspected unexpected serious adverse reactions
T/C	Tumor volume over control volume
T1/2	Terminal elimination half-life
TBili	Total bilirubin
tCa	Total calcium
TEN	Toxic Epidermal Necrolysis
TGI	Tumor growth inhibition
TKIs	Tyrosine kinase inhibitors
tmax	Time to reach maximum plasma concentration
TSH	Thyroid-stimulating hormone
TTP	Time to progression
ULN	Upper limit of normal
US	United States
Vss	Volume of distribution at steady state
WBC	White blood cells
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study.
Baseline	Baseline (i.e. Screening/baseline) assessments are the most recent assessments which are performed prior to the first administration of study treatment.
Cycle	Number and timing or recommended repetitions of therapy are usually expressed as number of days (i.e. every 28 days)
Dose cohort	A group of newly enrolled patients treated at a specific dose and regimen at the same time.
Dose level	The dose of drugs given to the patient.
Enrollment	Point/time of patient entry into the study; the point at which informed consent is obtained and patient meets all inclusion and none of the exclusion criteria.
Patient number	A unique identifier number (consisting of the center number and patient number) assigned to each patient who enrolls in the study.
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening/baseline, treatment, washout, etc.
Phase II	Selected group of patients enrolled during the Phase II part of the study.
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, completion of treatment, etc.
Study evaluation completion (SEC)	Point/time which marks the end of study for an individual patient. Survival continues beyond SEC.
Study treatment	Drugs whose properties are being tested in combination in the study (i.e. study drugs or study drugs combination).
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason (i.e. end of treatment).
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

Amendment 10

Amendment rationale

In 2018, LGX818 (encorafenib) 450 mg orally QD, in combination with MEK162 (binimetinib) 45 mg orally BID, received marketing approval in several jurisdictions, including the United States and the European Union, for the treatment of patients with unresectable or metastatic *BRAF* V600-mutant melanoma. This approval was based on the ongoing randomized Phase III COLUMBUS Study (CMEK162B2301).

At this stage of the trial, the safety and efficacy of the dual combination of LGX818/MEK162 and the triple combination of LGX818/MEK162/LEE011 have been thoroughly assessed. Therefore, Amendment 10 allows for patients still on treatment to be monitored in a manner that is consistent with local standard-of-care practice. In addition, post-treatment disease progression follow-up (if applicable) and/or survival follow-up (including documentation of subsequent antineoplastic therapies) will no longer be performed for patients in the Phase II part of the study.

As of the date of this amendment, 10 patients are still on study treatment, with 5 patients receiving the dual combination (LGX818/MEK162) and 5 patients receiving the triple combination (LGX818/MEK162/LEE011). In addition, 20 patients enrolled in the Phase II part of the study who have discontinued study treatment are still in the disease progression/survival follow-up period, with 12 patients who had received the dual combination (LGX818/MEK162) and 8 patients who had received the triple combination (LGX818/MEK162/LEE011).

The purpose of this amendment is to:

1. To modify the frequency of assessments to allow for patients still on treatment to be monitored in a manner that is consistent with local standard-of-care practice.
2. To discontinue post-treatment disease progression follow-up (if applicable) and/or survival follow-up (including documentation of subsequent antineoplastic therapies) for patients in the Phase II part of the study.
3. To revise the Adverse Event and Serious Adverse Events sections to align with Pfizer standard operating procedures, with SAE reporting directly to Pfizer Safety;
4. To reflect the dose modification and management related to MEK162- and LEE011-emerging ILD/pneumonitis and LEE011-emerging Toxic Epidermal Necrolysis (TEN);

Changes to the Protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol.

Section 1.2

- Section 1.2.1: addition of nomenclatures used for LGX818;
- Section 1.2.2: addition of nomenclatures used for MEK162;

- Section 1.2.3: addition of nomenclatures used for LEE0l 1 and references to the cmTent LEE0l 1 Investigator's Brochure.

Section 4

- Section 4.1 Description of study design: Section was updated to add text regarding study evaluation completion and discontinuation of post-treatment disease progression follow-up (if applicable) and/or smvival follow-up (including documentation of subsequent antineoplastic therapies).
- Section 4.3 Definition of end of study: The definition for the end of study was updated.

Section 6

- Section 6.3 Dose modifications: Table 6-4: Added dose modifications related to ILD/pneumonitis based upon MEK162 and LEE0ll prescribing info1mation and for TEN based upon LEE011 prescribing info1mation. In addition, clarifications were added to dose modifications related to ECG QTcF inte1val prolonged.
- Section 6.4.1: Pennitted concomitant therapy: Clarification that COVID-19 vaccination may be administered.

Section 7

- Section 7.1 Study flow and visit schedule: added new table outlining the visit evaluation schedule for patients (Table 7-2) along with references to Table 7-2 (multiple locations). This section was updated to allow for patients to be monitored in a manner that is consistent with local standard-of-care practice for patients with advanced or metastatic melanoma or advanced CRC.
- Section 7.1.3 Treatment period: This section was updated to indicate patients are to be monitored in a manner that is consistent with local standard-of-care practice.
- Section 7.1.4 End of treatment visit, including prematme withdrawal and study completion visit: This section was updated to define study completion for individual patients and to discontinue post-treatment disease progression follow-up (if applicable) and/or smvival follow-up (including documentation of subsequent antineoplastic therapies) for patients in the Phase II paiis of the study.
- Section 7.1.5.2 Disease progression follow-up period: This section was updated to discontinue post-treatment disease progression follow-up (if applicable) for patients in the Phase II paiis of the study.
- Section 7.1.5.3 Smvival follow-up period: This section was updated to discontinue smvival follow-up (including documentation of subsequent antineoplastic therapies) for patients in the Phase II paiis of the study.
- Section 7.2.2 Safety and tolerability assessments and subsections: These sections were updated to indicate assessments will be perfonned as outlined in Table 7-2.
- CCI [redacted]

Section 8

The following sections were revised or added to align with Pfizer standard operating procedures:

- Section 8.1 Adverse Events and Serious Adverse Events.
- Section 8.1.1 Time Period and Frequency for Collecting AE and SAE Information: Previous Section Definitions and Reporting was deleted. Definitions of AE and SAEs can be found in Section 14.7 Appendix 7.
- Section 8.1.1.1 Reporting SAEs to Pfizer Safety.
- Section 8.1.1.2 Recording Nonserious AEs and SAEs on the CRF.
- Section 8.1.2 Methods of Detecting AEs and SAEs.
- Section 8.1.3 Follow-up of AEs and SAEs
- Section 8.1.4 Regulatory Reporting Requirements for SAEs
- Section 8.1.5 Exposure During Pregnancy or Breastfeeding and Occupational Exposure
- Section 8.1.5.1 Exposure During Pregnancy
- Section 8.1.5.2 Exposure During Breastfeeding
- Section 8.1.5.3 Occupational Exposure
- Section 8.1.6 Cardiovascular and Death Events
- Section 8.1.7 Disease-Related Events and/or Disease Related Outcomes Not Qualifying as AEs or SAEs
- Section 8.1.8 Adverse Events of Special Interest
- Section 8.1.8.1 Lack of Efficacy
- Section 8.1.9 Medical Device Deficiencies
- Section 8.1.10 Medication Errors
- Section 8.2 Treatment Overdose: Section added to align with Pfizer standard operating procedures. Previous Section 8.2 *Serious Adverse Events* was revised and moved to Section 8.1 *Adverse Events and Serious Adverse Events*.

Section 11

- Section 11.6 Data Sharing: Added section to align with Pfizer standard operating procedures.

Appendices

The following Sections and Appendices were added to align with Pfizer standard operating procedures.

- Section 14.7 Appendix 7: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.
- Section 14.8 Appendix 8: Liver Safety: Suggested Actions and Follow-up Assessments.
- Section 14.9 Appendix 9 ECG Findings of Potential Clinical Concern.
- Section 14.10 Appendix 10: Alternative Measures During Public Emergencies

Amendment 9

Amendment rationale

As of the release date of this amendment, 20 patients in the CMEK162X2110 study (11 in Phase Ib/II dual combination [LGX818 + MEK162] and 9 patients in the Phase Ib/II triple combination [LGX818/MEK162/LEE011]) were continuing to derive benefit from study treatment. In order to minimize the burden on the patients and to reduce their radiation exposure, this amendment allows the frequency of tumor assessments in all continuing patients to be reduced to every 8-12 weeks based on Investigator discretion. Patients (both dual- and triple-combination patients) may be transitioned to this less frequent imaging schedule once they have completed ≥ 24 months of study treatment (Cycle 25 Day 1 onward). In order to more fully assess the safety and efficacy in all patients following prolonged treatment, the definition of end of study has been revised to be when all patients in Phase II have died or when all patients have completed study evaluation completion (SEC), or have been lost to follow-up or withdrew consent, whichever occurs first.

In addition, this protocol is also being amended to change the frequency and type of ophthalmologic examinations. In a separate Phase 3 study (CMEK162B2301; ClinicalTrials.gov identifier NCT01909453) in patients with *BRAF* V600-mutant melanoma treated with the combination of LGX818 (450 mg once daily [QD]) plus MEK162 (45 mg twice daily [BID]), the median time to onset of retinopathy (all grades) was 1.2 months, and there were no patients with a new onset event after 24 months. No patients treated with the combination LGX818 (450 mg once daily [QD]) plus MEK162 (45 mg BID) experienced a retinal vein occlusion (RVO) event. Based on these findings, and in order to minimize the burden on both dual- and triple-combination patients who continue to derive benefit from study treatment, this amendment allows patients who have been receiving study treatment ≥ 24 months (Cycle 25 Day 1 onwards) who have not had a retinal adverse event (AE) to be evaluated for visual acuity at each scheduled patient visit and at the End of Treatment. Patients with changes in visual acuity or other ocular complaints at any time on study should be referred to an ophthalmologist for full ophthalmic examination.

This protocol is also being amended to remove the collection of an unscheduled PK sample taken in the event of a QTcF change from baseline > 60 msec, or a new absolute QTcF interval ≥ 501 msec. This is being done to reduce burden on the patients and the sites and would not significantly contribute to the PK data already accumulated on this study. Additionally, collection of the PK data upon a specified DLT or QT prolongation provides minimal actionable information to the investigator in the event these adverse events happen due to the processing time of PK samples.

Additionally, the protocol is being amended to remove the fasting requirement for both the dual- and triple-combination treatments. Based on results of two dedicated clinical pharmacology studies, both binimetinib (CMEK162A2103) and encorafenib (ARRAY-818-102) exposures were unaffected by food, suggesting patients can take the dual-combination treatment with or without food. Since the package insert for LEE011 (ribociblib) indicates patients can also take LEE011 with or without food, the fasting restriction was removed for the triple combination.

Furthermore, the protocol is being amended to remove the restriction of agents that elevate gastric pH, including antacids, proton pump inhibitors and H2-antagonists. Based on the results of a dedicated clinical pharmacology study, both binimetinib and encorafenib (ARRAY-162-105) exposures were unaffected by rabeprazole, a proton pump inhibitor, suggesting patients can take the dual-combination treatment with agents that elevate gastric pH.

Additional revisions have been made to sections of the protocol that are specific to the triple-combination arms with LEE011 in order to reflect recent clinical development changes pertaining to dose modification for LEE011.

In Appendix 4 of the protocol, language was added to Table 14-9 through Table 14-11 stating that the substrates in the tables do not represent an exhaustive list of substrates, inducers or inhibitors.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol.

- 4.3 Definition of end of study, 7.1.5.2 Disease progression follow-up period, and 7.1.5.3 Survival follow-up period.

  The above section was amended to clearly define the end of study.

- 6.1.1.1 Dose Administration of dual combination (LGX818 and MEK162) and 6.1.1.2 Dose Administration of triple combination (LGX818 and MEK162 and LEE011)

  The above sections were modified to allow patients to take either the dual combination (LGX818 and MEK162) or the triple combination (LGX818 and MEK162 and LEE011) with or without food.

- 6.2.5 Definitions of dose limiting toxicities; 6.3.1 Dose modification and dose delay

  The above sections were modified to reflect the change in the CTCAE version to be used for data analysis, from version 4.0 to version 4.03. The CTCAE version 4.03 was implemented before patients were enrolled to the study.

- Table 6-4 Criteria for interruption and re-initiation of LGX818 and MEK162 or LGX818 and MEK162 and LEE011 treatment;

  Table 6-4 was amended to provide detailed dose modification guidelines for patients undergoing treatment with the dual combination (LGX818 and MEK162) and the triple combination (LGX818 and MEK162 and LEE011).

- 6.3.2 was Section 6.2.6.2 – Follow-up evaluations for appearance of central serous retinopathy (CSR)

  The above section was amended to include information on the ophthalmic examination schedule for patients without a retinal AE.

- 6.3.3 Additional follow-up for hepatic toxicities in patients receiving LEE011

  The above section was amended to provide the specifics of hepatic toxicity monitoring, and add additional guidance for the investigation of potential hepatic toxicity.

- 6.4.1 Permitted concomitant therapy

  The above section was revised to add a subsection with guidance on the use of corticosteroids while on study.

- 6.4.2 Permitted concomitant therapy requiring caution and/or action for LGX818 and MEK162

  The above section was revised to include drug-drug interaction risks of clinical relevance.

- 6.4.2.1 Additional permitted concomitant therapy requiring caution and/or action for addition of LEE011 in the triple combination

  The above section was amended to add additional guidance on the use of concomitant therapy requiring caution for patients during treatment with the triple combination LGX818 and MEK162 and LEE011.

- 6.4.3.1 Additional prohibited concomitant therapy for addition of LEE011 in the triple combination

  The above section was amended to add additional guidance on prohibited concomitant therapy for patients during treatment with the LGX818/MEK162/LEE011 triple combination.

- Table 7-1 Visit evaluation schedule; 7.1 Study flow and visit schedule.

  The above table was amended in the row for ophthalmologic examination to allow patients who have been on the LGX818/MEK162 dual-combination and LGX818/MEK162/LEE011 triple-combination treatment for ≥ 24 months (Cycle 25 Day 1 onward) without a retinal AE to be evaluated only for visual acuity at each scheduled patient visit and at the End of Treatment visit. These patients are also required to have a full ophthalmic examination if clinically indicated and at the End of Treatment visit.

  The above table was also amended in the row for tumor evaluation per the Response Criteria in Solid Tumors (RECIST) by computed tomography (CT)/magnetic resonance imaging (MRI) to allow patients who have been on the LGX818/MEK162 dual- combination and LGX818/MEK162/LEE011 triple-combination treatment for ≥ 24 months to have CT/MRI scans every 8-12 weeks (± 7 days) instead of every 8 weeks. Also, this row was amended to allow patients who have been on either combination treatment for ≥ 24 months and then discontinue study treatment for any reason other than disease progression to have CT/MRI scans every 8-12 weeks (± 7 days) instead of every 8 weeks.

The above table was amended to add the recommendation following the 30-day follow-up period and when clinically appropriate for patients to be monitored with physical examinations, dermatological examinations and chest CT scans for cutaneous and non-cutaneous secondary malignancies for up to 6 months after the last encorafenib dose or until initiation of another antineoplastic therapy.

The above section was amended to reflect the changes in the tumor evaluation schedule described as for Table 7-1.

- 7.1.5.2 Disease progression follow-up period

  The above section was amended for tumor evaluation per RECIST by CT/MRI to allow patients who have been on the LGX818/MEK162 dual-combination or LGX818/MEK162/LEE011 triple-combination treatment for ≥ 24 months and then discontinue study treatment for any reason other than disease progression to have CT/MRI scans every 8-12 weeks (± 7 days) instead of every 8 weeks.

- 7.1.5.3 Survival follow-up period

  The above section has been modified to remove the 18-month follow-up.

- 7.2.1 Efficacy assessments

  The above section was amended for tumor evaluation per RECIST by CT/MRI to allow patients who have been on the LGX818/MEK162 dual-combination treatment or LGX818/MEK162/LEE011 triple combination for ≥ 24 months to have CT/MRI scans every 8-12 weeks (± 7 days) instead of every 8 weeks until disease progression. The above section was also amended for tumor evaluation per RECIST by CT/MRI to allow patients who have been on the dual- or triple-combination treatment for ≥ 24 months and then discontinue study treatment for any reason other than disease progression to have CT/MRI scans every 8-12 weeks (± 7 days) instead of every 8 weeks. The above section was also amended to remove the note that all radiological assessments are to be centrally collected by an imaging CRO, and to remove the note that such assessments may be assessed centrally if deemed necessary.

- 7.2.2.7 Ophthalmologic evaluation

  The above section was amended to allow patients who have been on the LGX818/MEK162 dual-combination or LGX818/MEK162/LEE011 triple-combination treatment for ≥ 24 months without a retinal AE to be evaluated only for visual acuity at each scheduled patient visit and at the End of Treatment visit. These patients are also required to have a full ophthalmic examination if clinically indicated and at the End of Treatment visit.

- 7.2.2.8.2 Electrocardiogram (ECG) schedule for the triple combination

  The above section was amended to remove text around unscheduled PK sample collection when an ECG with a QTcF change from baseline > 60 msec or a new absolute QTcF ≥ 501 msec result is observed.

- 7.2.3.1.1 Pharmacokinetic blood sample collection and handling

  The above section was amended stop collection of unscheduled PK samples and text was removed where this practice was discussed. This includes addition of footnotes in Table 7-4 and Table 7-5 denoting collection should be stopped upon the effective date of this amendment.

- 8.1.1 Definitions and reporting

  The above section was modified to reflect the change in the CTCAE version to be used for assessment of AEs, from version 4.0 to version 4.03.

- 9.3 Data collection

  The above section was amended to remove the note that all imaging data to be centrally collected by an imaging CRO, and to remove the note that such imaging data may be assessed centrally if deemed necessary.

- 9.4 Database management and quality control

  The above section was amended to remove the note that all imaging data are to be assessed centrally.

- 10 Statistical methods and data analysis

  The above section was amended to indicate the final clinical study report will be completed once all patients have completed or discontinued from the study.

- 10.5.2.1 Adverse events and 10.5.2.2 Laboratory abnormalities

  The above sections were amended to reflect that CTCAE version 4.03 was used in the grading of AEs and laboratory abnormalities.

- Table 14-11 List of P-gp Inhibitors to be used with caution and Table 14-12 List of BCRP, OAT1, OAT3, OCT1, OCT2, OATP1B1 and OATP1B3 substrates to be used with caution

  Table 14-11 was combined with Table 14-12 and renamed to List of BCRP substrates, BSEP inhibitors, P-gp inhibitors/inducers, and MATE1, P-gp, OAT1, OAT3, OCT1, OCT2, OATP1B1 and OATP1B3 substrates to be used with caution. The List of BCRP OAT1, OAT3, OCT1, OCT2, OATP1B1 and OATP1B3 substrates to be used with caution was updated to add BSEP inhibitors, MATE1 and P-gp inhibitors/inducers (Table 14-11).

- Table 14-12 Drugs with a conditional risk of Torsades de Pointes, and a second Table 14-12 Drugs with a possible risk of Torsades de Pointes; Appendix 4 List of concomitant medications prohibited or to be used with caution for dual and triple combination

  Information regarding Torsades de Pointes and Drugs with a possible risk of Torsades de Pointes (in 2 tables labelled Table 14-12) were combined and updated and a new table (Table 14-12, List of QT prolonging drugs), was added. The new table updates and expands the list of QT prolonging drugs and matches the changes made in Section 6.4 on concomitant medications.

Other minor clarification changes and corrections to typographical errors have been made.

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 8

Amendment rationale

The main purpose of this amendment is to address recently observed safety findings from patients treated with LEE011 (Ribociclib) in other clinical trials.

1. Recent data suggests a potential risk of hepatic toxicity (drug induced liver injury [DILI] indicated by an increase of transaminases, in isolation or with bilirubin increase, in patients treated with LEE011. Updates to monitoring for hepatobiliary toxicities including ALT, AST, and total bilirubin have been added.
2. Updates to monitoring and dose adjustment guidelines for QTcF prolongation in order to improve patient safety based on program standard language recommendations have been implemented. Specific changes are as follows:
   a. Dose modification guidelines have been changed to more strictly manage QTcF prolongation
   b. Additional ECG assessments
   c. Follow-up of electrolyte abnormalities until normalization in the event of QTcF prolongation
   d. Mandated review of concomitant medications in the event of QTcF prolongation, also updated based on recent metabolism data for LEE011 or MEK162
   e. Mandated review of dosing regimen in the event of QTcF prolongation
   f. Addition of continued ECG monitoring for all cycles in the event of a patient QTcF $\geq$ 481 ms at any time before Cycle 7 Day 1

This amendment also documents a change in study sponsorship from Novartis to Array BioPharma. Study design and procedures are not affected by the sponsorship change.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

- The Protocol Summary is updated to reflect the changes to the inclusion and exclusion criteria
- Section 5.3 Exclusion criteria has been updated with the following:
  - Addition of criteria for the following laboratory values within normal limits or corrected to within normal limits with supplements before the first dose of study medication: sodium, inorganic phosphate, calcium (corrected for serum albumin)
  - Clarification of QTcF interval criteria on the ECG (ie: unreadable or not interpretable) or QTcF >450 ms. All as determined by screening ECG (mean of triplicate ECGs)
  - Addition of symptomatic pericarditis within 12 months prior to starting study drug
  - Addition of any other clinically significant heart disease (e.g. documented congestive heart failure, documented cardiomyopathy)
  - Increase in exclusion window from 3 months to 12 months prior to starting study drug for unstable angina pectoris and acute myocardial infarction

  - Addition exclusion window of 12 months prior to starting study drug for clinically significant resting bradycardia, history or presence of ventricular tachyarrhythmia, complete left bundle branch block, right bundle branch block and left anterior hemi block (bifasicular block)
  - Clarification that patients who are currently receiving agents known to cause QT prolongation, induce Torsades de Pointes, or that are metabolized predominantly through CYP3A4 and have a narrow therapeutic index, and cannot be discontinued 7 days prior to Cycle 1 Day 1, are excluded
- Section 6.1.1, added grapefruit hybrids, pummelos, starfruit and Seville (sour) oranges to list of items to be avoided due to CYP3A4 mediated interaction
- Table 6-4 - Dose modification guidelines, has been updated to:
  - Include new guidelines for the management of QTcF prolongation. Dose reduction is recommended in case of grade 2 QTc prolongation (QTcF 481-500 ms). For patients who experience grade 3 QTc prolongation (QTcF ≥ 501 ms) on at least two separate ECGs, local cardiologist consultation is also recommended in addition to dose reduction. Patients who experience grade 4 QTc prolongation must discontinue study treatment.
- Section 6.3.3 added to outline Additional follow-up for hepatic toxicities
- Section 6.4.3.1 updated to reference medications that are known to induce Torsades de Pointes
- Section 7.2.2.8.2 was updated to clarify follow-up guidelines in the event a QTcF value of ≥ 481 ms is observed prior to cycle 7
- Appendix 4 includes new tables listing medications with a risk of Torsades de Pointes

In addition to these changes, inconsistencies and typographical errors have been corrected as needed.

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 7

Amendment rationale

- This protocol amendment is based on Urgent Safety Measures (re: Investigator Notification letter dated 07Feb2014):
- A fatal event of intracranial hemorrhage occurred in a 21-year-old patient in a phase Ib study of LEE011 in combination with MEK162 [MEK162X2114]. Based on the normal laboratory assessments, absence of other known risk factors for intracerebral bleeding together with early signs of clinical response to treatment, the investigator suspected undetected intracranial metastases as the source of the bleeding. The relationship to study drugs cannot be ruled out. While the protocol excludes patients with symptomatic brain metastases, brain imaging prior to study entry had not been required and was not performed for this patient. As a precautionary measure, this amendment will mandate brain imaging for all patients at screening and will exclude patients with brain metastases from the triple-combination part of the study. Furthermore, patients with abnormal coagulation evaluations at Screening/baseline will be excluded from the triple-combination part of the study.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

- Section 5.3, Exclusion criteria has been updated for the triple-combination part of the study to include the following:
  1. Exclusion criterion no. 3 has been updated to exclude patients with brain metastases.
  2. Exclusion criterion no. 7 has been updated to exclude patients with abnormal coagulation evaluations: PT/INR >1.5 x ULN or aPTT >1.5 x ULN.
- Section 6.1.5, Treatment duration has been updated to exclude from treatment beyond progression patients in the triple-combination part of the study that appear with new brain metastases.
- Table 7-1, Visit evaluation schedule has been updated to include mandatory brain MRI/CT at Screening/baseline for patients in the triple-combination part of the study.
- Section 7.2.1, Efficacy assessment has been updated to include mandatory baseline brain imaging to access CNS disease for the patients in the triple-combination part of the study.

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

1. Urgent Safety Measures (re: Investigator Notification letter dated 07 Feb 2014):

This amendment is required for patient safety (i.e. necessary to eliminate immediate hazards to the trial subjects ICH GCP 3.3.8). Therefore updated exclusion criteria and baseline imaging assessments will be implemented prior to IRB/IEC approval, but will be sent for approval as well.

Amendment 6

Amendment rationale

1. Urgent Safety Measures (re: Investigator Notification letter dated 08 Nov 2013):
   - The main objective of this amendment is to modify existing safety monitoring for visual toxicities. This is based on a new unexpected non-clinical finding from the 13-week monkey toxicology study with LGX818. In this study, two monkeys treated at a dose of 60mg/kg/day presented retinal changes at the assessment on week 12 (please refer to the Investigator Notification letter dated 08 Nov 2013). As for this protocol sufficient ophthalmic examinations are already in place to monitor for the potential risk of retinal/ocular changes, these examinations and frequency of the examinations will not change. However this amendment includes modified recommendations for LGX818 dose modifications for visual toxicity and in addition, modified definitions of ophthalmologic DLT's are provided.
2. Other Changes Implemented under Protocol Amendment 6:
   - In addition, prohibited medications are updated. Since LGX818 is mainly metabolized by CYP3A4 (>80%), concomitant use of strong CYP3A4 inhibitors would likely significantly increase the exposure of LGX818. Therefore concomitant use of strong systemic CYP3A4 inhibitors is prohibited during this study. Language in Section 6.4.2 and Section 6.4.3, and Appendix 4 (Section 14.4) is amended accordingly and a corresponding exclusion criterion was added in Section 5.3.
   - Also, this amendment clarifies that any language regarding the triple combination of LGX818/MEK162/LEE011 in this protocol (introduced under protocol amendment 5) is not applicable to the USA and Singapore, as indicated in the applicable Protocol Sections. Any other changes introduced under protocol amendment 5, are by this amendment now made applicable to the USA and Singapore. Which are as follows:
     a. Table 6-4 under 'Creatine phosphokinase (CPK)' clarifying text added: If the LGX818 dose administered is > 450mg QD, then the LGX818 dose must be reduced to 450mg QD during the MEK162 dosing interruption. If the LGX818 dose was reduced to 450mg QD during MEK162 dosing interruption, the LGX818 dose must be re-escalated to the previous administered dose once MEK162 dosing is restarted. Section 6.3.2 was amended accordingly.
     b. Section 1.2.1.2 and Section 1.2.2.2 (and subsections) have been updated with data from the most recent Investigator Brochure for LGX818 and Investigator Brochure for MEK162, respectively.
     c. Section 6.4.2 was updated for new available data: 1) MEK162 is also an inhibitor of CYP2B6. 2) There is a potential for MEK162 to induce CYP3A4. 3) The solubility of LGX818 and MEK162 is pH dependent. Patients receiving concomitant treatments that could potentially modify the gastric pH (i.e. PPI) should be instructed to take them at least two hours after the administration of LGX818 and/or MEK162.

d. Section 7.2.2.2 was corrected for the collection of vital signs at Cycle 2 Day 15 also for patients enrolled in the Phase II part of the study.
e. For clarity of presentation, the description in Section 10.4.2.1 of the prior distributions for the 5 parameter BLRM has been moved to Appendix 5 (statistical methodology LGX818 and MEK162 dual combination).

This amendment occurs while the study drug dual combination of LGX818 and MEK162 is enrolling in the Phase II part of the study. In this ongoing study two RP2Ds were declared: 600mg/45mg and 450mg/45mg (LGX818 QD/ MEK162 BID). The dose escalation part for the triple combination LGX818, MEK162 and LEE011 is open for enrollment at participating sites.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

- Section 1.2.1.1.2 and Section 1.2.1.2 were updated with the new data of the 13-week monkey toxicology study.
- Table 6-3 and Table 6-4 have been amended to include the modified definitions of the ophthalmologic DLT and the modified recommendations for LGX818 dose modifications for visual toxicity, respectively. Section 6.2.6.2 and Section 6.3.2 have been updated accordingly.
- Section 6.4.2 and Section 6.4.3, have been updated to include the new data on concomitant use of strong systemic inhibitors of CYP3A4, which are as per this amendment prohibited. Section 6.4.3.1, Table 14-10 and exclusion criterion 17 (Section 5.3) were updated accordingly, as well was exclusion criterion 18 (Section 5.3) added.
- For the clarification that any language regarding the triple combination with LEE011 in this protocol is not applicable to the USA and Singapore, a statement was added to the Protocol Summary and to Section 1, Section 2, Section 3, Section 4, Section 5, Section 6, Section 7, Section 10, Section 11.3, Section 14.3, Section 14.4 and Section 14.6.
- Section 7.2.4.1.3 was updated to clarify that the collection of a fresh tumor biopsy at the time of relapse is strongly encouraged if feasible according to the investigator. Section 7.2.4.1.4 and Section 7.2.4.2.1 were updated to align the collection of the tissue with the requirements of the analysis lab. Table 7-5 was updated accordingly.

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

1. Urgent Safety Measures (re: Investigator Notification letter dated 08 Nov 2013):

This amendment is required for patient safety (i.e. necessary to eliminate immediate hazards to the trial subjects ICH GCP 3.3.8). Therefore dose modifications for ocular adverse events and updated DLT criteria will be implemented prior to IRB/IEC approval, but will be sent for approval as well.

2. Other Changes Implemented under Protocol Amendment 6:

All other changes described in this amendment require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Amendment 5

Amendment rationale

1. The main rationale for this amendment is to add LEE011 to the LGX818 and MEK162 combination treatment in order to explore safety and preliminary efficacy of this triple combination in patients with BRAF V600-dependent advanced solid tumors.
   Pre-clinical evidence suggests that the addition of LEE011 to the dual combination of MEK162 and LGX818, could potentially improve the clinical response in patients with BRAF V600-dependent melanoma (see Section 1.2.4.3). Although clinical trials with selective BRAF and MEK inhibitors have shown significant activity in patients with BRAF mutant melanoma, these patients ultimately relapse and fail to continue to respond to these therapies. Therefore, targeting both the RAS/RAF/MEK/ERK and the Cyclin D-CDK4/6 pathways downstream may improve and prolong response and be an effective strategy to expand therapeutic options for these patients with advanced melanoma that have very poor prognosis and constitute a high unmet medical need. Therefore the triple combination of LGX818 and MEK162 and LEE011 will be evaluated in a dose escalation to determine the MTD and/or RP2D in patients with BRAF V600-dependent advanced solid tumors. Once the MTD and/or RP2D is declared, the preliminary efficacy of the triple combination will be assessed in patients with BRAF V600 mutant advanced melanoma naïve to prior treatment with a BRAF inhibitor (arm A).
   The triple combination will be evaluated in parallel and separately from the evaluation of the dual combination.
2. In addition, this amendment was used to clarify that in those patients dosed with a LGX818 dose > 450mg QD, the LGX818 dose is recommended to be reduced to 450mg QD during a MEK162 dosing interruption while maintaining LGX818 dosing (as per Table 6-4 for grade 3 CPK, eye disorders - retinopathy and eye disorders – any other), to reduce any potential risk of developing adverse events to the patient. This is recommended since a dose of 450mg QD LGX818 is the maximum tolerated dose for LGX818 as a single agent, and there is an improved tolerability of LGX818 in the combination with MEK162 compared to LGX818 as a single agent. Once MEK162 dosing is restarted, the LGX818 dose can be re-escalated to the previous administered dose.

This amendment occurs while the study drug dual combination of LGX818 and MEK162 is enrolling in the Phase II part of the study at the RP2D of 600mg LGX818 QD and 45mg MEK162 BID. In this ongoing study two RP2Ds were declared: 600mg/45mg and 450mg/45mg (LGX818 QD/ MEK162 BID).

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and <u>red underlined for insertions.</u>

- All relevant Sections, Tables and Figures throughout the protocol were updated to include the evaluation of the triple combination of LGX818 and MEK162 and LEE011.

- Sections 1.2.1.2 and 1.2.2.2 (and subsections) have been updated with data from the most recent Investigator Brochures for LGX818 and MEK162, respectively.
- Sections 1.2.3 (and subsections), 1.2.4.3, 1.2.4.4, 1.3.2, 6.1.1.2, 6.4.2.1, 6.4.3.1, 7.2.2.8.2, and Tables 6-2, 6-4, 6-6 were added for the triple combination.
- Table 6-4 and Section 6.3.2 were amended to include the guidance on the LGX818 dose reduction/re-escalation during MEK162 dosing interruption for certain toxicities.
- Section 6.4.2 was updated for new available data
- Section 7.2.2.2 was corrected for the collection of vital signs at Cycle 2 Day 15 also for patients enrolled in the Phase II part of the study.
- For clarity of presentation, the description in Section 10.4.2.1 of the prior distributions for the 5 parameter BLRM has been moved to Appendix 5.
- Section 14.6 (Appendix 6) was added to describe the operating characteristics of the BLRM and hypothetical dose escalation scenarios of the triple combination.
- Other minor changes in the protocol text were made for consistency/clarification.
- The protocol summary has been updated according to the changes in the amended protocol.

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Amendment 4

Amendment rationale

The rationale for this amendment is to allow reduction of the MEK162 dose in case of MEK162 related toxicities. The current language in this protocol recommends a reduction to the next lower, previously tested (i.e. in this study) dose level of the respective study drug. This applied only to LGX818 and not to MEK162, since only the LGX818 dose has been escalated and no lower dose levels than 45mg MEK162 have been tested in this study.

Therefore this amendment introduces the modified recommendation: treatment at the next lower, previously tested dose level of LGX818 and the next lower dose level of MEK162 (please see Table 6-1). Treatment with LGX818 should be maintained at the same dose level if, in the judgment of the investigator, the adverse event is considered to be unrelated to LGX818.

In addition, this amendment introduces a number of further changes and clarifications:

- For patients considered for enrollment in this study for whom molecular status is not known and who have a tumor which is not routinely screened for a BRAF mutation at a local laboratory, both fresh and archival tumor tissue can be used for the local assessment of the mutational status. As the BRAF mutational status assessment for these cases is specifically performed for this study at the local laboratory, both patients giving fresh tumor sample and allowing use of archival tumor tissue must sign Molecular pre-screening Informed consent prior to this assessment. Therefore the language in the protocol was amended to require Molecular pre-screening Informed consent to be signed for allowing both collection of fresh tumor sample and use of archival tumor tissue. Previously this was required only for patients from whom fresh tumor sample was collected.
- Minimal criteria to allow dosing beyond progression were added: it was clarified that dosing beyond progression of disease is not allowed in situations where the patient has a rapid progression of disease and needs urgent alternative medical intervention, if patients have worsening of clinically relevant laboratory values or if patients have a clinically relevant decline in performance status at time of progression.
- The early tumor assessment on C1D28 has been removed from the Phase II part of the protocol in order to reduce the amount of irradiation patients enrolled in this part of the study would receive and for consistency with the tumor assessment schedule of future studies involving MEK162 and LGX818.
- As supported by additional data now available, the new MEK162 tablet variants as described in this protocol, no longer need to be administered to the patients under 1-hour fasting periods prior, and after dosing of the evening MEK162 doses. Therefore language referring to this fasting has been removed from the protocol.
- The frequency of physical examinations, vital signs and performance status assessments was reduced and the collection of several clinical chemistry laboratory parameters was removed for the Phase II part of the study, as sufficient safety data were collected during the Phase Ib part of the study.
- In order to assess the potential impact of demographic differences (e.g. Japanese vs Caucasian) on the PK of the LGX818 and MEK162 combination, the protocol has been

modified to allow PK samples to be collected from additional patients enrolled in the Phase II part.

- The time points and requirements for the fresh tumor biopsy and skin biopsy collection were clarified and further specified.

The current study began recruitment on 28-May-2012. As of 16-April-2013, 35 patients with advanced solid tumors with BRAF mutations have been enrolled and treated for at least 28 days. This amendment occurs while the study drug combination is being evaluated at the seventh dose cohort (800mg LGX818 QD and 45mg MEK162 BID) and expanded dose level cohort six of 450mg LGX818 QD and 45mg MEK162 BID. In parallel, recruitment to the Phase II part of the study started on 18-Apr-2013 with the RP2D of 600mg LGX818 QD and 45mg MEK162 BID.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

- Sections 1.2.1.1.1 and 6.4.2 were updated with newly available data. Table 14-12 was updated accordingly.
- Sections 4.1 and 7.1.1 were amended with the new requirements for signing of Molecular pre-screening ICF. The Molecular pre-screening ICF was corrected accordingly.
- Language referring to fasting for the new MEK162 tablet variants has been removed from Section 6.1.1.
- Section 6.1.5 was amended to included cases in which treatment beyond progression is not allowed.
- Section 6.3.2 and Table 6-3 have been amended to revise the wording on dose level reduction.
- The Visit Names/Numbers for the D28 visits were removed from Table 7-1 to be consistent with the clinical data base visit numbering.
- Section 7.2.1 was amended to indicate that the C1D28 tumor imaging assessment is not required for the patients enrolled in the Phase II part of the study. Section 7.1 and Table 7-1 were updated accordingly.
- Sections 7.2.2.1, 7.2.2.2, 7.2.2.3 and 7.2.2.5.2 were amended to reduce the frequency of physical examination, vital signs and performance status assessments, and to remove the collection of chloride, urea or BUN, uric acid, total cholesterol, triglycerides, HDL, LDL, TSH, T3 and T4 from the clinical chemistry laboratory assessment for patients enrolled in the Phase II part of the protocol. Table 7-1 was revised accordingly.
- Sections 7.2.3 and 7.2.3.1.1 were amended to include language that collection of PK samples from additional patients than previously specified, is allowed if required as per instruction from the Sponsor. Tables 3-1, 7-1, 7-4 and 7-5 were updated accordingly.
- Sections 7.2.4.1.2, 7.2.4.1.3 and 7.2.4.2 were amended to clarify and further specify the time points and requirements under which fresh tumor and skin biopsies should be collected. Tables 7-1 and 7-5 were revised accordingly.

- Sections 7.2.4.4 and 7.2.4.5 were updated to clarify which samples collected during the study, are meant to be stored for 15 years for optional additional exploratory biomarker assessments and to include further potential use of all remaining study samples.

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Amendment 3

Amendment rationale

The production of the original MEK162 tablet that is currently used in this study will cease. Two new MEK162 tablet variants have been developed. One variant is a modified formulation of the MEK162 drug product (hence forth referred to as "MEK162 smaller tablet") and the other variant has the same formulation but contains drug substance from a new manufacturer (hence forth referred to as "new MEK162 tablet variant").

Two relative bioavailability studies in humans are currently ongoing in order to compare a) the MEK162 smaller tablet with the original MEK162 tablet (CMEK162X2108 study) and b) the new MEK162 tablet variant with the original MEK162 tablet (CMEK162A2101 study).

Based on the results of these two relative bioavailability studies, the MTD/RP2D of the LGX818 and MEK162 combination may need to be established with one or both of the two new MEK162 tablet variants (for further details please see Section 6.2.3). This amendment will introduce this possibility.

If it is decided based on the results of the two relative bioavailability studies, that the MTD/RP2D can be determined using the original MEK162 tablet, then enrollment in the CMEK162X2110 study will continue in the dose escalation or the Phase II part will start with one or both of the two new MEK162 tablet variants, as applicable at that time.

- Since food interaction studies with the two new MEK162 tablet variants have not yet been performed at the time of this amendment, these new tablet variants would need to be administered to the patients under 1-hour fasting periods prior, and after dosing of the evening MEK162 doses.

In addition, this amendment was used to make a few changes for clarification (please see below Changes to the protocol for details).

The current study began recruitment on 28-May-2012. As of 05-Nov-2012, 20 patients with advanced solid tumors with BRAF mutations have been enrolled. This amendment occurs while the study drug combination is being evaluated in the fourth dose cohort.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

- Section 5.2 has been updated to clarify the collection of mandatory fresh tumor biopsies at Screening/baseline for patients to be enrolled in the Phase II part. Section 7.2.4.1.1 and Table 7-1 were amended accordingly.
- Section 6.2.3 has been updated to include the possibility to establish the MTD/RP2D with the MEK162 smaller tablet and/or new MEK162 tablet variant if needed. Sections 10.1.1, 10.3.1 and 10.4.2.1 have been updated accordingly.
- Section 6.1.1, Section 6.6.1 and Section 6.6.2 have been updated to include instructions on dose administration of, and (label) information on the two new MEK162 tablet variants.

- Sections 7.1, Section 7.2.1 and Table 7-1 have been updated to clarify the wording on imaging assessments. Sections 9.3 and 9.4 have been updated to accurately describe the process of central reviewing of the imaging assessments. Section 10.4.4 and Section 10.5.1 have been amended accordingly.

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Amendment 2

Amendment rationale

The main rationale of the amendment is to introduce a third arm in the Phase II part of the study to enroll 40 patients with locally advanced or metastatic BRAF V600 mutant melanoma who are naïve to previous treatment with a selective BRAF inhibitor. LGX818 has shown in the first in human Phase I single agent CLGX818X2101 study, clinical antitumor activity at all dose levels tested (50 mg/day to 300 mg/day) in patients with metastatic BRAF V600 mutant melanoma who did not receive prior treatment with a selective BRAF inhibitor. As of 03 July 2012, signs of clinical activity have been observed in 20 out of the 21 enrolled patients naïve for prior selective BRAF inhibitor treatment, with reductions in tumor volume of 8.3% to 100% (including 11 PR (of which 8 confirmed)), observed after initiation of LGX818 single agent treatment. In addition, MEK162 has demonstrated clinical activity in the human phase II single agent CMEK162X2201 study in patients with BRAF mutant metastatic melanoma (Ascierto 2012). Recent data from the phase Ib/II combination study of the BRAF inhibitor Dabrafenib and MEK inhibitor Trametinib also show that patients with BRAF mutated melanoma clinically benefit from a BRAF/MEK inhibitor combination with an improved durability of response over single agent therapy (Weber 2012). The anticipated sample size of n = 40 patients was chosen in order to ensure desirable statistical properties (correct declaration of activity/ inactivity) with respect to the primary analysis.

Additionally, this amendment will introduce the possibility to continue to treat patients beyond progression of disease. The recent overall survival data from the BRIM2 and BRIM3 clinical trials of the selective BRAF inhibitor Vemurafenib show that patients with BRAF mutated melanoma may clinically benefit from continued treatment beyond progression (Sosman 2012, Chapman 2011). This amendment will therefore allow that in special circumstances, such as cystic lesions, mixed responses, or new brain metastases treatable with stereotactic radiotherapy or surgery, patients to continue dosing with LGX818 and MEK162, if it is considered to be of benefit for the patient by the investigator, and in agreement with the Sponsor.

Moreover, collection of fresh tumor biopsies at Screening/baseline for all patients enrolled in the Phase II part, will be mandatory as per this amendment (unless sufficient fresh tumor tissue was collected during local molecular pre-screening which can be submitted to the Sponsor-designated laboratory at Screening (see Section 7.2.4). Clinical activity of BRAF inhibitors is substantial in terms of response rate. However, not all patients respond and some patients show progression of disease after relatively short time periods (Flaherty 2010, Chapman 2011, Sosman 2012). In order to fully characterize the tumor, a comprehensive genomic analysis of the tumor will be performed at baseline to better understand the genomic profile of the patient's tumors and potentially identify predictive markers of efficacy. As a result, characterization of select baseline gene mutation status in tumor tissue for the Phase II part will now be assessed as a secondary endpoint.

A number of additional changes and clarifications are introduced in this amendment:

- All patients enrolled in the Phase II part of the study will be followed for survival more frequently: every three months instead of every four months.

- The recommended dose modifications for Grade 2 and 3 eye disorders have been revised. The ocular toxicity profile of MEK162 is becoming better understood and investigators are gaining experience in assessing and managing these toxicities. Emerging data from several ongoing trials with MEK162 demonstrate that the events were low grade and appear to be reversible and manageable in all patients. In most cases, the events are transient in nature and resolve either without stopping treatment, upon dose reduction, or upon interruption of treatment and subsequent continuation at the same dose of MEK162. Based on these growing safety data from the clinical studies with MEK162, it is reasonable to consider maintaining the treatment of LGX818 and MEK162 for Grade 2 CSR (central serous retinopathy)/CSR-like events, and also to allow dose reduction of MEK162 for Grade 3 CSR/CSR-like events. As result the DLT criteria for Grade 2 and 3 Eye disorders have been revised accordingly.
- The recommended dose modifications for CTCAE Grade 3 and 4 CPK have been revised. Blood creatine phosphokinase (CPK) elevations are mostly asymptomatic and not clinically significant. Therefore and based on the growing safety data from the ongoing clinical studies with MEK162, it is reasonable to review and consider to not dose modify LGX818 and MEK162 treatment in asymptomatic cases of Grade 3 CPK elevations and to recommend dose reduction for symptomatic Grade 3 blood CPK and for all Grade 4 blood CPK. As result the DLT criteria for CTCAE Grade 3 and 4 CPK have been revised accordingly.
- The CYP inhibitors/inducers/substrates lists were updated according to the new lists published by FDA. Caution for co-medications that are UGT1A1 substrates was added since LGX818 was found to be an inhibitor of UGT1A1 in vitro. In addition, caution for co-medications that are substrates of renal transporters OAT1, OAT3 and OCT2 and hepatic transporters OATP1B1 and OATP1B3 was added because LGX818 was found to inhibit OAT1, OAT3, OCT2, OATP1B1 and OATP1B3.
- PK samples will be collected for the first 10 patients treated in each arm 2 and 3 in the Phase II part of the study. Previously, PK samples were collected in Phase II arm 2 from those patients from whom a fresh tumor biopsy could be collected (i.e. at least 15 patients). As per this amendment a fresh tumor biopsy at Screening/baseline is mandatory for all patients in the Phase II part, it was redefined which patients treated in the Phase II arms 2 and 3, will be selected to provide PK samples.
- To redefine the time of end of study (LPLV), the period of survival follow-up was amended to follow all patients enrolled in the Phase II part of the study for survival until death, or until all patients have completed SEC and have been followed for at least 18 months after their first dose of study treatment, or have been lost to follow-up or withdrew consent, whichever occurs first. Previously patients were followed for survival until death or up to 18 months after LPLT, whichever occurs first.
- Clarifications throughout the protocol.

The current study began recruitment on 28May2012. As of 12July2012, six patients with advanced solid tumors with BRAF mutations have been enrolled and have completed the first dose cohort. This amendment occurs while the study drug combination is being evaluated in the second dose cohort.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

- Section 1.2.1.1.1 and 1.2.2.1.2 has been updated to include more recent data on non-clinical pharmacokinetics of LGX818 and MEK162.
- Section 1.2.1.2 has been updated to include more recent clinical experience with LGX818.
- Sections 2.1, 3, 4.1 (including Figure 4-1), 5.1 and 5.2 Inclusion Criterion 2 have been amended to include the additional arm 3 in the Phase II part of the study and the objectives and endpoints associated with this population. Sections 10.4, 10.4.1, 10.4.2.2 and 10.8 have been updated accordingly.
- Sections 4.1, 6.1.5 and 7.1.3 were amended to include the possibility to continue treatment with LGX818 and MEK162 beyond progression of disease under certain circumstances.
- Section 5.2 Inclusion Criterion 8 was added to only allow patients to enroll in the Phase II part of the study that can provide a fresh tumor biopsy at Screening/Baseline. As consequence a secondary objective has been added in Table 3-1 to include the data analysis on these tumor samples. Sections 7.2.4 and 10.5.4.3.2, and Table 7-1 have been updated accordingly.
- Section 6.3.2 Table 6-3: recommended dose modifications for ‘creatine phosphokinase’ and ‘eye disorders’ have been amended. Table 6-2 Criteria for defining DLTs and Section 6.2.6.2 have been updated accordingly.
- Section 6.4.2 and Appendix 4 Tables 14-9 and 14-12, were updated with newest data on permitted drugs to be used with caution.
- Section 7.1.5.3 was revised to introduce survival follow-up phone calls every 3 instead of every 4 months. Table 7-1 was updated accordingly.
- Section 7.1.5.3 was revised to redefine the period of survival follow-up. Sections 7.1.5.2 and 4.3 were updated accordingly.
- Section 7.2.2.5.2 was updated to clarify that if total CPK is elevated ≥ CTCAE Grade 2, then isoenzymes in blood and myoglobin in blood and urine, should be weekly measured until resolved to ≤ CTCAE Grade 1.
- Section 7.2.3.1.1 was updated to add PK sample collection in Phase II arm 3 and was revised to collect PK samples in Phase II arms 2 and 3 from the first 10 patients treated in each arm, instead of from those patients who can provide fresh tumor biopsies.
- Sections 7.2.4.1.1, 7.2.4.1.2, 7.2.4.1.3 and 7.2.4.3, and Table 7-5 have been updated to clarify the tumor tissue analysis, the collection time point for the fresh tumor biopsy at C1D16 and relapse, and the collection time point for the whole blood sample.
- Section 13 was updated with new references added.
- Other minor changes/corrections in the protocol text were made for consistency and/or clarifications.
- The protocol summary has been updated according to the changes in the amended protocol.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Amendment 1

Amendment rationale

This amendment addresses the enhanced safety measures to be implemented in order to minimize risks to patients to be treated in this study, as result of two Investigator Notification letters (Case PHHO2012DE003954 - acute liver failure with a fatal outcome, Case PHHO2012CH005184 - decreased ejection fraction, heart failure, myocarditis, and tachycardia) issued by the Sponsor for patients treated with MEK162 at a 60mg BID dosing schedule in the CMEK162X2201 study.

PHHO2012DE003954 is describing a case of liver failure with fatal outcome. The investigator considered that the liver failure was related to the study drug. However other differential diagnoses such as muscular toxicity and /or thrombotic/vascular/ hepatic events may be considered in this case. This is the only fatal liver failure case reported in a total of more than 450 subjects/patients that have received at least 1 dose of MEK162 up to date.

PHHO2012CH005184 is describing a case of reduced ejection fraction, symptoms of congestive heart failure, myocarditis and tachycardia. The events were considered suspected to the study drug by the investigator. However also other differential diagnoses may be considered in this case. The toxicities stabilized after study treatment discontinuation. This is the only case of cardiac failure/myocarditis reported so far suspected to be related to MEK162.

The following will be implemented:

- Increase of the frequency of liver transaminase and function test monitoring.
- Revision of dose modification guidelines for patients with elevated transaminase levels, bilirubin levels and/or other liver function tests.
- Increase of the frequency of cardiac monitoring.

In addition, this amendment was used to correct a typo in Exclusion Criterion 7 and to make a few other minor corrections for consistency. This amendment occurs while several sites have received HA and IRB approval for the original protocol.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

- Section 5.3: in Exclusion Criterion 7 ‘directly measured CrCl ≥ 50% LLN’ was corrected to ‘directly measured CrCl < 50% LLN’.
- Section 6.3.2 Table 6-3: recommended dose modifications for ‘Bilirubin’, ‘AST or ALT’ and ‘AST or ALT and Bilirubin’ have been amended.
- Section 7.2.2.5.2: CPK was added to the clinical chemistry panel as a parameter to be measured.
- Section 7.2.2.5.2: Additional liver function test (LFT = AST, ALT, alkaline phosphatase and bilirubin (total, indirect and direct)) measurements have been added at Days 8 and 22 of Cycle 2 and Day 15 of Cycle 4. Table 7-1 has been amended accordingly.

- Section 7.2.2.8.2: Additional ECHO or MUGA evaluations have been added at Day 1 of Cycle 2, Day 1 of every third cycle until Cycle 11 and Day 1 of every fourth Cycle thereafter. Table 7-1 has been amended accordingly.

The changes in this protocol amendment should be considered as substantial, in Member States of the European Union and European Economic Area (Directive 2010/C80/01/EC).

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Protocol Summary

[Any language regarding the triple combination of LGX818/MEK162/LEE011 in this Section is <u>not</u> applicable to the USA and Singapore]

Study title: 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

Study phase: Ib/II

Study objectives:

Primary objectives:

Phase Ib: 1) To estimate the MTD(s) and/or RP2D(s) of oral LGX818 in combination with oral MEK162 in patients with BRAF V600-dependent advanced solid tumors. 2) To estimate the MTD(s) and/or RP2D(s) of oral LGX818 and MEK162 in combination with oral LEE011 in patients with BRAF V600-dependent advanced solid tumors.

Phase II: 1) To assess clinical efficacy of the LGX818 and MEK162 dual combination in the Phase II populations: BRAF V600 mutant metastatic colorectal cancer (mCRC) patients (arm 1), BRAF V600 mutant metastatic melanoma patients who have progressed after prior selective BRAF inhibitor treatment (arm 2) and BRAF V600 mutant metastatic melanoma patients who are naïve to previous treatment with a selective BRAF inhibitor (arm 3). 2) To assess clinical efficacy of the LGX818 and MEK162 and LEE011 triple combination in the Phase II population: BRAF V600 mutant metastatic melanoma patients who are naïve to previous treatment with a selective BRAF inhibitor (arm A).

Secondary objectives:

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:

- To determine the single and multiple dose PK profile of the LGX818 and MEK162 dual combination and LGX818 and MEK162 and LEE011 triple combination.
- To assess preliminary clinical anti-tumor activity of the LGX818 and MEK162 dual combination and LGX818 and MEK162 and LEE011 triple combination.

Phase II:

- To further assess clinical efficacy of the LGX818 and MEK162 dual combination in the Phase II populations, and of the LGX818 and MEK162 and LEE011 triple combination in the Phase II population.
- To characterize baseline molecular status of molecules relevant to RAF/MEK/ERK and EGFR/PI3K/AKT signaling in tumor tissue.

Study population: The dose escalation for both the dual and triple combination, will be conducted in adult patients with locally advanced or metastatic melanoma, mCRC or any other solid tumor upon agreement with the Sponsor, harboring the BRAF V600E mutation, or any other BRAF V600 mutation, whose disease has progressed despite previous anti-neoplastic

therapy or for whom no further effective standard therapy is available. Once MTD/RP2D has been determined for the dual combination, patients with BRAF V600 mutant mCRC for whom no further effective standard therapy is available will be enrolled in arm 1 of the Phase II part of the study. Patients with locally advanced or metastatic BRAF V600 mutant melanoma who have progressed after previous treatment with a selective BRAF inhibitor will be enrolled in the Phase II arm 2. Patients with locally advanced or metastatic BRAF V600 mutant melanoma who are naïve to previous treatment with a selective BRAF inhibitor will be enrolled in the Phase II arm 3. Once MTD/RP2D has been determined for the triple combination, patients with locally advanced or metastatic BRAF V600 mutant melanoma who are naïve to previous treatment with a selective BRAF inhibitor will be enrolled in the Phase II arm A.

Patients must be at least 18 year with a performance status ≤ 2 and have adequate hematologic, renal, and hepatic function.

Number of patients: Dual combination: approx. 127 (at least 18 in the dose escalation and 28+41+40 respectively in arms 1, 2 and 3 of the Phase II). Triple combination: approx. 52 (at least 12 in the dose escalation and 40 in arm A of the Phase II part).

Overview of 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 combinations of LGX818/ MEK162 and LGX818/ MEK162/ LEE011, followed by a Phase II part to assess the clinical efficacy and to further assess the safety of the combination in selected patient populations. Oral LGX818 and MEK162 will be administered on a continuous schedule, oral LEE011 will be administered continuously on a 3 weeks on, 1 week off schedule. Patients will be treated until progression of disease, unacceptable toxicity develops, or withdrawal of informed consent, whichever occurs first. Continued treatment beyond progression of disease will be allowed under certain circumstances. A cycle is defined as 28 days.

The dose-escalation part of the trial will be conducted in adult patients with BRAF V600-dependent advanced solid tumors and is expected to enroll at least 18 patients for the dual combination and at least 12 patients for the triple combination. The dose escalation will be guided by a Bayesian logistic regression model (BLRM). At each decision time point, the adaptive BLRM provides the upper boundary for the combinations that meet the escalation with overdose control (EWOC) criteria. Safety and tolerability data, PK, PD, and efficacy, as well as the recommendations from the Bayesian model are used to determine the dose combination for the next cohort(s) at a dose escalation teleconference. Provisional dose levels are given in Table 6-1 and Table 6-2. Various dose pairs 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 least 6 patients eligible for the dose determining set (DDS) must be treated at the dose(s) declared to be the MTD/RP2D.

Following MTD/RP2D declaration of the dual combination, patients will be enrolled in three Phase II arms. Phase II arm 1 will consist of 28 patients with non-resectable advanced BRAF V600 mutant mCRC for whom no further effective standard therapy is available. The Phase II arm 2 will consist of 41 patients with locally advanced or metastatic BRAF V600 mutant melanoma who have progressed after previous treatment with a selective BRAF inhibitor. The Phase II arm 3 will consist of 40 patients with locally advanced or metastatic BRAF V600 mutant melanoma who are naïve to previous treatment with a selective BRAF inhibitor.

Following MTD/RP2D declaration of the triple combination, patients will be enrolled in one Phase II arm (arm A) which will consist of 40 patients with locally advanced or metastatic BRAF V600 mutant melanoma who are naïve to previous treatment with a selective BRAF inhibitor.

All patients will be followed for 30 days for safety assessments after study drugs discontinuation. Patients enrolled in the Phase II parts of the study who discontinue study treatment for any reason other than disease progression will be followed up for progression of disease. All patients enrolled in the Phase II parts of the study will be followed for survival.

Note: As of protocol amendment 10, patients who remain on study treatment will have assessments performed as per local standard-of-care practice. In addition, post-treatment disease progression follow-up (if applicable) and/or survival follow-up (including documentation of subsequent antineoplastic therapies) will no longer be performed for any patient in the Phase II part of the study.

Statistical considerations: A BLRM employing the EWOC principle will be used during the escalation phase for selection of doses to investigate and for estimation of the MTD. Each cohort will consist of newly enrolled patients. Estimation of the MTD during the escalation phase of the study will be based upon the estimation of the probability of DLT in cycle 1 in patients in the dose-determining set (DDS). The MTD is defined as the highest drug dosage not causing in the first cycle of treatment medically unacceptable, dose-limiting toxicity (DLT) in more than 35% of the treated patients. The corresponding statistical methodology is described in Section 10.4.2.

The Sponsor and investigators will decide on next dose levels and dosing schedule(s) to be explored at the dose escalation teleconference. Dose escalation decisions will be based on a clinical synthesis of all relevant available data and not solely on DLT information. The Sponsor will prepare minutes from these meetings.

During the Phase II part of the dual combination, depending on the observed DLT rate, the BLRM will be re-run to confirm that the current dose combination still satisfies the overdose criteria. In the Phase II parts of the study, a Bayesian design will be used in order to estimate the true DCR for the dual-combination arm 1 and the true ORR for the dual-combination arms 2 and 3 populations and for the triple-combination arm A, respectively.

1 Background

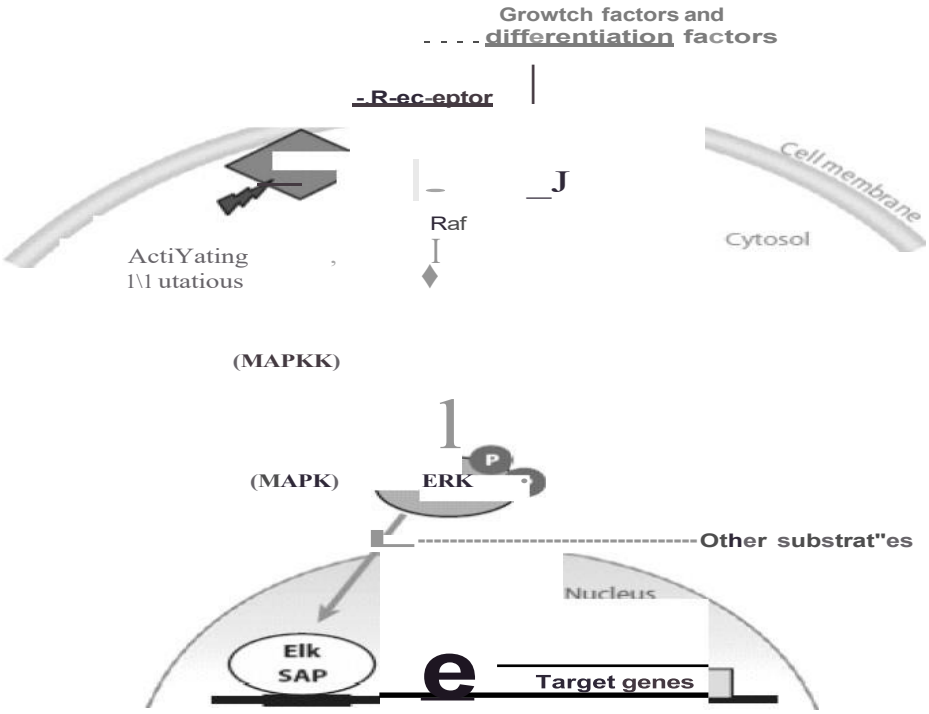
[Any language regarding LEE011 or CDK4/6 signaling in this Section is not applicable to the USA and Singapore]

1.1 Overview of disease pathogenesis, epidemiology and current treatments

1.1.1 The RAF/MEK/ERK pathway, BRAF-mutations and cyclin-dependent kinases 4 and 6 in solid tumors

Growth factor-mediated proliferative signals are transmitted from the extracellular environment to the nucleus through several pathways, including the RASIRAF/MEK/ERK pathway (Roberts 2007). This pathway comprises an evolutionarily conserved signaling cascade activated by the RAS small guanidine ti·iphosphatase (GTPase), which in tum activates RAF, which in tum phospho1ylates and activates MEK, which in tum activates exti·acellular signal-regulated kinase (ERK). ERK phospho1ylation of a variety of ti·anscriptional factors regulates several key cellular activities including proliferation, differentiation, Inigration, survival and angiogenesis. Abeffant signaling through this pathway has been shown to lead to unconsti·ained cell growth and cell transfo1mation (Yoon 2006; Scholl 2005) and is a characteristic feature of many cancers. fuappropriate activation of the RAS pathway can occur through several distinct mechanisms, including activating mutations in RAS and BRAF (Lea 2007), activated growth factor signaling (Nakazawa 2005), and cytokines and stress response signals (Mccubrey 2000; Chang 2003) (Figure 1-1).

Figure 1-1 Overview of Ras-Raf-ERK-MEK pathway (adopted from Cho 2009)



Recently activating mutations in the gene encoding the serine–threonine protein kinase B-RAF (BRAF) were identified in large-scale screens in human cancers (Davies 2002). Ninety percent of reported BRAF mutations result in a substitution of glutamic acid for valine at amino acid 600 (V600E mutation) which leads to a 500-fold increase in its activity compared to the wild type protein kinase (Wan 2004). Somatic mutations of BRAF occur in 60% of malignant melanomas and in 8-15% in colorectal, (Rajagopalan 2002), in 30% of serous borderline ovarian cancer (Singer 2003), in 40-70% of papillary thyroid carcinomas (Brose 2002; Cohen 2003; Nikiforova 2003; Fukushima 2003) and in 7-8% of all solid tumors (Brower 2010), implicating activating oncogenic mutations of BRAF as critical promoters of malignancy. Interestingly, BRAF and RAS mutations are restricted to the same tumor types usually in a mutually exclusive fashion, suggesting that these genes are on the same oncogenic signaling pathway and that RAS acts to activate BRAF in these mutations to these tumors (Davies 2002) (Table 1-1).

Table 1-1 Incidence of BRAF- mutations in human cancers

Cancer	Mutation incidence % BRAF
Melanoma	40-60
CRC	8-15
Pancreatic	5
NSCLC	2-5
BTC	25
Ovarian (serous)	30
PTC	40-70

In the mammalian cell cycle, entry into S phase is achieved by cyclin-dependent kinases 4 and 6 (CDK4/6). D-cyclins are the positive regulators of these kinases, while the p16 protein encoded by the INK4a gene functions as their major inhibitor. Signal transduction pathways including MAPK and PI3K increase cell proliferation upon mitogen stimulation by upregulating the expression of D-cyclins, which in turn activate the kinases. A wide range of human tumors harbor genetic aberrations that increase the activity of CDK4/6. These genetic aberrations include translocation, amplification and overexpression of D-cyclins, amplification of CDK4/6 kinases, a mutation of CDK4 resistant to p16 binding and inactivation of p16 (Lundberg 1998). Agents that inhibit the activity of CDK4/6 kinases may be able to stop the proliferation of these cancers and thereby function as effective anti-cancer drugs.

1.1.2 Malignant Melanoma

Malignant melanoma is one of the most aggressive human malignancies. Its incidence has rapidly increased throughout the world in the last few decades (in the order of 3-7% per year for fair skin Caucasian population) (Diepgen 2002), faster than that of all solid tumors, constituting a significant and growing health burden. It is estimated that 68,130 men and women will be diagnosed with, and 8,700 men and women will die of, melanoma of the skin in 2010 in the United States (Altekruse 2010). Although the majority of early stage patients can be treated with surgical resection, and have excellent survival rates (approximately 90% at 5 years), many will develop disseminated disease. The prognosis for patients with distant metastasis is, by contrast, very poor with survival rates ranging from 6.7% to 8% at 5 years, and a median survival of 6 to 9 months (Jemal 2009).

Currently, the existing therapeutic options for patients with melanoma comprise 4 therapies approved by the Food and Drug Administration (FDA): dacarbazine (DTIC), interleukin-2 (IL-2) ipilimumab (anti-CTLA-4) and vemurafenib (BRAF inhibitor). Single agent therapy with dacarbazine (DTIC), a cytotoxic chemotherapy, is generally well tolerated, but results in overall response rate of 10% and no survival benefit for patients with metastatic disease (median PFS of 2-3 months and OS of 6-10 months) (Anderson 1995; Chapman 1999; Serrone 2000). Immunotherapy with high-dose IL-2 was approved based on its ability to produce durable response in a small subset of patients (5 to 10%) with metastatic melanoma (Atkins 1999). Ipilumumab (Yervoy® Bristol-Myers Squibb) was approved by the FDA (25 March 2011) for the treatment of unresectable or metastatic melanoma based on a phase 3 randomized, double-blind study (MDX010-20) of 676 patients that demonstrated longer OS for patient treated with ipilimumab compared to tumor vaccine (median OS of 10 months vs 6 months, respectively). The best ORR was 10.9% in the ipilumumab arm compared to 1.5% in the tumor vaccine arm (Hodi 2010). The selective BRAF inhibitor PLX4032 (vemurafenib/Zelboraf® (Roche)), was approved by the FDA (17 August 2011) for the treatment of patients with unresectable or metastatic melanoma with the BRAF V600E mutation. In a phase 3, open-label, randomized study (BRIM3 trial) of 675 patients, the patients receiving PLX4032 experienced longer mPFS and OS compared to those randomized to DTIC (Chapman 2011). ORR was 48.4% vs 5.5% with a median PFS of 5.3 months vs 1.6 months, and an OS at 6 months of 84% vs 64% for PLX4032 and DTIC respectively.

Preliminary results from a phase 1/2 study with the selective BRAF inhibitor GSK2118436 (GlaxoSmithKline) were presented at ASCO 2010 (Kefford 2010). The drug was well tolerated with main toxicities as follows: cutaneous events (including 15% of SCC), headache, nausea/vomiting, and fatigue. Responses (PR) were observed in 63% of the patients with V600 BRAF mutant melanoma receiving ≥ 150 mg bid. Clinical trials with the selective allosteric MEK1/2 inhibitor, GSK1120212 have also shown promising activity in patients with BRAF mutant melanoma (Infante 2010; Kim 2011). In the phase 2 study, patients receiving GSK1120212 and previously treated with chemotherapy and/or immunotherapy had an ORR of 25% and a mPFS of 4 months. However, only minimal activity was observed in patients previously treated with a selective BRAF inhibitor (ORR 5%) (Kim 2011). Main toxicities included rash, diarrhea and central serous retinopathy. Two phase 3 randomized studies are currently ongoing in patients with BRAF mutant melanoma: NCT01227889 comparing selective BRAF inhibitor GSK2118436 to DTIC, and NCT01245062 comparing MEK inhibitor GSK1120212 to chemotherapy.

Although clinical trials with selective BRAF inhibitors PLX4032 and GSK2118426, have shown significant activity in patients with BRAF mutant melanoma, these patients ultimately relapse with a median PFS of 6 to 7 months, and up to 50 % fail to respond to these therapies (Flaherty 2010; Kefford 2010; Chapman 2011; Ribas 2011). These results strengthen the importance of exploring new selective BRAF inhibitors, as single agent or in combination, to expand therapeutic options for patients with advanced melanoma that have very poor prognosis and constitute a high unmet medical need.

1.1.3 Metastatic Colorectal Cancer (mCRC)

Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer and second leading cause of cancer death in the United States and in the European Union. In 2009, an estimated 150,000 new cases and 50,000 deaths from CRC in the US have occurred (Engstrom 2009). In the last decade, substantial advances in the treatment of metastatic CRC have resulted in an improvement in overall survival from 10-12 months to more than 20 months (Grothey 2004). This improvement has occurred with the addition of irinotecan, oxaliplatin, bevacizumab, cetuximab and panitumumab to the standard treatment with 5-fluorouracil (5 FU)/ leucovorin. However, because many patients eventually develop resistance to these agents, new agents to treat resistant tumors are an important area of investigation. The anti-EGFR monoclonal antibodies panitumumab and cetuximab were initially evaluated as monotherapy in patients with EGFR-expressing tumors after they became resistant to standard chemotherapy. Subsequent investigations discovered that oncogenic activation of signaling pathways downstream of the EGFR, such as mutations of KRAS and BRAF, play an important role in the progression of colorectal cancer. There is accumulating evidence that BRAF mutations, which may be present in up to 15% of patients with CRC have emerged as important predictive markers of resistance to the anti-EGFR monoclonal antibodies (Karapetis 2008; Amado 2008). BRAF mutation is also a negative prognostic marker in patients with metastatic CRC and this effect, in contrast to KRAS mutations, seems not to be restricted to the outcome of cetuximab treatment (Tol 2010). Therefore, patients with BRAF-mutation-related CRC have fewer treatment options. The highly selective BRAF inhibitor PLX4032 has shown some clinical activity in BRAF-mutant mCRC, albeit more modest than that observed in BRAF mutation-related melanoma (1/19 PR and 4 minor responses, mPFS 3.7 months); however, these findings confirm that BRAF mutation is a therapeutic target in mCRC strengthening the importance of evaluating the clinical activity of new selective and potent BRAF inhibitors in this indication (Kopetz 2010).

1.2 Introduction to investigational treatment(s) and other study treatment(s)

1.2.1 Overview of LGX818

NVP-LGX818 is a ((S)-methyl (1-((4-(3-(5-chloro-2-fluoro-3-(methylsulfonamido) phenyl)-1-isopropyl-1H-pyrazol-4-yl)pyrimidin-2-yl)amino)propan-2-yl)carbamate. LGX818 (also known as encorafenib, PF-07263896, ONO-7702, and W0090) is a highly selective ATP-competitive small molecule RAF kinase inhibitor, which suppresses the RAF/MEK/ERK pathway in tumor cells expressing BRAFV600E. Similar to other selective small molecule RAF kinase inhibitors, LGX818 inhibits CRAF (IC_{50} = 0.30 nM), BRAF (IC_{50} = 0.47 nM) as well as BRAFV600E (IC_{50} = 0.35 nM) in cell-free assays, however, this class of inhibitor does not inhibit RAF/MEK/ERK signaling in cells expressing wild-type BRAF. In the human melanoma cell line A375 (BRAFV600E), LGX818 potently inhibits phospho-MEK (EC_{50} = 2 nM) and phospho-ERK (EC_{50} = 3 nM) and proliferation (EC_{50} = 4 nM), resulting in cell cycle arrest and apoptosis. Given the high-degree of selectivity against other kinases, LGX818 has no antiproliferative activity in tumor cell lines that express wild-type BRAF and is highly selective for BRAF V600E/D/K containing cell lines, with the greatest sensitivity observed in BRAF mutant melanoma and CRC lineages.

The narrow kinase profile and potent anti-proliferative activity of LGX818 translates into a very wide therapeutic index *in vivo*. LGX818 has been evaluated in multiple human tumor xenograft models grown in nude mice. Similar to the *in vitro* profile, the antitumor activity was restricted to tumors expressing BRAFV600E, while there was no anti-tumor effect in xenograft models expressing wild-type BRAF. Preclinical *in vivo* data suggest that LGX818 has a wide therapeutic index and that regression of BRAFV600E human melanoma tumor xenografts is associated with a strong and sustained inhibition of the RAF/MEK/ERK pathway.

For further details on clinical and non-clinical experience, please refer to the current LGX818 Investigator's Brochure.

1.2.1.1 Non-clinical experience

1.2.1.1.1 Non-clinical pharmacokinetics and metabolism

Plasma pharmacokinetics of LGX818 has been investigated following single oral and IV dose in mouse, rat, dog and monkeys. LGX818 exhibited a low plasma clearance (CL) in the rat and mouse and a moderate to high plasma clearance in the monkey and dog. Volume of distribution at steady state (V_{ss}) was low in the rodents and moderate in the non-rodent species examined (0.1 - 2.6 L/kg). This was in agreement with the observed *in vitro* plasma protein binding where LGX818 showed high binding to plasma proteins in the mouse and rat and low to moderate binding to dog, monkey and human plasma proteins. Good bioavailability (F) was observed in the mouse, rat, and dog (~50%) and was low in the monkey at low doses (~5%). Moderate absorption and bioavailability (~ 40%) was also observed in the rat ADME study following oral administration of a suspension of [^{14}C] LGX818.

The predominant route of excretion of [^{14}C] LGX818 in rats was via fecal excretion while the urinary excretion was a minor route of elimination. LGX818 was eliminated in the rat mainly through oxidative metabolism and to a much smaller extent, through parent drug excretion. The major circulating component in rat plasma was LGX818 with only a minor fraction of metabolites.

LGX818 is a relatively potent reversible inhibitor of CYP2B6 (IC_{50} ~ 1 µM), CYP2C9 (IC_{50} ~ 5 µM), and CYP3A4/5 (IC_{50} = 8 µM) and a weak ($IC_{50} \geq 20$ µM) reversible inhibitor of CYP1A2, CYP2C8, CYP2C19 and CYP2D6. LGX818 is also a time-dependent inhibitor of CYP3A4 (K_I = 20.5 µM and K_{inact} = 0.0527 min $^{-1}$). Furthermore, LGX818 was identified to potentially induce CYP3A4 based on an *in vitro* PXR reporter gene assay at high concentrations (≥ 10 -50 µM), likely achievable at doses greater than 800 mg in humans based on predicted human PK data. LGX818 is also a UGT1A1 inhibitor with in vitro IC50 ranging from 4 to 7 uM. LGX818 is a substrate of P-glycoprotein with a high apparent passive permeability. It is a weak inhibitor of BCRP (IC_{50} = 10-25 µM). LGX818 is a potent inhibitor of the renal transporters, OCT1, OAT1, OAT3 and OCT2 (with IC50s at 4.2, 0.93 and 2.05 µM, respective) and hepatic transporters OATP1B1 and OATP1B3 (IC50 values of 5.35 µM and 6.16 µM, respectively). It is therefore advised that substrates for CYP2B6, CYP2C9, CYP3A4/5, OAT1, OAT3, and OCT2, OCT1, OATP1B1 and OATP1B3 with a narrow therapeutic index be taken with caution with LGX818 (see Appendix 4).

LGX818 is metabolized by CYP3A4, CYP2D6 and CYP2C19. The primary CYP responsible for this metabolism is CYP3A4 (>50%); it is therefore advised that strong inhibitors of CYP3A4 (see Appendix 4), be taken with caution.

1.2.1.1.2 Safety pharmacology and toxicology

LGX818 was evaluated in rats and Cynomolgus monkeys in toxicology studies ranging from 1 to 4 weeks in duration. Overall LGX818 was well tolerated at doses at which tumor regression was observed. Significant toxicities were mainly observed in the female rat at the highest dosage of 400 mg/kg/day, a dose well above the maximum dose level to be evaluated in this phase Ib/II study.

Preclinical cardiovascular safety pharmacology data did not indicate a clinical risk for QTc prolongation based on the findings of the hERG assay and ECG evaluation in the GLP 4-week monkey study. Also, there were no clinical signs in the 4-wk GLP rat and monkey studies that would indicate an effect on the CNS or respiratory system.

In a 13-week monkey toxicology study with LGX818, two monkeys treated at a dose of 60mg/kg/day presented retinal changes at the assessment on week 12. These non-clinical findings suggest a potential risk of retinal changes with LGX818.

Rat studies

The 4-week GLP toxicology study in rats was performed at daily doses of 20 mg/kg, 100mg/kg, and 400mg/kg. There were findings associated with the pharmacologic activity of a BRAF kinase inhibitor activation of the RAF/MEK/ERK pathway. These included hyperplasia and hyperkeratosis in the skin (plantar surface of feet) and non-glandular stomach in rats which was apparent at all dose levels in rats and presented with recovery 4 weeks after stopping treatment. Additional toxicity was observed in the 4-week GLP rat study in the testes/seminiferous tubules and epididymides that included an absence of the later stages of spermatid maturation. This finding did not appear to be reversible in affected tubules, but there were normal tubules present in recovery rats. There was significant mortality/morbidity in the female rats at the highest dose (400 mg/kg/day). In these early death rats (around Day 10), significant lesions were seen in the kidneys, liver, stomach, esophagus, bone marrow, spleen, thymus, lymph nodes, pancreas, adrenal glands, and parathyroid glands. However, in the 4 female rats that survived the recovery there were no histopathologic findings. Toxicity was more pronounced in females, where plasma exposure was noted to be approximately double that of males. One male rat at the highest dose of 400 mg/kg/day was also euthanized on Day 10, but the remaining male rats survived to their scheduled necropsy.

The dose of 100 mg/kg/day was tolerated in the rat and considered the appropriate dose for calculation of the initial starting dose in the first-in-man clinical trial.

Monkey studies

The studies in monkeys were performed at daily doses of 5, 20 and 100 mg/kg. All doses were well tolerated. At the highest dose of 100 mg/kg/day, the only toxicity observed was an increase in diarrhea and body weight loss, which was believed to be related partially to the vehicle. There were no histopathologic findings in the monkeys at this highest dose.

1.2.1.1.3 Genotoxicity study

The GLP AMES and Chromosomal Aberration assays indicate that LGX818 is not genotoxic. No *in vivo* genotoxicity studies have been conducted at this stage of development.

1.2.1.2 Clinical experience

Clinical safety

LGX818 is being tested in a first in human Phase I dose escalation ([CLGX818X2101]) study in patients with locally advanced or metastatic BRAF mutant melanoma as micro-emulsion (ME) and capsule formulation (CPS). As of 7 January 2013, 68 patients have been enrolled in the study. 54 Patients were treated in the dose escalation and 14 patients in the dose expansion. Patients were treated with LGX818 capsules (CPS) or micro-emulsion (ME) at 50 mg/day and 100 mg/day, and with LGX818 (CPS) at 150 mg/day, 200 mg/day, 300 mg/day, 450 mg/day, 550 mg/day, 700 mg/day, 75 mg BID, 100 mg BID and 150 mg BID.

In general LGX818 was well tolerated with mainly cutaneous adverse events reported. As per the cut-off date of 7 January 2013 seven dose limiting toxicities (DLTs) have been observed, all were grade 3 events and reversible: 5 DLTs occurred in the once daily dosing regimen (Palmar-plantar erythrodysaesthesia syndrome at 100 mg (with microemulsion)), pain in extremity at 300 mg, fatigue at 550 mg, diarrhea, headache and rash at 700 mg, and insomnia and asthenia at 700 mg) and 2 DLTs occurred in the twice daily regimen (facial paresis and confusional state at 100 mg BID, and neuralgia and musculoskeletal pain in shoulder at 150 mg BID).

The most frequently reported LGX818-related AEs regardless of CTCAE Grade occurring in ≥ 10% of patients overall (as per 7 January 2013) were: hyperkeratosis 25/54 (46%), Palmarplantar erythrodysaesthesia syndrome 25/54 (46%), keratosis pilaris 20/54 (37%), pruritus 20/54 (37%), alopecia 17/54 (32%), dry skin 17/54 (32%), arthralgia 16/54 (30%), fatigue 16/54 (30%), pain in extremity 15/54 (28%), nausea 13/54 (24%), asthenia 12/54 (22%), decreased appetite 12/54 (22%), melanocytic naevus 12/54 (22%), myalgia 12/54 (22%), xerosis 12/54 (22%), erythema 11/54 (20%), hair texture abnormal 10/54 (19%), headache 9/54 (17%), skin papilloma 9/54 (17%), dermal cyst 8/54 (15%), rash erythematous 8/54 (15%), insomnia 7/54 (13%), musculoskeletal pain 7/54 (13%), alanine aminotransferase increased 6/54 (11%), and hypotrichosis 6/54 (11%).

Different types of rash included erythema (20%), rash erythematous (15%), rash (9%), dermatitis acneiform (9%), eczema (9%) rash maculopapular (9%), rash follicular (6%), rash macular (6%), rash papular (4%), dermatitis exfoliative (2%), exfoliative rash (2%), livedo reticularis (2%), rash pruritic (2%), and rosacea (2%). At the cut-off date, 2 patients had a keratoacanthoma and 2 patients had a squamous cell carcinoma (SCC), related to the study drug.

The MTD for LGX818 has been declared at 450 mg QD. This dose is well tolerated and is the recommended phase II dose (RP2D).

As of 7 January 2013, preliminary efficacy results are available for the 54 patients (26 BRAF inhibitor-naïve and 28 BRAF inhibitor-pretreated) enrolled in the dose escalation phase (all dose levels pooled). Among the 26 BRAF inhibitor-naïve patients, 16 (62%) had a partial response (PR) [14 confirmed PR (54%)], and 7 (27%) had stable disease; in the 24 naïve patients

with at least 1 post-baseline tumor assessment all had a tumor reduction (decrease of 6% to 100%). Out of the 28 BRAF inhibitor-pretreated patients, 3 (11%) had a PR [2 confirmed PRs (7%)], and 10 (36%) had stable disease, which includes the unconfirmed PRs.

While retinal changes were observed in two monkeys treated at a dose of 60mg/kg/day at the assessment on week 12, no cases of retinal toxicity were reported in patients who received LGX818 monotherapy or in combination with any other compounds except for MEK162, a drug known to be associated with a risk of retinal changes. In addition, as of November 2013 it is noteworthy that uveitis, a suspected class effect of BRAF inhibitors (according to the vemurafenib and dabrafenib prescribing information), has been reported in 2 patients treated with LGX818 monotherapy and in combination with MEK162, one each respectively.

For further details, please refer to the current LGX818 Investigator's Brochure.

Clinical pharmacokinetics

As of 7 January 2013, patients with locally advanced or metastatic BRAF mutant melanoma received escalating doses of LGX818. Oral doses of 50 mg, 100 mg (both capsule and microemulsion), 150 mg, 200 mg, 300 mg, 450 mg, 550 mg or 700 mg were administered once daily and oral doses of 75 mg, 100 mg and 150 mg were administered twice daily. The pharmacokinetics was investigated after a single dose (Day 1) and multiple doses (Day 15) in Cycle 1. Trough samples were collected on Day 1 of Cycle 2 to 10. In the expansion phase, an additional C1D8 PK profile was collected from 0 to 8 hr. As this study is on-going, all data presented are considered preliminary. The capsule and microemulsion formulations of LGX818 produced similar PK profiles. The median Tmax was around 2 hr for capsule formulation and 0.5-2 hr for the microemulsion formulation. The half-life of LGX818 was approximately 3 hours. From 50 mg to 700 mg QD Cmax and AUC increased in an approximately dose-proportional manner with increasing dose. The BID regimen resulted in a smaller Cmax/Ctrough ratio as expected compared to QD regimen. At the same total daily dose per day, the total AUC under BID regimen appears to be similar to the QD regimen. With QD or BID dosing, the Day 15 exposures were consistently lower (30-60%) than the Day 1 exposures within subjects, probably due to induction of CYP enzymes. AUC and Cmax ratios at steady state (Day 15) relative to Day 1 did not appear to change with dose. The trough concentration on and after Cycle 2 Day 1 did not show a trend of further decline, suggesting that C1D15 was close to or at steady state. So far limited data on C1D8 PK showed that Cmax and AUC were similar on C1D8 and C1D15 with a small decrease. At the above doses tested, the average concentrations of LGX818 reached or exceeded the predicted efficacious concentrations based on preclinical xenograft models (0.135 μg/mL).

For further details, please refer to the current LGX818 Investigator's Brochure.

1.2.2 Overview of MEK162

MEK162 (also known as binimetinib, PF-06811462, ARRY-438162, ONO-7703, and W0074), is an oral, ATP non-competitive, highly selective inhibitor of MEK1/2 that has nanomolar activity against purified MEK enzyme (IC50 = 12 nM) and inhibits both basal and induced levels of ERK phosphorylation in numerous cancer cell lines with IC50s as low as 5 nM. MEK162 is especially potent at inhibiting the cell proliferation of mutant BRAF and RAS

human cancer cell lines *in vitro*. *In vivo*, MEK162 has demonstrated dose-dependent tumor growth inhibition in various subcutaneous tumor transplants harboring $BRAF^{V600E}$ or RAS mutations, including HT29, MIA PaCa2, A549, LoVo, Calu6, DU145 and COLO 205. These data suggest that MEK162 may provide a potential therapeutic benefit in cancer indications, harboring these mutations. MEK162 is currently being investigated in Phase I clinical testing and has been well tolerated up to a maximum tolerated dose (MTD) of 60mg BID in cancer patients.

For further details on clinical and non-clinical experience, refer to the current MEK162 Investigator's Brochure.

1.2.2.1 Non-clinical experience

1.2.2.1.1 Pharmacology studies

The biological activity of MEK162 has been evaluated *in vitro* (enzymatic and cell culture) and *in vivo* mouse xenograft studies.

In vitro efficacy studies

In biochemical studies, MEK162 has been shown to be a potent and highly selective inhibitor of MEK. In cellular assays, MEK162 has been shown to markedly inhibit the phosphorylation of ERK in human cell lines as well as human whole blood. In human MALME-3M melanoma cells and in HT29 colorectal cancer cells, MEK162 significantly inhibited proliferation and viability, respectively. The ability of MEK162 to inhibit cancer cell growth in culture was evaluated using a standard 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) assay. In the human HT-29 colorectal cell viability assay, the IC_{50} of cell growth was observed at a concentration of 163 nM MEK162. In the human melanoma Malme-3M cell proliferation assay, the IC_{50} of cell growth was observed at a concentration of 30 nM MEK162.

In vivo efficacy studies

In vivo studies were performed to evaluate the activity of MEK162 with respect to inhibiting tumor growth and tumor ERK phosphorylation. In the HT29 and in the COLO 205 colon carcinoma models, dose-dependent inhibition of tumor growth (up to 75% tumor growth inhibition TGI) was observed at doses ranging from 3 to 30 mg/kg, QD, by mouth (PO) for 21 days. In the sensitive COLO 205 colon carcinoma model, MEK162 treatment resulted in 84% TGI with significant tumor regressions at a dose of 30 mg/kg. In the BxPC3 pancreatic carcinoma model (which does not harbor either RAS or RAF mutations, but harbors MAP2K4 mutation), significant tumor regressions (59%) were seen at doses of 30 mg/kg. In the BxPC3 pancreatic carcinoma model (which does not harbor either RAS or RAF mutations, but harbors MAP2K4mutation), ~70% TGI and 13% PRs were seen at doses of 30 mg/kg, QD, PO for 21 days. Consistent with the mechanism of action for MEK162, TGI correlates with decreased phospho-ERK levels in tumor xenografts.

Overall, MEK162 has demonstrated potent activity against MEK1/2 and broad anti-proliferative activity in vitro and in vivo.

1.2.2.1.2 Non-clinical pharmacokinetics and metabolism

Pharmacokinetic (PK) studies were conducted with MEK162 in rats, dogs and monkeys. After oral administration, the AUC and C_{max} values for MEK162 increased in a nearly dose-proportional manner in rats and monkeys. The mean bioavailability was lowest in monkeys, higher in dogs, and highest in rats at equivalent doses (range across species: 13% to 72%). Following intravenous (IV) administration, the plasma clearance (CL) values were low-to-moderate (range: ~2 to 8 mL/min/kg) and tended to increase across species such that monkey > dog > rat. Mean plasma $t_{1/2}$ values showed a similar trend where monkey > dog > rat (range: ~2 to 9 hrs). The volume of distribution at steady state (V_{ss}) values ranged from 0.189 to 1.57 L/kg.

In vitro experiments in Caco-2 and LLC-PK1 cells indicated that MEK162 had moderate membrane permeability and may be a substrate for active efflux. MEK162 was determined to be a substrate for both BCRP and P-gp transporters. MEK162 exhibited high plasma protein binding in vitro (> 95%) and is predicted to have good stability with respect to hepatic metabolism. Nonclinical *in vitro* and *in vivo* data indicate that main pathways of metabolism for MEK162 including oxidation by CYP2C19 and CYP1A2 and glucuronidation by UGT1A. In human plasma, major entities include glucuronides of MEK162, as well as the primary active metabolite, AR00426032, which is equipotent to MEK162. Formation of AR00426032 that has been monitored in clinical studies was found to be mediated primarily by CYP1A2 with minor contributions from other cytochrome P450 enzymes (CYPs). MEK162 did not significantly inhibit (IC50> 25μM) the major CYP isoforms. MEK162 was not a time-dependent inhibitor of CYP3A.

Based on results from the rat ADME study, the absorption of MEK162 was approximately 50% of dose and bioavailability was 47%. Following oral dosing at 4 mg/kg to rats, fecal and urinary excretion accounted for 69.4% and 23.1% of total radioactivity, respectively. Unchanged MEK162 accounted for approximately 5% of dose in urine and 22% of dose in feces. In addition, the glucoronide conjugate M10.9 accounted for 13% of dose in urine and metabolite M4 (loss of ethane diol) accounted for 34% of dose in feces. Overall, MEK162 is mainly excreted through urine and feces as unchanged parent drug, glucoronide conjugates and M4.

Following single- and repeat-dose administration of MEK162 to Sprague-Dawley rats for up to 6 months, females were found to have approximately 2-fold higher exposure than males at equivalent doses. The values for C_{max} and area under the plasma concentration-time curve for a dosing interval from time 0 extrapolated to infinity (AUC_{inf}) increased with dose, although the increase in exposure was less than dose proportional. Cynomolgus monkeys receiving MEK162 for 28 days or 9 months showed no consistent differences in exposure between females and males. There were no significant changes in exposure versus day.

1.2.2.1.3 Safety pharmacology and toxicology

The toxicological evaluations of MEK162 include single-dose, and 28-day and 6-month repeat-dose studies in Sprague Dawley rats and 28-day and 9-month repeat-dose studies in cynomolgus monkeys, all of which were conducted in accordance with international regulatory guidelines for nonclinical toxicity studies and in adherence to current GLP guidelines. These studies were supplemented with local tolerance, 9 safety pharmacology studies (hERG channel

assay and behavioral, cardiovascular, renal, pulmonary and 2 gastrointestinal function/tolerability studies as well as 2 non-GLP studies evaluating wound healing and immune function) and 3 developmental toxicity studies in the rat and the rabbit.

In all of the GLP toxicology studies conducted, there was no significant effect of MEK162 on vital signs, coagulation parameters, complement, organ weights or urinalysis parameters in doses up to 100 mg/kg in rats and 10 mg/kg in monkeys. Administration of MEK162 to rats by oral gavage was associated with skin lesions (inflammation/scabbing), microscopic findings of soft tissue mineralization (which did not occur with the 26-week dosing regimen) and reversible minimal to mild clinical pathology changes.

Safety pharmacology studies were conducted to assess the effects of MEK162 on key organ systems (cardiovascular, respiratory, neurobehavioral, renal and gastrointestinal function). Rats received single oral doses of 10, 30 or 100 mg/kg and monkeys were given single oral doses of 1, 3 and 10 mg/kg. There were no significant *in vivo* safety findings at doses up to 100 mg/kg in rats and 10 mg/kg in monkeys in any of these studies.

1.2.2.1.4 Genotoxicity study

MEK162 is not genotoxic *in vitro* and *in vivo*, based on the results of 3 genotoxicity assays (*in vitro* bacterial mutagenicity, mouse lymphoma assay and *in vivo* mouse micronucleus assay).

1.2.2.2 Clinical experience

As of the data-cut-off date of 07 Jan 2013, a total of 686 patients and healthy volunteers have received at least one dose of MEK162, either as a single agent or in combination with paclitaxel, PI3K, RAF 1 or IGF-1R inhibitors and have been evaluated for safety, including 90 healthy volunteers, 164 patients with rheumatoid arthritis and 432 patients with advanced cancer.

MEK162 has been evaluated in 3 completed studies in healthy subjects (single ascending dose, multiple ascending dose, single-dose relative bioavailability and food effect) and 2 completed studies in patients with rheumatoid arthritis (a Phase I multiple ascending dose study and a Phase II study, both in combination with methotrexate).

The experience with MEK162 as a single agent in oncology patients includes 3 ongoing studies with a total of 216 patients enrolled as of the cut-off date. These are 2 Phase I studies: [ARRAY-162-111] in patients with solid tumors with an expansion phase in biliary and colorectal cancer, (in this study a dose range from 30 to 80 mg BID has been explored), and [CMEK162X1101] in Japanese patients with solid tumors and an expansion in patients with RAS or BRAF mutations, and one Phase II study: [CMEK162X2201] in patients with advanced melanoma, (45 mg and 60 mg BID dose levels have been explored).

The experience with MEK162 in cancer patients in combination studies comprises 7 ongoing Phase I studies as of the cut-off date.

For detailed information regarding clinical studies with MEK162, refer to the MEK162 Investigator's Brochure.

1.2.2.2.1 Clinical safety and efficacy

Frequently reported AEs suspected to be related to study drug in single agent studies for advanced cancer are dermatitis acneiform, diarrhea, peripheral edema, increased blood CK, nausea, fatigue, rash and vomiting. Most of these AEs were Grade 1 or 2 with less than 5% of cases Grade 3-4, with the exception of elevation of blood CK.

Other less frequent but clinically relevant toxicities include left ventricular ejection fraction (LVEF) decrease and increase of liver enzymes. Four patients had Grade 2 LVEF decrease, and one patient had Grade 3 LVEF decrease. Most of the liver enzyme increases were Grade 1 or 2. Grade 3 or 4 liver enzyme elevations were reported in 2/106 (1.8%) patients with AST elevation and 1/106 (0.9%) patient with ALT elevation. No Grade 3-4 elevation of bilirubin was reported.

In combination studies, the most frequently reported AEs suspected to be related to study drug were diarrhea, CK elevation, dermatitis acneiform/rash, nausea/vomiting and fatigue.

CMEK162X2201

[CMEK162X2201] is a phase II study assessing the safety and efficacy of MEK162 in patients with locally advanced and metastatic BRAF and NRAS mutated melanoma. As of the cut-off date, a total of 106 patients have received at least 1 dose of MEK162. Initially, the study explored the 60 mg BID dose, but due to the occurrence of 2 unexpected suspected severe adverse events (one case of fatal acute liver failure and another case of decreased ejection fraction), subsequent patients received 45 mg BID, which was the dose selected as the recommended Phase II dose. Thus, from the 106 patients who received at least 1 dose of MEK162, 25 patients were treated with 60 mg BID MEK162 and 81 patients were treated with 45 mg BID MEK162. At the time of the cut-off, 93 (87.7%) patients have discontinued treatment with 22 (21%) having discontinued due to an AE; 13 (12.3%) patients are still ongoing.

The most frequently treatment-related occurring events (≥ 20%) were dermatitis acneiform, diarrhea, peripheral edema, increase in CK levels, nausea, fatigue and rash. The most common treatment-related Grade 3-4 AEs were CK increased (20/106), dermatitis acneiform (4/106) and diarrhea (3/106). CSR-like events were reported by 40/106 (38%) patients regardless of relationship to MEK162 including Grade 3-4 events in 3/106 (3%) patients. These events included retinopathy, blurred vision, retinal edema, generalized eye disorder, vitreous floaters, retinal detachment, retinal pigment epitheliopathy, and visual impairment. Most CSR-like events were Grade 1, transient in nature and resolved without treatment modification, after dose reduction, or after interruption of treatment. Cardiac events regardless of relationship to MEK162 were reported by 4/106 (4%) patients. All were Grade 3-4. Three reports of syncope (1 related to MEK162) were recorded. A serious and possibly drug related adverse event of ventricular ejection fraction decreased, heart failure, myocarditis and tachycardia was reported at a starting dose of 60 mg BID. No other case of decreased LVEF was reported.

As of 7-Jan-2013, in the [CMEK162X2201] study, among the 35 patients evaluable for efficacy with mutant BRAF melanoma treated with MEK162 at 45mg BID, 2 confirmed and 6 unconfirmed partial responses (23%) and 14 patients with stable disease were recorded. In this group 63% of the patients achieved disease control. In the 35 patients evaluable for efficacy with NRAS mutant melanoma treated at 45 mg BID, 6 confirmed and 2 unconfirmed partial

responses (23%) and 15 patients with stable disease were recorded. Sixty six % of the patients achieved disease control.

1.2.2.2.2 Clinical Pharmacokinetics

In healthy subjects and patients with rheumatoid arthritis, the analysis of PK data was done using model independent (NCA) methods only. These analyses suggested that absorption was rapid, that there was extensive distribution and that the apparent terminal half-life was short. Contrary to expectation, given the short half-life, accumulation greater than that predicted by linear PK was observed. Overall when given BID, accumulation was around 1.5 to 1.7 fold. This apparent non-linearity in the PK of MEK162 may have been related to a combination of a relatively high LLOQ of the assay used (5 ng/mL) and the schedule of blood collection for PK used. In order to overcome these limitations and to fully characterize the PK of MEK162 in cancer patients a model based analysis was conducted using a population PK method. For this analysis, information from 130 subjects from two clinical studies, [CMEK162X2201] and [ARRAY-162-111], were used. Dose levels range from 30 mg BID to 80 mg BID.

MEK162 PK was best described by a two compartment disposition model with first-order elimination and first-order absorption with a lag time. The estimated between subject variability on apparent clearance (CL/F) was moderate (44%) and very high (~150%) for the apparent central volume of distribution (Vc/F) and apparent peripheral volume of distribution (Vp/F). The covariate effect of dose on relative bioavailability was identified as significant (at an α = 0.001 significance level). Relative to the 45 mg dose, the bioavailability of the 30 mg dose level was 120%; while the relative bioavailability of 60 mg and 80 mg doses were 88% and 77%. This dose dependence was not seen using model independent methods but most likely represents either solubility limited absorption of MEK162 or the impact of P-gp or a combination of the two. Based on the PK parameters estimated in this analysis when administered BID, MEK162 steady state is reached around Day 15 and the accumulation is around 1.7 fold, which is consistent with observation.

For further information refer to the current MEK162 Investigator's Brochure.

1.2.3 Overview of LEE011

LEE011 (also known as ribociclib) is an orally bioavailable, small molecule inhibitor of CDK4/6. LEE011 exhibits highly specific inhibitory activity against CDK4/cyclinD1 and CDK6/cyclinD3 complexes, with concentration resulting in 50% inhibition (IC50) values of 10 nM and 39 nM, respectively, in isolated enzyme assays. It is inactive against the majority of other kinases. It is currently being tested in a clinical trial [CLEE011X2101] in adult cancer patients.

For further details on clinical and non-clinical experience, please refer to the current LEE011 Investigator's Brochure.

1.2.3.1 Pharmacology of LEE011

LEE011 inhibits the growth of many tumor cell types *in vitro* and *in vivo*, including mantle cell lymphoma, liposarcoma, rhabdoid tumors, neuroblastoma, and carcinomas of the esophagus, breast, lung and pancreas. Regardless of the various genetic aberrations that may be present in

the cancer cells, the anti-tumor activity of LEE011 requires the presence of functional retinoblastoma protein (Rb).

LEE011 has demonstrated tumor growth suppression in multiple melanoma xenograft models including BRAF wild type and mutant ones as a single agent. Tumor regression was achieved in two models while tumor stasis was observed in five models. In primary V600E BRAF mutated melanoma models, LEE011 in combination with LGX818 (a potent and selective RAF inhibitor), produced significant delay in tumor re-growth. In mouse models resistant to LGX818, LEE011 demonstrated tumor growth inhibition as single agent and in combination with LGX818, showed enhanced growth inhibition.

1.2.3.1.1 Nonclinical pharmacokinetics (PK) and metabolism of LEE011

The PK of LEE011 was investigated in four different species: mouse, rat, dog and monkey. After oral administration to rats, LEE011 was moderately absorbed (48 to 84%), with bioavailability ranging between 10% and 65% across animal species. Maximum serum drug concentration (Cmax) was observed between 2 and 4 hours post-dose. Terminal half-life (T1/2) of LEE011 was moderate in rodents and monkeys (2 to 7 h), and was comparatively longer (18 h) in dogs.

The binding of LEE011 to plasma proteins was moderate (unbound fraction in plasma for humans is 30 ± 2%). ^{3}H-LEE011 and its metabolites were extensively distributed into the organs and tissues of rats including choroid, ciliary body and meninges with the exception of the brain. The highest radioactivity concentrations were found in tissues such as pituitary gland, pineal gland, spleen, kidney and adrenal medulla with remarkably high exposure in the thyroid gland. Distribution of LEE011 and/or its metabolites into melanin-containing structures was seen in pigmented rats.

Oxidative metabolism of LEE011 is dominated by CYP3A4 with a minor contribution by flavin-containing monooxygenase 3 (FMO3). *In vitro* studies indicate LEE011 is a reversible inhibitor of CYP1A2 (K_i = 16 µM), CYP3A4 (K_i = 35 µM), and CYP2E1 (IC50 = 62µM). LEE011 is also a time-dependent inhibitor of CYP3A4 (K_I = 5.06 µM, k_{inact} = 0.0245 min^{-1}). LEE011 was identified as inhibitor of the efflux transporter MDR1 (IC50 = 143µM) and MXR (IC50 = 24µM). LEE011 could affect substrates of the MDR1 transporter, depending on the LEE011 dose and intestinal concentration. LEE011 inhibited the human bile salt export pump (BSEP) transporter (IC50 = 4.7 µM).

PK data from the ongoing phase I study ([CLEE011X2101]) show that the plasma Cmax of LEE011 at steady state after 600 mg QD dosing in humans ranges from 943-5860 ng/mL (arithmetic mean = 2940 ng/mL or 5.32 µM), which is well below the above mentioned Ki or IC50s for reversible inhibition of CYPs and transporters. The major DDI risk identified for LEE011 is its time-dependent inhibition of CYP3A4, which could increase exposures of major CYP3A4 substrates.

LEQ803 (N-demethylation) is a major metabolite in the rat and monkey, the main metabolite in humans and the only metabolite in dogs. This metabolite was found to interact with hERG channels *in vitro*.

In rat ADME studies, LEE011 was predominantly excreted with bile. The elimination of unchanged drug was limited. A minor proportion of the administered dose is excreted in urine. The bulk of the administered dose (87.3%) was excreted within 24 hours post-dose.

Overall, the elimination of LEE011 may potentially be affected by co-administered drugs that inhibit or induce CYP3A4. LEE011 may inhibit the metabolism/transport of sensitive substrates of CYP3A4, CYP1A2, and BSEP.

1.2.3.1.2 Safety pharmacology and toxicology of LEE011

In vitro, LEE011 did not show mutagenic or phototoxic potential.

Safety pharmacology studies did not reveal any effects on CNS or respiratory functions. In the dog telemetry study, prolongation of the average QT and QTc was observed with the potential to induce PVCs at higher exposure levels. NVP-LEE011 and LEQ803 likely contributed to the QT prolonging effects seen *in vivo*.

In rats and dogs, LEE011 induced bone marrow hypocellularity, lymphoid depletion, atrophy of the skin and intestinal mucosa, decreased bone formation and testicular atrophy. These are consistent with the mechanism of action of LEE011. In addition, an increased number of ovarian corpora lutea was observed in a single female dog at the highest dose tested. The liver, bile system and gall bladder (proliferative changes, cholestasis, sand-like gallbladder calculi, and inspissated bile) were identified as additional target organs of toxicity which are not likely related to the primary pharmacology of LEE011. Correlating hematological and/or biochemistry changes were seen for the effects described in the bone marrow, lymphoid system and liver. All the described changes were fully reversible in rats and dogs.

Based on its mechanism of action and preclinical toxicology studies, the major potential toxicities for LEE011 include myelosuppression, hepatic toxicity, and prolongation of the QT interval. The risk of these toxicities may be amplified by concomitant administration of strong inhibitors of CYP3A4.

Please refer to the current LEE011 Investigator's Brochure for additional details.

1.2.3.2 Clinical Study with LEE011

As of 4 February 2013, 56 patients have been treated with single agent LEE011 in the first-in human phase I study [CLEE011X2101] in which LEE011 is administered orally, once daily for 21 days followed by a 1 week rest (28-day cycle). Doses tested include 50 mg (n=4), 70 mg (n=2), 140 mg (n=4), 260 mg (n=4), 280 mg (n=4), 350 mg (n=5), 400 mg (n=5), 600 mg (n=4), 900 mg (n=13), 750 mg (n=8), and 1200 mg (n=3). In all, 8 DLTs have been observed. DLTs include grade 3 mucositis (n=1) in the 50 mg cohort, grade 3 pulmonary embolism (n=1) in the 280 mg cohort, grade 3 hyponatremia (n=1) and prolonged grade 3/4 neutropenia (n=1) in the 400 mg cohort, grade 4 thrombocytopenia (n=1) in the 750 mg cohort, grade 3 asymptomatic QTc prolongation with grade 3 neutropenia (n=1) in the 900 mg cohort and grade 4 febrile neutropenia (n=1) and grade 4 thrombocytopenia (n=1) in the 1200 mg cohort. The grade 3 mucositis observed in the 50 mg cohort was later determined to be due to herpes simplex virus (HSV) infection. A DLT related to mucositis has not been observed since. Four cases of Grade 1 or 2 mucositis have been observed in doses up to 350 mg; mucositis has not been observed at higher doses. The grade 3 pulmonary embolism was observed in a patient with NSCLC who

had diffuse bilateral lung disease and a central venous catheter. The grade 3 hyponatremia was asymptomatic and readily corrected with saline infusion. Grade 3 or 4 neutropenia and/or thrombocytopenia not meeting DLT criteria were seen in increasing frequency starting from 600 mg up to 1200 mg. Asymptomatic grade 1 or 2 QTc prolongation were observed in increasing frequency starting at 600 mg up to 1200 mg; 1 patient (25%) in the 600 mg cohort, 2 patients (25%) in the 750 mg cohort, 4 patients (31%) in the 900 mg cohort, and 3 patients (100%) in the 1200 mg cohort. The most frequently reported treatment-related AEs include fatigue, nausea, anemia, asthenia, neutropenia, vomiting, leukopenia, increased blood creatinine, decreased appetite, diarrhea, hypoalbuminemia, lymphocytopenia, myalgia, thrombocytopenia, dizziness, erythema, hyperglycemia, mucosal inflammation and stomatitis. The majority have been grades 1 or 2 and reversible.

The MTD of LEE011 for the 3 weeks on/1 week off schedule is 900 mg. The study continues with exploration of alternate dosing schedules and further assessment of safety, tolerability, and preliminary anti-tumor activity of LEE011.

Please refer to the current LEE011 Investigator's Brochure for additional details.

1.2.3.2.1 Clinical pharmacokinetics of LEE011

Preliminary pharmacokinetics data for LEE011 demonstrate that peak plasma concentrations were achieved by 1 to 5 hours (range of median T_{max} values) following oral dosing. LEE011 pharmacokinetics data up to 1200 mg exhibit slightly over-proportional increases in exposure across the dose range tested. Steady-state is reached by day 8 and effective $T_{1/2}$ values based on accumulation ($T_{1/2}$, acc) ranged from 24 hours (50 mg QD dose) to 40 hours (600 mg QD dose), and 31 hours (900 mg QD dose). The accumulation ratio (R_{acc}) across the studied daily dose of 50 to 1200 mg ranged from 1.55- to 2.94-fold.

Please refer to the current LEE011 Investigator's Brochure for additional details.

1.2.4 Overview of combination treatment

1.2.4.1 Pre-clinical studies with combinations of RAF and MEK - inhibitors

Combining inhibitors of sequential steps in the MAPK signal transduction pathway have the potential to provide several advantages when compared to single agent treatments. These advantages could include reduction or elimination of the emergence of resistance that might arise in the single agent setting, greater overall efficacy via more complete pathway suppression, and provision of the ability to dose-reduce one or more of the drugs to avoid or minimize toxicities. To assess whether either of these latter two benefits might be the case, the effect of combining LGX818 and MEK162 on the *in vitro* proliferation of cell line models that harbor BRAFV600E alterations was examined. These studies were carried out in both melanoma and colorectal cancer-derived cell lines with standard measures of synergy used to determine whether the combination was, dose-shifting, able to boost the overall effects of the single agents, or both (Lehar 2009). These studies indicated a statistically significant synergy ($p = <0.0001$, one-tailed T-Test) for the combination when compared to the single agents (Caponigro 2011, Novartis, data on file). In cell lines where significant synergy was measured (5/6 CRC and 6/12 melanoma) both dose-shifting and effect boosts were observed. In addition, in cases where synergy was not observed, combining the two inhibitors resulted in dose-additivity.

In vivo, the combination of LGX818 and MEK162 has been evaluated in a mouse primary xenograft model of human melanoma that expresses BRAFV600E. While there was increase in the degree of tumor regression observed in the combination groups compared to single-agent MEK162 (3 mg/kg or 10 mg/kg bid) or LGX818 (3 mg/kg bid) respectively, the most dramatic effect was on the duration of response. Over the course of 116 days of treatment, the vast majority of tumors developed resistance to single-agent MEK162 (8/8 at low dose and 7/8 at high dose) or LGX818 (6 out of 7). In contrast, treatment with LGX818 and low dose MEK162 combination, resulted in only one out of eight tumors developing clear resistance and no tumors developed resistance to combination treatment of LGX818 and high dose MEK162. These data support the hypothesis that combining RAF and MEK inhibitors will result in a more sustained tumor response.

Collectively these *in vitro* and *in vivo* results strongly suggest that combining these inhibitors in the clinic in the BRAFV600E setting is likely to result in an increase of anti-tumor activity compared to either single agent.

1.2.4.2 Clinical studies with combinations of selective RAF and MEK - inhibitors

The concept of dual, vertical inhibition of the ERK/MAPK- pathway is currently being explored within a Phase I/II clinical trial. [Study NCT01072175] investigates the safety, PKs, PDs and clinical activity of the combination of the BRAF-inhibitor GSK2118436 (GlaxoSmithKline) and the selective MEK1/2- inhibitor GSK1120212 in patients with advanced BRAF- mutation positive tumor types. One hundred nine patients have been enrolled in the study and preliminary results were presented at ASCO 2011 (Infante 2011). Both investigational drugs could be administered at full dose in combination, GSK2118436 150 mg BID and GSK1120212 2mg QD, showing a significant tumor shrinkage in the majority of the patients with an ORR of 70%. The combination was well tolerated and the most common AEs included pyrexia, fatigue, rash, diarrhea and nausea. Interestingly, patients experienced less skin toxicities compared to monotherapy.

BRAF-inhibitors including PLX4032, XL-281 and GSK2118436 are associated with hyperproliferative skin lesions (ie, keratoacanthomas and squamous-cell carcinomas) in up to 31% of patients (Flaherty 2009; Flaherty 2010; Kefford 2010), indicating that BRAF inhibitors can paradoxically activate the RAF/MEK/ERK pathway and promote growth in RAS mutant/BRAF wt tumors (Hatzivassiliou 2010; Cichowski 2010). The decreased occurrence of SCC in the GSK2118436/GSK1120212 combination trial, suggests that MEK inhibitors by acting downstream of RAF in the RAF/MEK/ERK pathway, may potentially block inappropriate signal transduction, originating either from the cell surface or due to RAS/RAF mutations, further strengthening the rationale for combining MEK inhibitors with BRAF inhibitors in the clinic.

1.2.4.3 Pre-clinical studies with combinations of RAF, MEK and CDK - inhibitors

Increased CDK4/6 activity and the accompanying loss of G1/S phase cell cycle control is a hallmark of melanoma. This increased activity can occur as a result of several non-exclusive events. For instance, one consequence of ERK/MAPK pathway activation due to oncogenic

lesions in BRAF and NRAS is the elevation of cyclin D1 levels which in turn interact with and activate the CDK4/6 kinases. In addition, molecular alterations that directly increase CDK4/6 activity such as loss of expression of the CDKN2A gene, which encodes p16 a negative regulator CDK4/6, and amplification of CCND1, the gene encoding CyclinD1 are collectively observed in a majority of melanomas. Further underscoring the importance of CDK4/6 kinases in melanoma, combining the CDK4/6 inhibitor LEE011 with either LGX818 or MEK162 in BRAF and NRAS-mutant models of melanoma, respectively, leads to both improved efficacy and prolonged anti-tumor responses *in vivo* (RD-2012-50372, RD-2012-50370).

The effect of simultaneously combining LGX818, MEK162 and LEE011 on the proliferation of BRAF-mutant melanoma cell lines in vitro was examined. The cell lines used were the A-375 and WM-266-4 models, both of which are highly sensitive to LGX818 and MEK162, and derivatives of each of these lines engineered to express one of several proteins known to confer resistance to RAF inhibitors including NRASQ61K (Nazarian 2010), BRAF p61 (Poulikakos 2011), MEK1C121S, and MEK1P124L (Emery 2009). When a fixed ratio of MEK162 and LGX818 (1:1, 0–2.7uM) was combined with LEE011 (0–10uM), either synergy or dose-additivity was observed in all models. Synergy was observed in both the parental A-375 and WM-266-4 cell lines as well as in the NRASQ61K-expressing variant of A-375. In all other models either weak synergy or dose-additive effects were observed.

Collectively these results suggest that adding the CDK4/6 inhibitor LEE011 to the LGX818/MEK162 combination in the clinic in BRAFV600 mutant patients is likely to further increase the anti-tumor activity of the LGX818/MEK162 combination.

1.2.4.4 Clinical studies with combinations of selective RAF, MEK and CDK4/6 inhibitors

No studies are currently reported and/or ongoing with a selective RAF, MEK and CDK4/6 inhibitor triple combination.

1.3 Anticipated risks and safety considerations of the study drug combinations

1.3.1 Dual combination LGX818 and MEK162

While preliminary clinical data available from ongoing studies with LGX818 and MEK162 as single agents suggest overlapping toxicities for the proposed combination which may potentially be dose-limiting, including effects on the skin (e.g. rash), initial reports with similar class of compounds have shown that selective BRAF inhibitor combines safely with MEK inhibitor with a decreased occurrence of skin toxicities (rash, SCC). This data suggests that the combination of LGX818 with MEK162 may have an improved safety profile compared the respective single agent therapies.

Retinal toxicity (CSR), GI toxicity (i.e. diarrhea; nausea/vomiting), body edema, and elevations in CPK are associated specifically with MEK162. HFSR, photosensitivity and hyperesthesia were reported with the use of LGX818. MEK162 also caused ectopic soft tissue mineralization in pre-clinical toxicology studies, exclusively in rats. However, the plasma exposure margins for soft tissue mineralization in rats are 60-fold above those seen in humans at 60 mg bid. To

date there have been no reports of a calcium-phosphate imbalance, including ectopic calcifications, associated with the clinical use of MEK162.

Based on the available data, no significant metabolism-based DDI is foreseen with the LGX818 and MEK162 combination. Although LGX818 is a UGT1A1 inhibitor and MEK162 is a UGT1A1 substrate, the average concentration of LGX818 with 50 mg ME QD dose is expected to be well below the IC50 (~4 uM). LGX818 is both a substrate as well as an inhibitor/inducer of CYP3A.The inhibition and induction effects of LGX818 on CYP3A do not appeared to be significant since the human PK profile on Day15 was similar to Day 1 and no accumulation was observed.

LGX818 is a BCRP inhibitor (IC50 at 10-25 uM) and MEK162 is a BCRP substrate. Since the concentration of LGX818 in the gut is expected to be ~0.4 mM with a 50 mg dose (assuming all drug dissolved in 250 mL volume), there is a potential for increased MEK162 exposure due to BCRP-inhibition by LGX818. A rat ADME study showed that 50% MEK162 was absorbed after oral dose. If human is similar to rat, the maximum potential increase in MEK162 exposure is 100% with the LGX818 and MEK162 combination.

For the safety of the study patients, the starting dose of the combination will include a 75% fraction of the single agent MTD of MEK162. As the MTD of LGX818 is still under consideration, the starting dose will be selected based on a well tolerated dose from the ongoing [CLGX818X2101] clinical study. Doses of LGX818 and MEK162 will be alternately escalated for each compound during dose escalation (see Section 6.2.3 and Section 6.2.4.2 for provisional dose levels and details on the dose escalation process). Furthermore, appropriate eligibility criteria and specific DLT criteria as well as specific dose modification and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities are provided in Section 6.1.2 and Appendix 3. The PKs of MEK162 and LGX818 will also be assessed in the current study to further evaluate the potential for a PK drug-drug interaction.

1.3.2 Triple combination LGX818 and MEK162 and LEE011

Based on the most frequent observed adverse events described for the LGX818 and MEK162 dual combination (see current LGX818 Investigator Brochure or MEK162 Investigator Brochure) and for LEE011 (see Section 1.2.3.2 and current LEE011 Investigators Brochure), overlapping toxicities can be expected for gastrointestinal events (such as nausea, vomiting, diarrhea) as well as fatigue.

Since (asymptomatic) QTc prolongation has been observed with LEE011 as a single agent, additional collection of post-dose ECGs are implemented into this trial for the triple combination. ECGs be collected in triplicate (vs. single ECGs) and the entry criteria for the triple-combination study exclude patients with congenital long QT syndrome or family history of unexpected sudden cardiac death and/or hypokalemia CTCAE Grade ≥ 3, and patients who are currently receiving treatment with agents that are known to cause QTc prolongation in humans. During study treatment with the triple combination, use of concomitant medication known to cause QTc prolongation is prohibited.

LEE011 inhibited CYP3A4-catalyzed marker substrate reactions in vitro in human liver microsomes with Ki values of 35 μM. Time-dependent inhibition of CYP3A4 was observed

with a Ki value of 5 μM and a Kinact value of 0.0245 min-1. Since LGX818 is a substrate for CYP3A4, LEE011 has a potential to increase PK exposures of LGX818. *In vitro* studies indicated that LEE011 was mainly metabolized by CYP3A4. Since LGX818 is a more potent inducer than an inhibitor of CYP3A4, LGX818 may decrease the exposure of LEE011.

Quantitative assessment of potential drug-drug interaction was performed using a dynamic physiologically based PK (PBPK) model in Simcyp and the simulation confirmed the qualitative assessment. At LGX818 450 mg QD and LEE011 200 mg QD, the model predicts 29% and 14% increase in AUC and Cmax of LGX818, respectively, as well as 47% and 30% decrease in AUC and Cmax of LEE011, respectively.

MEK162 is mainly metabolized by glucuronidation and is not a strong CYP3A4 inhibitor. In vitro data and some clinical data suggest MEK162 might have CYP3A4 induction potential. However, no significant PK exposure changes for LGX818 were observed in the LGX818 and MEK162 dual-combination phase up to date. Even if the induction occurs between MEK162 and LEE011, it will likely decrease LEE011 exposure and therefore will not pose a safety risk. Overall the PK drug-drug interaction between MEK162 and LEE011 is expected to be minor and not pose significant safety risk.

In this ongoing [CMEK162X2110] study, the PK profiles of LGX818 and MEK162 when given in combination were generally similar to those in their corresponding single agent studies. With increasing LGX818 doses (50mg, 100mg, 200mg, 400mg, 450mg and 600mg), the PK exposure of MEK162 did not change. These data indicated that no significant PK drug-drug interactions between LGX818 and MEK162 were observed.

For the safety of the study patients to be treated with the triple combination, the starting dose of LEE011 in the triple combination will include a 1/9 fraction of the single agent MTD of LEE011 (i.e. MTD 900 mg QD 3 week on/1 week off schedule), i.e 100 mg QD. For the starting dose of LGX818 and MEK162, the RP2D of 450mg QD and 45mg BID was selected as a well-tolerated dose from the ongoing CMEK162X2110 clinical study for the dual combination. Doses of LEE011 and possibly of LGX818 will be alternately escalated for each compound during dose escalation (see Section 6.2.3 and Section 6.2.4.2 for provisional dose levels and details on the dose escalation process). Furthermore, appropriate eligibility criteria and specific DLT criteria as well as specific dose modification and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities are provided in Section 6.1.2 and Appendix 3. Specific safety assessments (i.e. post-dose ECGs/ triplicate ECGs) will be performed to monitor cardiac safety during triple-combination study treatment. The PKs of MEK162, LGX818 and LEE011 will also be assessed in the current study to further evaluate the potential for a PK drug-drug interaction.

2 Rationale

[Any language regarding the triple combination of LGX818/MEK162/LEE011 in this Section is <u>not</u> applicable to the USA and Singapore]

2.1 Study rationale and purpose

About half of the patients with melanoma have an activating mutation in BRAF that results in the activation of the RAF/MEK/ERK pathway and plays an important role in the development of melanoma. BRAF mutations may also be present in up to 15% of patients with colorectal cancer and are associated with a poorer clinical outcome. A number of preclinical studies have validated BRAF as a therapeutic target in melanoma, and two selective BRAF inhibitors, PLX4032 and GSK2118436, have shown clinical activity in patients with BRAF V600E mutated melanoma. The selective BRAF inhibitor, vemurafenib/PLX4032 (Zelboraf®), was recently approved by the FDA for the treatment of patients with unresectable or metastatic melanoma with the BRAF V600E mutation. However, data also indicate that the duration of response to BRAF inhibitors is often short lived (median PFS ~ 6 to 7 months), with resistance developing quickly. LGX818 is a highly potent and selective BRAF inhibitor, and preclinical data suggest that LGX818 could lead to more sustained clinical responses in patients with advanced and/or metastatic BRAF V600 mutant melanoma compared to competitor RAF inhibitors (Stuart 2011) (see also Section 1.2.1).

The redundancy within the multiple signaling pathways activated in cancer, along with the likelihood of drug resistance, suggests that combination therapy strategies will be required for effective disease management (Smalley 2009). There is preclinical evidence of emerging resistance to BRAF- and MEK1/2- inhibitors treatment through MEK1-mutations (Montagut 2008; Emery 2009). As demonstrated pre-clinically, the combination of a BRAF and a MEK1/2- inhibitor may help to prevent the emergence of resistance to single agent small molecule inhibitor therapy, targeting the RAF/MEK/ERK pathway by dual node inhibition (Emery 2009; Fremin 2010). The concept of a simultaneous, dual, vertical pathway inhibition of the RAF/MEK/ERK pathway is currently being explored by the combination treatment of a selective MEK1/2- (GSK1120212) and BRAF- inhibitor (GSK2118436) in cancer patients with advanced BRAF mutation positive tumor types. Preliminary results presented at ASCO 2011 (Infante 2011) [Study NCT01072175] shows significant tumor shrinkage in the majority of the patients with an ORR of 70%. Furthermore, results from the NCT01072175 study show that selective BRAF inhibitor combines safely with MEK inhibitor with a decreased occurrence of cutaneous side effect, such as rash and SCC in comparison to single agent therapy, which further strengthen the rationale for combining MEK inhibitors with BRAF inhibitor in the clinic.

Together, this provides a strong rationale for the combination therapy of selective RAF and MEK inhibitors in patients with BRAF V600 dependent advanced or metastatic solid tumor.

The addition of LEE011 to the dual combination of LGX818 and MEK162 in BRAF-mutant melanoma *in vitro* models displays either additivity or modest synergy. Therefore the triple combination will be evaluated in order to (1) investigate whether LEE011 can be safely combined with LGX818 and MEK162, (2) whether effects observed in vitro are either recapitulated or enhanced in patients and to (3) evaluate whether an improved anti-tumor activity and prolonged anti-tumor response can be shown with the triple combination over the dual combination.

The population of BRAF mutant melanoma patients who are naïve for prior treatment with a selective BRAF inhibitor, was chosen for the Phase II arm A, to allow a preliminary assessment

whether the triple combination is at least as active as the dual combination, with a comparable safety profile.

The primary purpose of the proposed dose-finding Phase Ib study is to estimate the MTD(s) and/or the recommended Phase II dose(s) (RP2D(s)) of the dual (LGX818 and MEK162) and triple (LGX818 and MEK162 and LEE011) combinations in patients with locally advanced or metastatic melanoma, mCRC or any other solid tumor upon agreement with the Sponsor, positive for either V600E BRAF mutation, or any other BRAF mutation at the V600 codon (e.g. V600K/D/R).

Once the MTD/RP2D has been determined for the dual combination, additional patients will be enrolled in three Phase II arms to further assess the clinical anti-tumor efficacy of the combination. The Phase II arm 1 will assess the disease control rate (DCR) of the LGX818 and MEK162 combination in patients with BRAF V600 mutant metastatic CRC. In the Phase II arm 2, the study will assess the objective response rate (ORR) of the combination in metastatic BRAF mutant melanoma patients who have progressed after prior treatment with a selective BRAF inhibitor (e.g. PLX4032, GSK2118436). In the Phase II arm 3, the study will assess the objective response rate (ORR) of the combination in metastatic BRAF mutant melanoma patients who are naïve to prior treatment with a selective BRAF inhibitor. The DCR (defined as patients with CR or PR or SD) rather than the ORR (defined as patients with CR or PR) will be used to evaluate clinical benefit in Phase II arm 1, as only a limited number of patients with BRAF mutant mCRC have experienced tumor shrinkage in clinical studies with RAF or MEK inhibitors (see Section 1.1.3), with more patients achieving stable disease (SD) than response. Also an interim analysis for futility will be performed in arm 1 after 50% of the total number of patients in this arm have completed four cycles of treatment, to allow stopping early for futility when there is no treatment effect. All three Phase II arms will further assess the safety of the LGX818 and MEK162 combination.

For the triple combination, once the MTD/RP2D has been determined additional metastatic BRAF mutant melanoma patients who are naïve to prior treatment with a selective BRAF inhibitor will be enrolled in arm A to assess the ORR of this triple combination. The safety of the triple combination will also be assessed in the Phase II population.

2.2 Rationale for the study design

The design of this Phase Ib/II, open label, dose escalation study was chosen in order to establish a dose of the dual (LGX818 and MEK162) and triple (LGX818 and MEK162 and LEE011) combinations for which the safety and tolerability is acceptable, in patients with BRAF V600 dependent advanced solid tumors. The dose escalation will be guided by a Bayesian logistic regression model (BLRM). During the Phase II part, depending on the observed DLT rate, the BLRM will be re-run to confirm that the current dose combination still satisfies the overdose criteria. Refer to Section 10.4.2.2 for further information. In the Phase II part of the study, a Bayesian design will be used in order to estimate the true DCR for the dual-combination arm 1 population and the true ORR for the dual-combination arms 2 and 3, and the triple-combination arm A populations.

The current open-label dose escalation study design using a BLRM is a well-established method to estimate the MTD(s) and/or RP2D(s) in cancer patients. The adaptive BLRM will be guided

by the escalation with overdose control (EWOC) principle to control the risk of DLT in future patients on study. The use of Bayesian response adaptive models for small datasets has been accepted by EMEA ("Guideline on clinical trials in small populations", February 1, 2007) and endorsed by numerous publications (Babb 1998; Neuenschwander 2008; Neuenschwander 2010), and its development and appropriate use is one aspect of the FDA's Critical Path Initiative.

2.3 Rationale for dose and regimen selection

Refer to Section 6.2.2 for detailed information on the rationale for the starting dose and regimen selection.

2.4 Rationale for choice of combination drugs

Data from pre-clinical and clinical studies suggest that by simultaneous, dual, vertical pathway inhibition of the RAF/MEK/ERK signaling pathways, the LGX818 and MEK162 combination could lead to increased clinical efficacy and possibly prevent and/or overcome early resistance to either single agent in patients with BRAF V600-dependent advanced solid tumors (see also Section 1.2.1.2, Section 1.2.2.2 and Section 1.2.4.1). Data from preclinical studies suggest that by simultaneous triple-pathway inhibition of the RAF/MEK/ERK and CDK/cyclin signaling pathways, the LGX818 and MEK162 and LEE011 combination could possibly prevent and/or overcome resistance to and lead to increased clinical efficacy compared to the LGX818 and MEK162 dual combination.

3 Objectives and endpoints

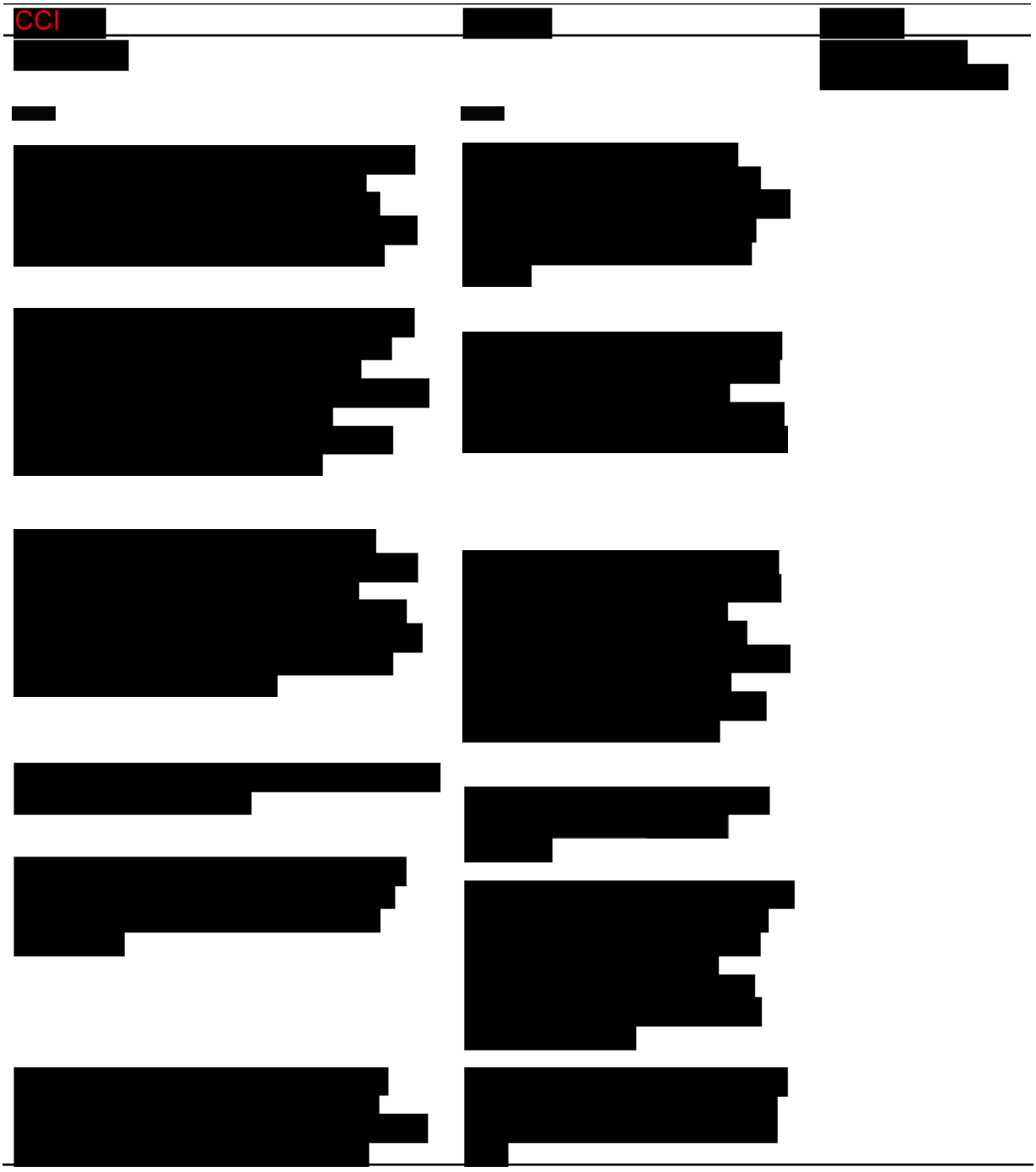
[Any language regarding the triple combination of LGX818/MEK162/LEE011 in this Section is <u>not</u> applicable to the USA and Singapore]

Objectives and related endpoints are described in Table 3-1.

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4

Objective	Endpoint	Analysis
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)	Phase II arm 1: Disease control rate (DCR) as per RECIST v1.1	
Arm 2: metastatic BRAF V600 mutant melanoma patients who have progressed after prior selective BRAFi treatment (dual combination)	Phase II arms 2 and 3 / arm A: Objective Response Rate (ORR) as per RECIST v1.1	
Arm 3/ Arm A: metastatic BRAF V600 mutant melanoma patients who are naïve to prior selective BRAFi treatment (dual and triple combination)		
Secondary		Refer to Section 10.5 / Section 10.5.4
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 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 EGFR/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)	



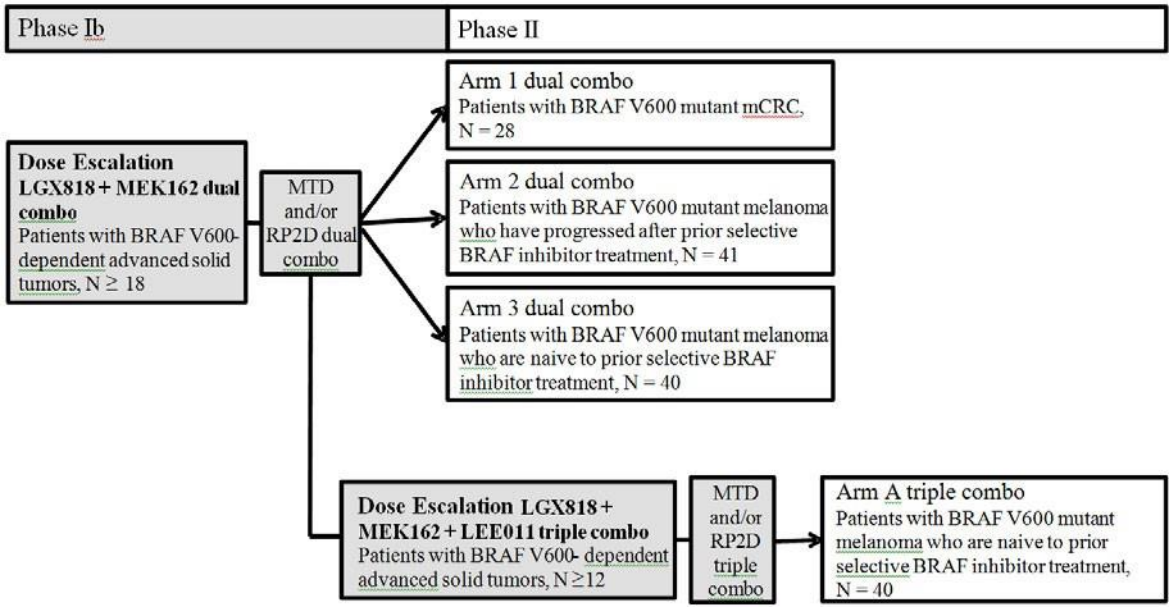
4 Study design

[Any language regarding the triple combination of LGX818/MEK162/LEE011 in this Section is <u>not</u> applicable to the USA and Singapore]

4.1 Description of 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 dual 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 BID, respectively, on a continuous schedule. Oral LGX818 and MEK162 and LEE011 will be administered once daily on a continuous schedule (LGX818), BID on a continuous schedule (MEK162) and once daily three weeks on, one week off (LEE011), respectively. Patients will be treated until progression of disease, unacceptable toxicity develops, or withdrawal of informed consent, whichever occurs first. Continued treatment beyond progression of disease will be allowed under certain circumstances (see Section 6.1.5) Provisional dose levels are given in Table 6-1 and Table 6-2. A cycle is defined as 28 days.

Figure 4-1 Study Design



Molecular pre-screening

Patients whose tumors have a documented mutation of BRAF V600 will be enrolled based on available local documentation. For patients for whom the molecular status is not known and who have a tumor which is routinely screened for a BRAF mutation at a local laboratory, the mutation can be determined on either fresh or archival tumor by local routine procedure without the need for signing the Molecular pre-screening Informed Consent. However, patients for whom molecular status is not known at the time of consideration for enrollment in this study **and** who have a tumor which is not routinely screened for a BRAF mutation at a local laboratory, will sign a Molecular pre-screening Informed Consent allowing for the collection of fresh tumor sample or use of archival tumor tissue for local assessment of the mutational status. Only once the BRAF V600 mutational status is known or determined, the patient is allowed to sign the Study Informed Consent Form and start screening (see also Section 7.1.1).

Screening period

Upon signing the Study Informed Consent Form, patients will be evaluated against study inclusion and exclusion criteria. Eligible patients will be enrolled in the study within 14 days of the commencement of the screening assessments and evaluations (Table 7-1 and Section 7.1.2).

Dose escalation (Phase Ib)

The dose escalation part of the trial will be conducted in adult patients with BRAF V600-dependent advanced solid tumors (see also Section 5.1). This part of the trial is expected to enroll at least 18 patients for the dual combination (LGX818 and MEK162) and at least 12 patients for the triple combination (LGX818 and MEK162 and LEE011).

For the dual combination, dose escalation will start at 50mg QD for LGX818 and 45mg BID for MEK162. Provisional dose levels are given in Table 6-1. For the triple combination, dose escalation will start at 450mg QD LGX818 and 45mg BID MEK162 and 100mg QD LEE011. Provisional dose levels are given in Table 6-2. When enrollment of a cohort is complete, further enrollment will only resume after the investigators and the Sponsor have jointly decided on the next dose escalation step of the combination. At each decision time point, the adaptive BLRM provides the upper boundary for the combinations that meet the EWOC criteria. Safety and tolerability data, PK, PD, and efficacy, as well as the recommendations from the Bayesian model are used to determine the dose combination for the next cohort(s) at a dose escalation teleconference. If deemed appropriate and supported by the available and relevant safety, PK, PD and efficacy data (and in agreement between the Sponsor and the Investigators), the dosing regimen of LGX818 may be changed to BID and/or every-other-day (QOD) dosing (as long as the new initial dosing regimen will not exceed the maximum total daily dose tested in this study). Should the new dosing regimen of LGX818 be explored, this will be achieved by enrollment of patients into a new cohort.

Various dose pairs will be explored following the recommendation of an adaptive Bayesian logistic regression model (BLRM) for dose escalation with overdose control (EWOC) 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 least 6 patients eligible for the dose determining set (DDS) must be treated at the dose(s) declared to be the MTD/RP2D. 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. Note: more than one combination and/or dosing schedule may be defined as MTD/RP2D. In the case that all dose combinations are considered to be too toxic by the 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 consist of 28 patients with non-resectable advanced BRAF V600 mutant metastatic colorectal cancer (mCRC) for whom no further effective standard therapy is available. An interim analysis for futility will be performed in arm 1 after 50% of the total number of patients in this arm have completed four cycles of treatment, to allow stopping early for futility when there is no treatment effect. The Phase II arm 2 will consist of 41 patients with locally advanced or metastatic BRAF V600 mutant melanoma who have progressed after

previous treatment with a selective BRAF inhibitor. The Phase II arm 3 will consist of 40 patients with locally advanced or metastatic BRAF V600 mutant melanoma who are naïve to previous treatment with a selective BRAF inhibitor. An interim analysis for futility will not be performed for arms 2 and 3, as signs of clinical activity have been reported for both MEK162 and LGX818 as single agent in patients with BRAF mutant melanoma patients (see Section 1.2.1.2 and Section 1.2.2.2.1).

For the triple combination following MTD/RP2D declaration, 40 patients with locally advanced or metastatic BRAF V600 mutant melanoma who are naïve to previous treatment with a selective BRAF inhibitor will be enrolled in the Phase II arm A.

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. This decision will be driven by the data available and will be discussed and agreed on between the Sponsor and the investigators.

30-day safety follow-up assessments

After study drug discontinuation, all patients must complete End of Treatment assessments within 14 days and the safety follow-up assessments for 30 days after the last dose of the study treatment (see also Section 7.1.4 and Section 7.1.5.1).

Study evaluation completion (SEC)

Note: As of protocol amendment 10, patients will be considered to have completed the study after the 30-day safety evaluation or 30 days after treatment discontinuation, whichever is earlier.

The study evaluation completion (SEC) eCRF page records the end of study for every individual patient. For details on the time point of completion of SEC, please refer to Section 7.1.4.

Disease progression and Survival follow-up assessments (Phase II only)

Note: As of protocol amendment 10, post-treatment disease progression follow-up (if applicable) and/or survival follow-up (including documentation of subsequent antineoplastic therapies) will no longer be performed for any patient in the Phase II part of the study.

Patients enrolled in the Phase II part of the study who discontinue study treatment for any reason other than disease progression will be followed up for progression of disease as detailed in Table 7-1 and Section 7.1.5.2. All patients enrolled in the Phase II part of the study will be followed for survival (for details see Section 7.1.5.3).

4.2 Timing of interim analyses and design adaptations

An interim analysis for futility will be performed during the Phase II part of the study in arm 1 dual combination (BRAF mutant mCRC patients) after 50% of the total number of patients in this arm have completed four cycles of treatment, to allow stopping early for futility when there is no treatment effect (see also Section 4.1-Phase II and Section 10.7).

4.3 Definition of end of the study

Note: As of protocol amendment 10, the end of study will be when the last patient on treatment completes the 30-day follow-up visit or 30 days after treatment discontinuation.

End of study (Last Patient Last Visit [LPLV]) will be upon completion of the follow-up period for the last patient treated with either the dual (LGX818 and MEK162) or triple (LGX818 and MEK162 and LEE011) combination as described in Section 4.1. This will occur once the last patient in the Phase II part has died or all patients have completed SEC, or have been lost to follow-up or withdrew consent, whichever occurs first.

4.4 Early study termination

The study can be terminated at any time for any reason by the Sponsor. Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 7.1.4 for a prematurely withdrawn patient. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The Investigator will be responsible for informing IRBs and/or IECs of the early termination of the trial.

5 Population

[Any language regarding the triple combination of LGX818/MEK162/LEE011 in this Section is <u>not</u> applicable to the USA and Singapore]

5.1 Patient population

The dose escalation will be conducted in adult patients with locally advanced or metastatic melanoma, metastatic colorectal cancer (mCRC) or any other solid tumor upon agreement with the Sponsor (like serous ovarian, biliary tract or pancreatic carcinomas; see also Section 1.1.1 and Table 1-1) harboring the BRAF V600E mutation, or any other BRAF V600 mutation, whose disease has progressed despite previous anti-neoplastic therapy or for whom no further effective standard therapy is available. Once MTD/RP2D has been determined with either the dual and triple combination, additional patients will be enrolled in the respective Phase II parts of the study. Patients with BRAF V600 mutant mCRC for whom no further effective standard therapy is available, will be enrolled in arm 1 dual combination of the Phase II part of the study. Patients with locally advanced or metastatic BRAF V600 mutant melanoma who have progressed after previous treatment with a selective BRAF inhibitor will be enrolled in the Phase II arm 2 dual combination. Patients with locally advanced or metastatic BRAF V600 mutant melanoma who are naïve to previous treatment with a selective BRAF inhibitor will be enrolled in the Phase II arm 3 dual combination and in the triple combination Phase II arm A.

Patients enrolled in this study are not permitted to participate in parallel investigational drug or device studies. Additionally, patients who have completed the study must not be re-enrolled for a second course of treatment.

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered enrollment in the study.

5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

1. Age ≥ 18 years.
2. **For the dose escalation (Phase Ib):** Histologically confirmed diagnosis of locally advanced or metastatic melanoma (stage IIIB to IV per American Joint Committee on Cancer [AJCC]), or confirmed diagnosis of non-resectable advanced metastatic colorectal cancer (mCRC), or any other indication upon agreement with the Sponsor, whose disease has progressed despite previous anti-neoplastic therapy or for whom no further effective standard therapy is available.
   For Phase II arm 1 dual combination: Confirmed diagnosis of non-resectable advanced metastatic colorectal cancer (mCRC) for whom no further effective standard therapy is available.
   For Phase II arm 2 dual combination: Histologically confirmed diagnosis of locally advanced or metastatic melanoma (stage IIIB to IV per American Joint Committee on Cancer [AJCC]) in patients who have progressed after previous treatment with a selective BRAF inhibitor.
3. **For Phase II arm 3 dual combination and Phase II arm A triple combination:** Histologically confirmed diagnosis of locally advanced or metastatic melanoma (stage IIIB to IV per American Joint Committee on Cancer [AJCC]) in patients who are naïve to previous treatment with a selective BRAF inhibitor.
4. Written documentation of BRAF V600E mutation, or any other BRAF V600 mutation.
5. Evidence of measurable disease as determined by RECIST v1.1.
6. World Health Organization (WHO) Performance Status ≤ 2.
7. Negative serum pregnancy test within 72 hours prior to the first study dose in all women of childbearing potential.
8. Able to understand and voluntarily sign the informed consent form, and ability to comply with the study visit schedule and other protocol requirements. Written informed consent must be obtained prior to any screening procedures.
9. **For Phase II**: Availability of a fresh tumor biopsy at Screening/Baseline, unless sufficient fresh tumor tissue was collected during local molecular pre-screening which can be submitted to the Sponsor-designated laboratory at Screening. If a tumor biopsy was collected after the last anti-neoplastic treatment within 2 months prior to study enrollment, the archival tissue of this tumor biopsy will be acceptable for enrollment instead of the fresh tumor biopsy (for further details please see also Section 7.2.4).

5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Progressive disease following prior treatment with RAF-inhibitors in combination with MEK-inhibitors.
2. Symptomatic or untreated leptomeningeal disease.
3. Symptomatic brain metastases. Patients previously treated or untreated for brain metastases that are asymptomatic in the absence of corticosteroid therapy are allowed to

enroll. Brain metastases must be stable with verification by imaging (e.g. brain MRI completed at screening demonstrating no current evidence of progressive brain metastases). Patients are not permitted to receive enzyme inducing anti-epileptic drugs. **For the triple combination:** patients presenting any brain metastases detected by CT/MRI of the brain at screening are excluded.

4. Known acute or chronic pancreatitis.
5. History or current evidence of retinal disease (e.g. central serous retinopathy (CSR), retinal vein occlusion (RVO)) or ophthalmopathy as assessed by ophthalmologic examination at baseline that would be considered a risk factor for CSR/RVO (e.g., optic disc cupping, visual field defects, IOP > 21 mmHg).
6. Clinically significant cardiac disease and/or recent cardiac events including any of the following:
   - CHF requiring treatment (NYH grade ≥ 2), LVEF < 45% as determined by MUGA scan or ECHO (for addition of LEE011 in the triple combination please note: patients with LVEF less than institutional lower limit of normal are also excluded from study), or uncontrolled hypertension (please refer to WHO-ISH guidelines)
   - History or presence of clinically significant ventricular arrhythmias or atrial fibrillation
   - Clinically significant resting bradycardia within 12 months prior to starting study drug
   - Unstable angina pectoris or symptomatic pericarditis within 12 months prior to starting study drug.
   - Acute Myocardial Infarction (AMI) within 12 months prior to starting study drug.
   - QTcF > 480 msec for dual combination. For addition of LEE011 in the triple combination, mean triplicate QTcF > 450 ms at screening or indeterminate (i.e., unreadable or not interpretable) at screening.
   - For addition of LEE011 in the triple combination, any of the following within 12 months prior to starting study drug: history or presence of ventricular tachyarrhythmia, complete left bundle branch block, or right bundle branch block and left anterior hemi block (bifascicular block).
   - For addition of LEE011 in the triple combination, congenital long QT syndrome or family history of unexpected sudden cardiac death.
   - For addition of LEE011 in the triple combination, any heart disease that requires the use of a cardiac pacemaker or implantable cardioverter defibrillator ≤ 3 months prior to starting study drug or any other clinically significant heart disease (e.g. documented congestive heart failure, documented cardiomyopathy).
7. Patients with any of the following laboratory values at Screening/baseline:
   - Absolute neutrophil count (ANC) <1,500/mm^3 [1.5 x 10^9/L]
   - Platelets < 100,000/mm^3 [100 x 10^9/L]
   - Hemoglobin < 9.0 g/dL
   - Serum creatinine >1.5 x ULN or calculated or directly measured CrCl < 50% LLN (lower limit of normal)
   - Serum total bilirubin >1.5 x ULN

- AST/SGOT and/or ALT/SGPT > 2.5 x ULN, or > 5 x ULN if liver metastases are present
- For addition of LEE011 in the triple combination, serum magnesium, potassium, sodium, inorganic phosphate and calcium (corrected for serum albumin) < LLN or not correctable with supplement to within normal limits prior to study treatment start, and PT/INR >1.5 x ULN or aPTT >1.5 x ULN

8. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral LGX818, MEK162 or LEE011 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection).
9. Previous or concurrent malignancy. Exceptions: adequately treated basal cell or squamous cell skin cancer; in situ carcinoma of the cervix, treated curatively and without evidence of recurrence for at least 3 years prior to study entry; or other solid tumor treated curatively, and without evidence of recurrence for at least 3 years prior to study entry.
10. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/mL).
    Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, are not allowed to participate in this study UNLESS they are using highly effective methods of contraception throughout the study and for 3 months after study drug discontinuation. Highly effective contraception methods include:
    - Total abstinence or
    - Male or female sterilization
    - Combination of any two of the following (a+b or a+c or b+c)
        a. Use of oral, injected, or implanted hormonal methods of contraception
        b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
        c. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

    Post-menopausal women are allowed to participate in this study. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum Follicle-Stimulating Hormone (FSH) levels > 40 mIU/mL or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to screening. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of child bearing potential.
    Sexually active males must use a condom during intercourse while taking the drug and for 5 T1/2 after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.
11. History of thromboembolic or cerebrovascular events within the last 6 months, including transient ischemic attack, cerebrovascular accident, deep vein thrombosis, or pulmonary embolism.

12. Patients who have received radiation therapy (that includes > 30% of the bone marrow reserve), chemotherapy, biological therapy (e.g., antibodies) within ≤ 4 weeks (6 weeks for nitrosourea, mitomycin-C), or who have been treated with continuous or intermittent small molecule therapeutics or investigational agents within 5-half-lives of the agent (or ≤ 4 weeks when half-life is unknown) prior to starting study drug or who have not recovered from the side effects of such therapy (except alopecia).
13. Patients who have undergone any major surgery within the last 2 weeks prior to starting study drug or who would not have fully recovered from previous surgery.
14. Known Human Immunodeficiency Virus (HIV) infection.
15. Other severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or that may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for the study.
16. For addition of LEE011 in the triple combination, patients who are currently receiving treatment with agents that are known to cause QTc prolongation or induce torsades de pointes in humans and cannot be discontinued 7 days prior to Cycle 1 Day 1.
17. For addition of LEE011 in the triple combination, patients who are currently receiving treatment with drugs or herbal medications that are strong inducers of CYP3A4 enzyme or substrates of CYP3A4 with a narrow therapeutic index (NTI) and cannot be discontinued 7 days prior to Cycle 1 Day 1. See Appendix 4, Table 14-9, and Table 14-10 for a partial list of CYP3A4 substrates or inducers.
18. Patients who are currently receiving strong systemic inhibitors of CYP3A4 (refer to Table 14-10 in Appendix 4 for a partial list of CYP3A4 inhibitors).

6 Treatment

[Any language regarding the triple combination of LGX818/MEK162/LEE011 in this Section is <u>not</u> applicable to the USA and Singapore]

6.1 Investigational treatment, other study treatment, supportive treatment

6.1.1 Dosing regimen

The investigator or responsible site personnel should instruct the patient to take the study drugs as per protocol (promote compliance). All dosages planned and dispensed to the patient and all dose changes and all missed doses during the study must be recorded on the Dosage Administration Record eCRF. Drug accountability must be performed on a regular basis. Patients will be instructed to return unused study drugs to the site at the end of each cycle. The site personnel will ensure that the appropriate dose of each study drug is administered at each visit and will provide the patient with the correct amount of drugs for subsequent dosing.

On days when blood collection is scheduled at the clinic, patients will take the study drugs (either in the dual or triple combination) in the clinic under the supervision of the investigator or designee. On all other days patients will take the study drugs at home.

Patients should be instructed to swallow the capsules and tablets whole and not to chew, crush or open them.

If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. The occurrence and frequency of any vomiting and/or diarrhea (or increase stool frequency) during treatment must be noted in the adverse events section of the eCRF. In addition, on the days of full pharmacokinetic sampling, the exact time of any episodes of vomiting and diarrhea (or increase stool frequency) within the first 4 hours post-dosing on that day must be noted in a separate section of the eCRF.

Any doses that are missed should be skipped and should not be replaced or made up during the evening dosing or on a subsequent day, whichever applies.

Patients must avoid consumption of grapefruit, grapefruit hybrids, pummelos, starfruit, or Seville (sour) oranges during the entire study and preferably 7 days before the first dose of study medications, due to potential CYP3A4 interaction with the study medications. Orange juice is allowed.

6.1.1.1 Administration of dual combination (LGX818 and MEK162)

LGX818 capsules will be co-administered orally initially once daily with MEK162 tablets twice daily. The study drugs will be administered as a flat-fixed dose, and not by body weight or body surface area.

- Patients must be instructed to take the study drug combination of one or more tablets of MEK162 and one or more capsules of LGX818 together with a large glass of water (~250 ml) daily in the morning at approximately the same time every day. On all dose administration days patients can take MEK162 and LGX818 with or without food.
- The second daily dose of MEK162 should be taken together with a glass of water irrespective of food. In case the dosing regimen of LGX818 is changed to BID (see Section 4.1), the evening dose of MEK162 should be taken together with 2nd (i.e. evening) daily dose of LGX818.
- The prescribed BID doses for MEK162 (and LGX818 in case the dosing schedule would be changed to BID) should be taken 12 ± 2 hours apart.
- In case the dosing regimen of LGX818 is changed to an once-a-day every-other-day (QOD) dosing schedule (see Section 4.1), the patients must be instructed to take the first dose of the study drug combination on Day 1 of Cycle 1 and afterwards on alternating days (D3, D5, D7 etc.). On the non-dosing days of LGX818 (i.e. D2, D4, D6 etc), MEK162 should be taken at approximately the same time every morning, with a glass of water irrespective of food. There should be at least one day and not more than 2 days without LGX818 dosing between cycles.

6.1.1.2 Administration of triple combination (LGX818 and MEK162 and LEE011)

LGX818 and LEE011 capsules will be co-administered orally once daily with MEK162 tablets twice daily. The study drugs will be administered as a flat-fixed dose, and not by body weight or body surface area.

- Patients must be instructed to take the study drug combination of one or more tablets of MEK162 and one or more capsules of LGX818 and LEE011 together with a large glass of water (~250 ml) daily in the morning at approximately the same time every day. On all dose administration days patients can take MEK162 and LGX818 and LEE011 with or without food.
- The second daily dose of MEK162 should be taken together with a glass of water irrespective of food.
- The prescribed BID doses for MEK162 should be taken 12 ± 2 hours apart.
- LEE011 will be taken for 21 consecutive days followed by a 7-day planned break (3 weeks on, 1 week off schedule). LGX818 and MEK162 are taken on a continuous schedule.

6.1.2 Supportive treatment/precautions

Because the LGX818 and MEK162 or LGX818 and MEK162 and LEE011 combination could trigger photosensitizing reactions, it is recommended that patients should be instructed to avoid exposure of skin and eye to direct sunlight as much as possible and to apply sun protection (e.g. sunscreen, sunglasses and protective clothing), for the duration of the trial and for at least 1 week after discontinuation of trial treatment. Any symptoms of photosensitivity must be reported on the Adverse Event eCRFs and institutional standard-of-care treatment should be initiated promptly.

For skin toxicity or nausea/vomiting prophylactic treatment may be initiated in all patients at the dose level where these toxicities have been observed and in all further patients if at least 1 patient has experienced skin toxicity or nausea/ vomiting ≥ CTCAE Grade 3 or if at least 2 patients experienced skin toxicity or nausea/ vomiting ≥ CTCAE Grade 2. However anti-emetics may be applied for treatment if the patient has experienced nausea/vomiting CTCAE Grade ≥ 1, at the discretion of the physician.

For rash-like events, institutional standard-of-care treatment should be initiated promptly upon occurrence of such events. Treatment of rash may include, but is not limited to, topical or oral antibiotics, topical or oral anti-inflammatories, topical or oral corticosteroids and oral anti-histamines. The use of emollients and sunscreens has not been evaluated with LGX818/ MEK162 or LGX818 /MEK162 /LEE011 but may be used prophylactically or as treatment for rash (see also Appendix 3, Section 14.3.1 for guidelines for the treatment of study drug combination induced skin toxicity).

Because hand foot skin reaction (HFSR) has been reported in some patients during LGX818 single agent treatment, it is recommended that patients are educated prior to starting study treatment which activities to avoid like activities that cause friction on hands and feet, and on supportive measures for prevention and/or management of HFSR. As guidance for recommendations on supportive measures for prevention and/or management, the publication with recommendations of an international panel of experts of (van Moos R et al 2008) can be used (see also Section 14.3.2). A visit at a podiatrist may also be recommended at the discretion of the investigator. Any symptoms of HFSR must be reported on the Adverse Event eCRFs and should be treated further according to institutional standard-of-care.

Optimal therapy for vomiting or diarrhea will be based on institutional standard-of-care with consideration of the medications to be used with caution listed in this protocol (see Section 6.4.2 and Appendix 4).

Patients with edema may be treated with diuretic medications if indicated.

For stomatitis/mucositis-like events, institutional standard-of-care treatment should be initiated promptly upon occurrence of such events.

6.1.3 Ancillary treatments

Not applicable.

6.1.4 Guidelines for continuation of treatment

Not applicable.

6.1.5 Treatment duration

Patients may continue treatment with LGX818 and MEK162 or LGX818 and MEK162 and LEE011 combination until disease progression, unacceptable toxicity occurs that precludes any further treatment and/or treatment is discontinued at the discretion of the investigator or by patient refusal (withdrawal of consent). Continued treatment beyond progression of disease will be allowed only under special circumstances. For example when according to the assessment of the investigator, a patient with progression of disease may benefit from continuation of LGX818 and MEK162 or LGX818 and MEK162 and LEE011 treatment, treatment beyond progression can be considered. Therefore, if it is judged by the investigator in agreement with the Sponsor to be in the best interest of the patient, that patient may remain on study treatment as long as the patient continues to benefit from the study drug treatment per investigator assessment. Special circumstances can be defined by, for example, cystic lesions, mixed responses, and new brain metastasis which is treatable with stereotactic radiotherapy or surgery, but not requiring whole brain radiotherapy.

Dosing beyond progression is not allowed in the following cases:

- Patients with rapid progression of disease at critical anatomical sites (e.g. cord compression) requiring urgent alternative medical intervention.
- Patients who have clinically relevant worsening of laboratory values.
- Patients who have a clinically significant decline in performance status at time of progression.
- Patients in the triple combination of LGX818 and MEK162 and LEE011 that appear with new brain metastases.

6.2 Dose escalation guidelines

6.2.1 Definition of treatment cycle

A complete treatment cycle is defined as 28 days of daily continuous treatment of LGX818 and MEK162 and of 21 consecutive days of LEE011 treatment followed by a 7-day planned break in combination with daily continuous treatment of LGX818 and MEK162. The first dose of

LGX818 plus MEK162 or LGX818 plus MEK162 plus LEE011 defines Day 1 of Cycle 1. All treatment cycles have duration of 28 days. There will be no delays between cycles, i.e. study day 29 represents Cycle 2 Day 1.

6.2.2 Starting dose rationale

LGX818 and MEK162 dual combination

The starting dose for the study drug combination is 50mg QD for LGX818 and 45mg BID for MEK162, and is based on available data from the ongoing first in human studies ([CLGX818X2101]) (Novartis) and (ARRAY-162-111) (Array Biopharma) respectively. The MTD of single agent MEK162 was established at 60mg/d twice daily. The MTD of LGX818 is still under investigation, and current data indicate that 50mg of LGX818 is a well-tolerated dose (the most severe toxicity observed at doses ≤ 100 mg micro-emulsion formulation LGX818 thus far was a CTCAE grade 3 HFSR toxicity at 100mg/day (see also Section 1.2.1.2). Taking into consideration all information currently available about the dose-DLT relationships of LGX818 and MEK162 as single agents and the uncertainty about the toxicity of the combination, the prior distribution of DLT rates derived from the BLRM presented in Appendix 5 indicates that the proposed starting dose combination meets the escalation with overdose control (EWOC) criteria. Before the first patient first visit, the prior distribution for LGX818 will be updated with the most recent data from the LGX818X2101 trial and the model will be re-run in order to confirm the proposed starting dose for LGX818 is still eligible, i.e. fulfills the EWOC criteria.

LGX818 and MEK162 and LEE011 triple combination

The starting dose for the triple study drug combination is 450mg QD for LGX818 and 45mg BID for MEK162 (both continuous schedule) and 100mg QD for LEE011 (3 weeks on, 1 week off schedule), and is based on available RP2D dual-combination data from this ongoing study and on the first in human study (CLEE011X2101) (Novartis), respectively. The MTD of single agent LEE011 was established at 900mg/d once daily on a three week on, one week off schedule. The MTD of single agent LGX818 was established at 450mg/d once daily, and the MTD of single agent MEK162 was established at 60mg/d twice daily. The RP2Ds for the LGX818 and MEK162 dual combination were determined at 450mg LGX818 QD + 45mg MEK162 BID and at 600mg LGX818 QD + 45mg MEK162 BID.

Quantitative DDI assessment using Simcyp simulation predicts 29% and 14% increase in AUC and Cmax of LGX818, respectively, as well as 47% and 30% decrease in AUC and Cmax of LEE011, respectively when 450 mg QD LGX818 and 200 mg QD LEE011 are co-administered. In clinic, LGX818 has been tested at up to 700 mg QD dose and the observed adverse events are reversible and manageable. While the potential DDI between the two molecules may result in LGX818 concentrations higher than the currently established RP2D, it is not expected to pose a significant risk. In addition, no significant DDI risk is expected between 45 mg BID MEK162 and 100 mg QD LEE011. Therefore, the starting dose of 450mg QD for LGX818 and 45mg BID for MEK162 (both continuous schedule) and 100mg QD (3 weeks on, 1 week off schedule) for LEE011 is considered acceptable.

Escalating doses of LEE011 will be used in combination with the 450mg LGX818 QD + 45mg MEK162 BID (i.e. RP2D of LGX818 and MEK162 dual combination). The starting dose of

LEE011 is proposed at 100mg (1/9 of single agent MTD). Depending on the PK and toxicities observed and in accordance with the recommendations from the BLRM, escalating doses of LEE011 might also be evaluated in combination with the 600mg LGX818 QD + 45mg MEK162 BID (i.e. 2nd RP2D of LGX818 and MEK162 dual combination).

Taking into consideration all information currently available about the dose-DLT relationships of LGX818 and MEK162 and LEE011 as single agents, as well as LGX818/MEK162 dual combination and the uncertainty about the toxicity of the triple combination, the prior distribution of DLT rates derived from the BLRM presented in Appendix 6 indicates that the proposed starting dose combination meets the escalation with overdose control (EWOC) criteria.

Before the first patient is dosed with the triple combination, the Bayesian model will be updated with the most recent data from the ongoing LEE011 single agent trial and CMEK162X2110 dual (LGX818 and MEK162) combination study, to confirm that the proposed starting dose combination is still appropriate (i.e. fulfills the EWOC criteria). If the proposed starting doses do not meet the criteria, a lower dose combination that satisfies the EWOC criteria will be used.

6.2.3 Provisional dose levels

Provisional dose levels for the dual and triple combination are listed in Table 6-1 and Table 6-2, respectively. With the exception of starting dose level 1, actual dose levels will be determined following a discussion with participating investigators during dose escalation teleconferences. Dose escalation will continue until MTD(s)/RP2D(s) is/are reached.

Table 6-1 Provisional dose levels dual combination

Dose level	LGX818 mg QD	MEK162 mg BID
-1	30	45
-1a	50	30
1 (starting dose)	50	45
2	100	45
3	100	60
3a*	150	45
4	150	60
5	200	45
5a*	200	60

* "#" dose levels and "#a" dose levels may be explored in parallel.

Table 6-2 Provisional dose levels triple combination

Dose level	LGX818 mg QD	MEK162 mg BID	LEE011 mg QD
-1	300	30	50
0	**450**	**45**	**100**
1	450	45	200
2	450	45	300
3	450	45	400
4	450	45	800
5	450	45	900

Dose level	LGX818 mg QD	MEK162 mg BID	LEE011 mg QD
NB. If LGX818 is escalated from 450 mg to 600 mg, the dose of MEK162 and LEE011 with remain fixed during that escalation step. Dose levels of 600mg LGX818 in combination with MEK162 and LEE011 might be explored in parallel with a dose level of 450mg LGX818 in combination with MEK162 and LEE011.			

At all decision time points, the adaptive Bayesian logistic model permits alterations in the dose increments based on the observed DLTs. Only one of the 2 or 3 combination partners can be escalated (e.g., for provisional dose level 3 dual combination only MEK162 is escalated from 45 mg to 60 mg, and for provisional dose level 3a only LGX818 is escalated from 100 mg to 150 mg when compared to dose level 2) and the maximum inter-cohort dose escalation is limited to 100%, (i.e. up to 100% and 0% increase for LGX818 and MEK162 respectively or 0% and up to 100% increase for LGX818 and MEK162 respectively for dual combination. i.e. up to 33% and 0% and 0% increase for LGX818 and MEK162 and LEE011 respectively or 0% and 0% and up to 100% increase for LGX818 and MEK162 and LEE011 respectively for triple combination.) Note, however, that dose levels may be explored in parallel, as illustrated in Table 6-1 and Table 6-2 above. If a decision is made to explore two dose levels at the same time, the next dose escalation decision will be made after patients in all dose cohorts have finished cycle 1.

Based on the BLRM rules, it will be possible for intermediate dose levels or doses higher than the highest provisional dose given or doses lower than the lowest provisional dose given in Table 6-1 and Table 6-2 to be explored. Recommendation to study these dose levels will take into account the Bayesian model inference, as well as the consideration of the totality of the available study data (safety, PK and PD) (see Section 6.2.4.2).

Process to establish the MTD/RP2D with new MEK162 tablet variants if needed based on results of CMEK162X2108/ CMEK162A2101 relative bioavailability studies

If based on the results of the two relative bioavailability studies, the MTD/RP2D of the LGX818 and MEK162 combination will need to be established (in case dose escalation is ongoing at that time) or re-established (in case MTD/RP2D was already determined with original MEK162 tablet at that time) with one or both of the two new MEK162 tablet variants, a new cohort of 3 to 6 patients will be enrolled using either the MEK162 smaller tablet or new MEK162 tablet variant in combination with LGX818.

The patients in this cohort will be treated at the highest dose (or MTD/RP2D as applicable) of the LGX818 and MEK162 drug combination, that has been evaluated previously in at least 3 patients and for which safety data was reviewed and was found to satisfy the overdose control criteria of the Bayesian model, and will be followed for at least one cycle. The dose of the MEK162 smaller tablet and/or new MEK162 tablet variant will be adjusted to the dose of the original MEK162 tablet as established in the healthy volunteer relative bioavailability studies ([CMEK162X2108] and [CMEK162A2101] respectively). The dose of the original MEK162 tablet will be multiplied by the established factors (as obtained by the CMEK162X2108 or CMEK162A2101 studies) to achieve a comparable exposure with the MEK162 smaller tablet and/or new MEK162 tablet variant. The dose will be rounded to the lowest dose considering the MEK162 tablet available strength.

If at the following dose escalation teleconference meaningful differences in terms of safety, tolerability and/or PK are observed between the MEK162 smaller and original tablet and/or the new MEK162 tablet variant and the original MEK162 tablet both in combination with LGX818, then dose adjustments (escalation or de-escalation) may be made to new cohorts in accordance with the recommendations of the BLRM until a dose level fulfilling the overdose control criteria and/or achieving appropriate PK is reached. Dose escalation will continue until the MTD/RP2D is determined (according to procedures outlined in Section 6.2.4).

Based upon the above outlined evaluation, the patients ongoing on treatment with the original MEK162 tablet may transition to the MEK162 smaller tablet or new MEK162 tablet variant at the equivalent dose of MEK162, while continuing the same dose level with LGX818.

6.2.4 Criteria for dose escalation and determination of MTD

6.2.4.1 Definition and estimation of MTD

The primary objective of the study is to estimate the maximum tolerated dose(s) (MTD(s)) and/or RP2D(s) for the (LGX818 and MEK162) dual and (LGX818 and MEK162 and LEE011) triple combination. The MTD is defined as the highest drug dosage not causing in the first cycle of treatment medically unacceptable, dose-limiting toxicity (DLT) in more than 35% of the treated patients. AEs and laboratory abnormalities considered to be DLTs are defined in Table 6-2. Since several combinations may correspond to this definition more than one MTD/RP2D may be identified with different doses of the combination partners.

The applied adaptive Bayesian methodology provides an estimate of the dual- and triple-drug combinations not exceeding the dual- and triple-combination MTDs. Typically the MTD is a tested dose with maximum probability of targeted toxicity (DLT rate between 16%-35%). The use of EWOC principle limits the risk that a potential next dose will exceed the MTD (Section 10.4.2).

6.2.4.2 Dose escalation

For the purposes of dose escalation decisions, each cohort will consist of 3 to 6 newly enrolled patients who will be treated at the specified combination dose levels. The first cohort will be treated with the starting combination doses as shown in Table 6-1 and Table 6-2.

Patients must complete a minimum of 1 cycle of treatment with the minimum safety evaluation and drug exposure or to have had a DLT within the first cycle of treatment to be considered evaluable for dose escalation decisions. Dose escalation decisions will occur when the cohort of patients has met these criteria. If a patient drops-out for reason other than adverse event prior to becoming evaluable for the DDS, a new patient may be recruited to the cohort until the required number is reached (see Section 7.1.4.2). If only 2 of the 3 patients in a cohort are evaluable and neither patient has experienced a treatment-related toxicity > CTCAE grade 1, dose escalation decisions may be considered.

Dose escalation decisions will be made by Investigators and Sponsor study personnel (see Section 6.2.4.2.1). Decisions will be based on a synthesis of all relevant data available from all dose levels evaluated in the ongoing study including safety information, DLTs, all CTCAE Grade ≥ 2 toxicity data during Cycle 1, PK, and PD data from evaluable patients. The

recommended combination doses for the next cohort of patients will be guided by the Bayesian logistic regression model (BLRM) with EWOC principle (Section 2.2). The adaptive Bayesian methodology provides an estimate of all combination dose levels of LGX818 and MEK162 or LGX818 and MEK162 and LEE011 that do not exceed the corresponding MTD and incorporates all DLT information at all dose levels for this estimation. In general, the next combination dose will have the highest chance that the DLT rate will fall in the target interval (16-35%) and will always satisfy the EWOC principle. In all cases, the combination dose for the next cohort will not exceed a 100% increase from the previous combination dose. Smaller increases in doses may be recommended by the Investigators and Sponsor upon consideration of all of the available clinical data. Clinically relevant toxicities to be taken into consideration for dose recommendations will be those assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications. In addition, for certain toxicities such as hematologic toxicity (e.g., lymphopenia), and toxicities not associated with end-organ damage (e.g., nausea, pain, headache, fever, alopecia), toxicity ≥ CTCAE G2 must be observed in at least two thirds of the patients in the previous cohort, to impact the dose escalation. The likelihood of appearance of keratoacanthomas (KA) and/or squamous cell carcinomas (SCC) with specific and potent BRAF inhibitors is high (~ 35%) and occurs early during the course of treatment (median time of 4-12 weeks), as reported for the selective BRAF inhibitors PLX4032 and GSK2118436 (Flaherty 2010; Kefford 2010; Robert 2011). No metastatic evolution of RAF inhibitor-induced SCCs has been reported so far. Patients will be carefully monitored for the occurrence of this anticipated on-target side-effect. However, in the context of this study, these benign KA and SCC tumors will not be considered for the dose escalation decisions, unless judged to be clinically significant by the investigators. If needed to better define the dose-toxicity relationship, additional patients may be enrolled to the current combination dose level, to a preceding combination dose level, or to an intermediate combination dose level before proceeding with further dose escalation.

If the first 2 patients in a cohort experience a DLT, further enrollment to that cohort will stop and the BLRM will be updated with this new information. Re-evaluation of the available safety, PK, and PD data will occur. By incorporating information gained at the preceding dose levels, additional patients may be enrolled at this combination dose level or a lower combination dose level as agreed by Investigators and Sponsor personnel and if the BLRM predicts that the risk that this dose exceeds the MTD remains below 25% (EWOC).

Dose escalation will continue until identification of the MTD or a suitable lower dose for the Phase II part of the study. This will occur when the following conditions are met:

1. at least 6 patients have been treated at this combination dose
2. this combination dose satisfies one of the following conditions:
    - the posterior probability of targeted toxicity at this combination dose exceeds 50% and is the highest among potential doses, or
    - a minimum of 18 patients have already been treated on the trial for the dual combination or a minimum of 12 patients have been treated on the trial for the triple combination.
3. it is the dose recommended for the next cohort of patients (either per the model or by review of all clinical data by the Sponsor and Investigators in a dose escalation teleconference, see Section 6.2.4.2.1)

To better understand the safety, tolerability, efficacy, PD and PK of LGX818 and MEK162 or LGX818 and MEK162 and LEE011 study drug combinations, additional cohorts of 1 to 6 patients may be enrolled at preceding dose levels, or to intermediate dose levels before or while proceeding with further dose escalation.

If a decision is made to escalate to a higher dose level but one or more additional patient(s) treated at the preceding dose level experiences a DLT during the first cycle of treatment, then the BRLM will be updated with this new information before any additional patients are enrolled at that higher dose level. Subjects ongoing will continue treatment at their assigned dose levels.

6.2.4.2.1 Implementation of dose escalation decisions

To implement dose escalation decisions, the available toxicity information (including AEs and laboratory abnormalities that are not DLTs), the recommendations from the BLRM, and the available PK and PD information will all be evaluated by the Investigators and Sponsor study personnel (including the study physician and statistician) during a dose decision meeting by teleconference. Drug administration at the next higher dose level may not proceed until the Investigator receives written confirmation from the Sponsor indicating that the results of the previous dose level were evaluated and that it is permissible to proceed to a higher dose level.

6.2.4.2.2 Intra-patient dose escalation

Intra-patient dose escalation is not permitted at any time within the first four Cycles of treatment. After the fourth cycle is completed, individual patients may be considered for treatment at a dose of LGX818 or MEK162 or LEE011 higher than the dose to which they were initially assigned. Only one of the investigational study drugs will be escalated at any one time. In order for a patient to be treated at a higher dose of either LGX818 or MEK162 or LEE011, he or she must have tolerated the lower dose pair for at least four cycles of therapy, e.g., he or she must not have experienced at the lower dose pair originally assigned a toxicity of CTCAE Grade ≥ 2 for which relationship to study drug cannot be ruled out. Moreover, the new, higher dose pair with which the patient is to be treated must be a dose pair that has completed evaluation in a dose escalation meeting and that has not exceeded the MTD estimated by the Bayesian model given all available data.

There is no limit to the number of times a patient may have his or her dose of either LGX818 or MEK162 or LEE011 increased. In any further escalation, again only one study drug will be increased at any time. Any further increases after the initial intra-patient dose escalation are subject to the same rules as for the initial intra-patient escalation. Consultation with the Sponsor must occur prior to any intra-patient dose escalation occurring. These changes must be recorded on the Dosage Administration Record eCRF.

6.2.5 Definitions of dose limiting toxicities (DLTs)

A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as at least possibly related to the study medication, as clinically relevant, as unrelated to disease, disease progression, inter-current illness, or concomitant medications, which occurs ≤ 28 days following the first dose of LGX818 and MEK162 or LGX818 and MEK162 and LEE011 (Cycle 1) and meets any of the criteria listed in Table 6-3, as applicable. Toxicity will

be assessed using the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.03 unless otherwise specified.

Whenever a patient experiences toxicity that fulfills the criteria for a DLT, treatment with the study drug combination will be interrupted and the toxicity will be followed up as described in Section 6.2.6. For the purposes of dose escalation and determination of the MTD, DLTs that occur during the first cycle will be necessarily considered and included in the BLRM, including those in which the event has started in cycle 1 and the confirmation of the DLT occurs in subsequent cycles.

The investigator must notify the Sponsor immediately of any DLT observed. The investigator must notify the Sponsor immediately of any unexpected CTCAE grade ≥ 3 adverse events or laboratory abnormalities.

The rules for re-initiation and dose modification of LGX818 and MEK162 or LGX818 and MEK162 and LEE011 treatment are outlined in Section 6.3.

Table 6-3 Criteria for defining dose-limiting toxicities for dual and triple combination

Toxicity	Any of the following criteria:
Blood and lymphatic system disorders[a]	Febrile neutropenia (ANC < 1.0 x 10^9/L with fever ≥ 38.5°C)[b]
Investigations (Blood)	Absolute Neutrophil count CTCAE Grade 3 for > 7 consecutive days
	Absolute Neutrophil count CTCAE Grade 4
	Platelet count CTCAE Grade 3 for > 7 consecutive days and/or with signs of bleeding
	Platelet count CTCAE Grade 4
Skin and subcutaneous tissue disorders: Rash, HFSR and/or photosensitivity	Rash, HFSR or photosensitivity CTCAE Grade 3 > 7 consecutive days despite skin toxicity treatment (as per local practice)
	Rash, HFSR or photosensitivity CTCAE Grade 4
Eye disorders-Retinopathy / Uveitis	CSR/ CSR-like events CTCAE Grade 3 for > 21 consecutive days confirmed by ophthalmologic examination
	CSR/ CSR-like events CTCAE Grade 4 confirmed by ophthalmologic examination
Eye disorders - RVO	Any grade
Eye disorders- any other	CTCAE Grade 3 for > 14 consecutive days
	CTCAE Grade 4
Gastrointestinal disorders	Diarrhea CTCAE Grade ≥ 3 ≥ 48 hrs, despite the use of optimal anti-diarrhea therapy
	Nausea or vomiting CTCAE Grade ≥ 3 ≥ 48 hrs, despite the use of optimal anti-emetic therapy
	Pancreatitis CTCAE Grade ≥ 3
Investigations (Renal)	Serum creatinine CTCAE Grade ≥ 3
Investigations (Hepatic)[c]	Blood bilirubin (total bilirubin) CTCAE Grade ≥ 3
	AST or ALT CTCAE Grade ≥3 in conjunction with blood (total) bilirubin CTCAE Grade ≥ 2 of any duration
	AST or ALT CTCAE Grade 3 for > 7 consecutive days
	AST or ALT CTCAE Grade 4.
	Serum alkaline phosphatase CTCAE Grade 4 > 7 consecutive days

Toxicity	Any of the following criteria:
Investigations (Metabolic)	Serum lipase and/or serum amylase (asymptomatic) CTCAE Grade 3 > 7 consecutive days
	Serum lipase and/or serum amylase (asymptomatic) CTCAE Grade 4
Cardiac disorders	≥ CTCAE Grade 3
Investigations (Cardiac)	Serum CK/CPK CTCAE Grade 3 for > 14 consecutive days if clinically significant (symptomatic)
	Serum CK/CPK CTCAE Grade 4 for > 14 consecutive days
	QTcF interval ≥ 501 ms on at least two separate ECGs (only for triple combination)
Vascular disorders	Persistent hypertension CTCAE Grade ≥ 3 requiring more than one drug or more intensive therapy than previously
General disorders and administration site conditions	Fatigue CTCAE Grade 3 for > 7 consecutive days
	Edema CTCAE grade 3 for > 14 consecutive days
Other Adverse Events[d]	Any other CTCAE Grade ≥ 3 toxicity (except SCC[e])

[a.] ≥ CTCAE grade 3 anemia will not be considered a DLT unless judged to be a hemolytic process secondary to study drug. ≥ CTCAE grade 3 lymphopenia will not be considered a DLT unless clinically significant.

[b.] Not according to CTCAEv4.03

[c.] For any CTCAE grade ≥ 3 hepatic toxicity that does not resolve within 7 days to CTCAE Grade ≤ 1 (or CTCAE Grade ≤ 2 if liver infiltration with tumor present), an abdominal CT scan has to be performed to assess if it is related to disease progression.

[d.] An AE must be clinically significant to be defined as a DLT: study drug-related fever, alkaline phosphatase elevation, electrolyte abnormalities (including K, NA, Cl, HCO_3, Mg, Ca, PO_4) that are CTCAE grade 3 abnormalities will not be considered a DLT unless clinically significant.

[e.] SCC has been reported to be an on-target side-effect that is manageable and will not be considered a DLT.

6.2.6 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first.

Appropriate clinical experts such as an ophthalmologist, dermatologist or cardiologist should be consulted as deemed necessary. Further guidelines and recommendations for the management of specific study drug combination induced toxicities are provided in Table 6-4.

6.2.6.1 Follow-up evaluations for appearance of keratoacanthoma (KA) and/or squamous cell carcinoma (SCC)

The skin of patients treated with the LGX818 and MEK162 or LGX818 and MEK162 and LEE011 combination will be examined regularly to monitor for the possible development of KA and/or SCC, as these have been reported to occur under selective BRAF inhibitor treatment (see Section 1.2.4.2). Dermatologic evaluations for this adverse effect will be performed at Screening/baseline, every 2 months thereafter and at End of Treatment.

In case of occurrence of KA and/or SCC, patients will undergo complete surgical excision of the skin lesion following institutional standards.

6.2.6.2 Follow-up evaluations for appearance of central serous retinopathy (CSR)

The patients treated with the LGX818 and MEK162 or LGX818 and MEK162 and LEE011 combination will be examined regularly to monitor for the possible development of CSR, as the appearance of CSR has been associated with MEK162 treatment (see Section 1.3). Ophthalmologic examinations to check for this adverse effect will be performed at Screening/baseline, at Day 15 of Cycle 1, at Days 1 and 15 of Cycle 2, on Day 1 of every month thereafter and at End of Treatment.

Patients who have been on LGX818/MEK162 dual-combination and or LGX818/MEK162/LEE011 triple-combination treatment for ≥ 24 months (Cycle 25 Day 1 onward) without a retinal AE should be evaluated for visual acuity at each scheduled patient visit and at the End of Treatment visit. A full ophthalmic examination is required if clinically indicated and at the End of Treatment visit.

Patients developing a CTCAE grade 1 or 2 CSR can be maintained on the study drug combination as is detailed in Table 6-4. For these patients it is recommended to follow up the CSR with an ophthalmological exam every two weeks (CTCAE Grade 1) or weekly (CTCAE Grade 2) for 8 weeks, and subsequently at approximately a 4-weeks interval. The study drug dosages of patients developing CSR > CTCAE grade 2 should be interrupted/modified according to Table 6-4 and should be followed as described above (Section 6.2.6).

6.3 Dose modifications

6.3.1 Dose modification and dose delay

Patients will be monitored for adverse events at each visit with the NCI CTCAE version 4.03 used for all grading. If a patient develops toxicity, the dose may be adjusted as outlined in Table 6-4, which includes criteria for interruption and re-initiation of LGX818 and/or MEK162 and/or LEE011, as applicable. All dose modifications should be based on the worst preceding toxicity (CTCAE version 4.03).

All dosing interruptions and changes must be recorded on the Dosage Administration Record eCRF.

If a patient experiences a DLT, study treatment should be interrupted and the toxicity should be followed as described in Section 6.2.6.

6.3.2 Treatment interruption and treatment discontinuation

Each patient is only allowed a maximum of two dose reductions after which the patient will be discontinued from the study treatment. In addition, a patient should discontinue treatment with the LGX818 and MEK162 dual or LGX818 and MEK162 and LEE011 triple combination if, after treatment is resumed at a lower dose, the toxicity recurs with the same or worse severity. However, the patient may continue to receive study treatment at the next lower dose level, if appropriate, at the discretion of the Investigator and in discussion with the Sponsor. If, after interruption of treatment and resolution, treatment is resumed at the same dose following the criteria in Table 6-4 and the same toxicity recurs with the same or worse severity, next treatment re-initiation must resume at the next lower dose level irrespective of duration. For each patient,

once a dose level reduction has occurred, the dose level may not be re-escalated during subsequent treatment cycles, except in cases where LGX818 dosing was reduced to 450mg QD during MEK162 dosing interruption.

Dose reduction for LGX818 and/or MEK162 and/or LEE011, as applicable means treatment at the next lower dose level of the respective study drug. For LGX818 and LEE011, this is the next lower previously tested dose level. For MEK162 this is the next lower dose level (please see Table 6-1 and Table 6-2). If a patient requires a dose interruption of >21 days from the intended day of the next scheduled dose, then the patient must be discontinued from the study treatment unless the patient has experienced objective evidence of clinical benefit. If the patient has experienced objective evidence of clinical benefit, and in the opinion of the investigator it is in the best interest of the patient to remain on study, then following discussion with the sponsor, the patient may continue on study treatment.

Table 6-4 Criteria for interruption and re-initiation of LGX818/MEK162/LEE011 triple-combination treatment

Recommended Dose Modifications for (dual) LGX818 and MEK162 or (triple) LGX818 and MEK162 and LEE011 combination study treatment	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
No toxicity	Maintain dose level
Blood and lymphatic system disorders	
Anemia (Hemoglobin)	
Grade 1 (≥10.0 – LLN g/dL) Grade 2 (≥8.0 – <10.0 g/dL)	No dose adjustment required
Grade 3 (<8.0 g/dL)	Interrupt LEE011 dosing until recovery to ≤ Grade 2; then re-initiate LEE011 at same dose level. Maintain dose level of LGX818 and MEK162.
Grade 4 (life threatening consequences; urgent intervention indicated)	Discontinue patient from study drug treatment.
Febrile neutropenia	
ANC < 1.0 x 10^9/L, fever ≥ 38.5°C[b]	Interrupt dosing until resolved, then ↓ 1 dose level
Grade 3 (ANC <1.0 x 10^9/L with a single temperature of >38.3 ºC [101 ºF] or a sustained temperature of ≥38 ºC [100.4 ºF] for more than one hour)	Interrupt dosing until improvement to ANC ≥ 1.0 x 10^9/L with no fever. Restart at the next lower dose level. If febrile neutropenia recurs, discontinue patient from study drug treatment.
Grade 4 (life-threatening consequences; urgent intervention indicated)	Discontinue patient from study drug treatment.

Recommended Dose Modifications for (dual) LGX818 and MEK162 or (triple) LGX818 and MEK162 and LEE011 combination study treatment	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
Investigations (Blood)	
Neutropenia (neutrophil count [ANC] decreased)	
Grade 1 (ANC < LLN – 1.5 x 10^9/L) or Grade 2 (ANC < 1.5 – 1.0 x 10^9/L)	Maintain dose level of LGX818 and MEK162 (and LEE011 if applicable)
Grade 3 (ANC < 1.0 – 0.5 x 10^9/L)	Interrupt dosing of LGX818 and MEK162 (and LEE011 if applicable) until resolved to ≤ Grade 2, then: - If resolved in ≤ 7 days, maintain dose level of LGX818 and MEK162 (and LEE011 if applicable) - If resolved in > 7 days, then ↓ 1 dose level* of LGX818 (and LEE011 if applicable) and maintain dose level of MEK162
Grade 4 (ANC < 0.5 x 10^9/L)	Interrupt dosing of LGX818 and MEK162 (and LEE011 if applicable) until resolved to ≤ Grade 2, then ↓ 1 dose level* of LGX818 and MEK162 (and LEE011 if applicable)
Thrombocytopenia (platelet count decreased)	
Grade 1 (PLT < LLN – 75 x 10^9/L)	Maintain dose level of LGX818 and MEK162 (and LEE011 if applicable)
Grade 2 (PLT < 75 – 50 x 10^9/L)	Interrupt dosing of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm) until resolved to ≤ Grade 1
Grade 3 (PLT < 50 – 25 x 10^9/L)	Interrupt dosing of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm) until resolved to ≤ Grade 1, then: - If resolved in ≤ 7 days, then maintain dose level of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm). - If resolved in > 7 days and/or with signs of bleeding, then ↓ 1 dose level* of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm)
Grade 4 (PLT < 25 x 10^9/L)	Discontinue patient from study drug treatment.

Recommended Dose Modifications for (dual) LGX818 and MEK162 or (triple) LGX818 and MEK162 and LEE011 combination study treatment	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
Gastrointestinal disorders	
Diarrhea	
Grade 1	Maintain dose level of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm), but initiate anti-diarrhea treatment.
Grade 2	Interrupt dosing of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm) until resolved to Grade ≤ 1 with proper therapy and monitoring and then maintain dose level of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm) - For 2nd occurrence of diarrhea Grade 2 within 15 days, interrupt dosing of LGX818 and MEK162 (and LEE011 if applicable) until resolved to Grade ≤ 1, then reduce MEK162 and LGX818 (and LEE011 in patients treated in triple-combination arm) by 1 dose level* and maintain dose level of LGX818 (and LEE011 in patients treated in triple-combination arm)
Grade 3	Interrupt dosing of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm) until resolved to Grade ≤ 1, then reduce dose of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm) by 1 dose level*.
Grade 4	Discontinue patient from study drug treatment.
Note: Anti-diarrhea medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea.	
Nausea / Vomiting	
Grade 1	Maintain dose level of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm)
Grade 2	Interrupt dosing until recovery to G1 with proper therapy and monitoring – Re-initiate MEK162 and LGX818 (and LEE011 in patients treated in triple-combination arm) at same dose level – If recurs at G2, interrupt dosing of MEK162 and LGX818 (and LEE011 in patients treated in triple-combination arm) until recovery to G1 and then re-initiate at next lower dose level

Recommended Dose Modifications for (dual) LGX818 and MEK162 or (triple) LGX818 and MEK162 and LEE011 combination study treatment	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
Nausea / Vomiting (continued)	
Grade 3	Interrupt dosing of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm), until resolved to Grade ≤ 1, then ↓ 1 dose level* of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm)
Grade 4	Discontinue patient from study drug treatment.
Note: Interrupt dosing for ≥ grade 3 vomiting or nausea only if the vomiting or nausea cannot be controlled with optimal antiemetics (as per local practice).	
Pancreatitis	
Grade 1	Maintain dose level of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm)
Grade 2	Interrupt dosing until recovery to G1 with proper therapy and monitoring – Re-initiate MEK162 and LGX818 (and LEE011 in patients treated in triple-combination arm) at same dose level – If recurs at G2, interrupt dosing of MEK162 and LGX818 (and LEE011 in patients treated in triple-combination arm) until recovery to G1 and then re-initiate at next lower dose level
Grade ≥3	Discontinue patient from study drug treatment.
Investigations (Renal)	
Serum creatinine	
Grade 1 (> ULN – 1.5 x ULN)	Maintain dose level of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm)
Grade 2 (> 1.5 – 3.0 x ULN)	Interrupt dosing until recovery to G1 with proper therapy and monitoring – Re-initiate MEK162 and LGX818 (and LEE011 in patients treated in triple-combination arm) at same dose level – If recurs at G2, interrupt dosing of MEK162 and LGX818 (and LEE011 in patients treated in triple-combination arm) until recovery to G1 and then re-initiate at next lower dose level
Grade ≥3	Discontinue patient from study treatment.

Recommended Dose Modifications for (dual) LGX818 and MEK162 or (triple) LGX818 and MEK162 and LEE011 combination study treatment	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
Investigations (Hepatic)**	
Bilirubin: total bilirubin without ALT/AST increase above baseline value (confirmed 48-72hr later)[c]	
Grade 1 (> ULN – 1.5 x ULN)	Maintain dose level of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm) with LFTs monitored bi-weekly.
Grade 2 (> 1.5 – 3.0 x ULN)	Interrupt dosing of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm) until resolved to Grade ≤ 1, then: - If resolved in ≤ 21 days, then maintain dose level of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm) - If resolved in > 21 days, then ↓ 1 dose level* of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm) - If not resolved within 28 days, or if toxicity recurs, discontinue patient from all study drug treatment. **Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption.**
Grade 3 (> 3.0 x ULN)	Interrupt dosing of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm) until resolved to Grade ≤ 1, then ↓ 1 dose level - Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption - If not resolved within 28 days, or if toxicity recurs, discontinue patient from all study drug treatment.
Grade 4 (> 10.0 x ULN)	Discontinue patient from study treatment.
Note: If Grade 3 or 4 hyperbilirubinemia is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level* and continue treatment at the discretion of the investigator.	
AST or ALT without bilirubin elevation > 2 ULN (confirmed 48-72hr later)[c]	
Grade 1	Maintain dose level of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm) and monitor LFTs biweekly.

Recommended Dose Modifications for (dual) LGX818 and MEK162 or (triple) LGX818 and MEK162 and LEE011 combination study treatment	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
AST or ALT without bilirubin elevation > 2 ULN (confirmed 48-72hr later)[c] (continued)	
Grade 2	Interrupt dosing of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm) until resolved to Grade ≤ 1 (or Grade ≤ 2 in case of liver metastasis), then: - If resolved in ≤ 21 days, maintain dose level of LGX818 and MEK162 (and LEE011 for triple-combination arm). - If resolved in > 21 days, then ↓ 1 dose level* of LGX818 and MEK162 (and LEE011 for triple-combination arm). - If not resolved within 28 days, discontinue patient from all study drug treatment. **Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption.**
Grade 3 (> 3.0 x ULN)	Omit dose of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm) until resolved to ≤ baseline grade, then ↓ 1 dose level of dose level of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm). If not recovered to ≤ baseline grade within 28 days, discontinue patient from all study drug treatment. **Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption. If toxicity recurs, discontinue patient from all study drug treatment.**
Grade 4 (> 10.0 x ULN)	Discontinue patient from study drug treatment.
AST or ALT and Bilirubin[d]	
For patients with normal ALT and AST and total bilirubin at baseline: AST or ALT > 3.0 x ULN combined with total bilirubin > 2 x ULN without evidence of cholestasis[e]	Discontinue patient from study drug treatment.
For patients with elevated AST or ALT or total bilirubin at baseline: baseline: (AST or ALT > 2 x baseline AND > 3.0 x ULN) OR (AST or ALT 8.0 x ULN) — whichever is lower — combined with (total bilirubin > 2 x baseline AND > 2.0 x ULN)	Discontinue patient from study drug treatment.

Recommended Dose Modifications for (dual) LGX818 and MEK162 or (triple) LGX818 and MEK162 and LEE011 combination study treatment	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
Investigations (Metabolic)	
Asymptomatic amylase and/or lipase elevation	
Grade 1 (> ULN – 1.5 x ULN)	Maintain dose level of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm) and initiate appropriate medical therapy and monitoring.
Grade 2 (> 1.5 – 2.0 x ULN)	Interrupt dosing until recovery to G1 with proper therapy and monitoring – Re-initiate MEK162 and LGX818 (and LEE011 in patients treated in triple-combination arm) at same dose level – If recurs at G2, interrupt dosing of MEK162 and LGX818 (and LEE011 in patients treated in triple-combination arm) until recovery to G1 and then re-initiation at next lower dose level.
Grade 3 (> 2.0 – 5.0 x ULN)	Interrupt dosing of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm) until resolved to Grade ≤ 2, then: - If resolved in ≤ 7 days, maintain dose level of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm) - If resolved in > 7 days, ↓ 1 dose level* of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm).
Grade 4 (> 5.0 x ULN)	Discontinue patient from study drug treatment.
Note: A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within 1 week of the first occurrence of any grade ≥ 3 of amylase and/or lipase. In cases of asymptomatic elevations of lipase and/or amylase with imaging study which does not show damage to pancreas, liver, and gallbladder, if the patient is asymptomatic Grade 2 elevations of lipase and/or amylase occur again at the reduced dose, patients will be discontinued permanently from study treatment.	

Recommended Dose Modifications for (dual) LGX818 and MEK162 or (triple) LGX818 and MEK162 and LEE011 combination study treatment	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
Cardiac disorders	
Cardiac general	
Grades 1 or 2	Maintain dose level of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm)
Grade 3	Interrupt dosing of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm) until resolved to Grade ≤ 1, then ↓ 1 dose level* of LGX818 and MEK162 (and LEE011 for triple-combination arm)
Grade 4	Discontinue patient from study drug treatment.
Investigations (cardiac)	
Creatine phosphokinase (CPK)	
Grade 1 (> ULN – 2.5 x ULN) or Grade 2 (> 2.5 – 5.0 x ULN)	Maintain dose level of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm)
Grade 3 (> 5.0 – 10.0 x ULN)	If asymptomatic: Maintain dose level of LGX818 and MEK162 (and LEE011 in triple-combination arm) If symptomatic: Interrupt dosing of MEK162 and maintain dose of LGX818[1] (and LEE011 in patients treated in triple-combination arm) until resolved to Grade ≤ 1, then: - If resolved in ≤ 14 days, then ↓ 1 dose level* of MEK 162 and maintain dose level of LGX818[2] (and LEE011 in patients treated in triple-combination arm) - If unresolved after > 14 days, then discontinue patient from study drug treatment.
Grade 4 (> 10.0 x ULN)	Interrupt dosing of MEK162 and maintain dose of LGX818[1] (and LEE011 in triple-combination arm) until resolved to CTCAE Grade ≤ 1, then: - If resolved in ≤ 14 days, then ↓ 1 dose level of MEK162 and maintain dose level of LGX818[2] (and LEE011 in patients treated in triple-combination arm) - If unresolved after > 14 days, then discontinue patient from study drug treatment.

[1] If the LGX818 dose is > 450mg QD, then the LGX818 dose must be reduced to 450mg QD during the MEK162 dosing interruption.
[2] If the LGX818 dose was reduced to 450mg QD during an MEK162 interruption, it must be re-escalated to the previous dose once MEK162 dosing resumes.

Recommended Dose Modifications for (dual) LGX818 and MEK162 or (triple) LGX818 and MEK162 and LEE011 combination study treatment	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
Left ventricle (LV) systolic dysfunction (not according to CTCAE)	
Asymptomatic decrease of > 10% in left ventricle ejection fraction (LVEF) compared to baseline and the ejection fraction is below the institution's lower limit of normal and CTCAE Grade 2	Interrupt dosing of MEK162 until LVEF recovers (defined as ≥ LLN and decrease ≤ 10% compared to baseline). - If the LVEF recovers ≤ 21 days, then ↓ 1 dose level of MEK162, maintain dose of LGX818 and LEE011 in patients treated in triple-combination arm, monitor LVEF 2 weeks after restarting on MEK162, every 4 weeks for 12 weeks and subsequently as per protocol - If the LVEF recovers > 21 days, then discontinue patient from study drug treatment and closely monitor LVEF until resolution (or for 16 weeks).
Grade ≥ 3	Discontinue patient from study drug treatment.
Electrocardiogram QTcF interval prolonged	
Grade 1 (QTcF 450-480 ms)[f]	Maintain dose level(s). Perform steps 1-4 as directed in "For all grades."
Grade 2 (QTcF 481-500 ms)[f]	Interrupt dosing of MEK162 and LGX818 (and LEE011 in patients treated in triple-combination arm). Perform steps 1-4 as directed in "For all grades." Perform a repeat ECG within 1 hour of the first QTcF of ≥ 481 ms. Repeat ECG as clinically indicated until the QTcF returns to < 481 ms, restart MEK162 and LGX818 at the same dose (if triple combination, restart LEE011 with dose reduced one level. If QTcF ≥ 481 ms recurs, MEK162 and LGX818 (and LEE011 in patients treated in triple-combination arm) should be reduced by 1 dose level. Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patients who had therapy interrupted due to QTcF ≥ 481 ms.
Grade 3 (QTcF ≥ 501 ms on at least two separate ECGs)[f]	Interrupt dosing of MEK162 and LGX818 (and LEE011 in triple-combination arm). Perform steps 1-4 as directed in "For all grades." Transmit ECG immediately and confirm prolongation/abnormalities with central assessment. Perform a repeat ECG within one hour of the first QTcF of > 501 ms. If QTcF remains ≥ 501 ms, consult with a cardiologist (or qualified specialist) and repeat cardiac monitoring as clinically indicated until the QTcF returns to < 481 ms. • If QTcF returns to < 481 ms, reduce MEK162 and LGX818 (and LEE011 in triple-combination arm) by 1 dose level.

Recommended Dose Modifications for (dual) LGX818 and MEK162 or (triple) LGX818 and MEK162 and LEE011 combination study treatment	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
	• If QTcF remains ≥ 481 ms after performing steps 1-4 as directed in "For all grades," discontinue all study treatments. Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patients who had therapy interrupted due to QTcF ≥ 501 ms If QTcF of ≥ 501 ms recurs, discontinue patient from study drug treatment.
Electrocardiogram QTcF interval prolonged (continued)	
Grade 4 [g] (QTcF ≥ 501 or > 60 ms change from baseline and Torsades de pointes or polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia)	Discontinue patient from study drug treatment, then: - Obtain local cardiologist consultation. - Perform a repeat ECG within one hour of the first QTcF of ≥ 501 ms. - If QTcF remains ≥ 501 ms, repeat ECG as clinically indicated, but at least once a day until the QTcF returns to < 501 ms.
For all grades: • Check the quality of the ECG and the QT value and repeat if needed. • Perform analysis of serum electrolytes (K+, Ca++, Phos, Mg++). If outside of the normal range, interrupt LGX818 and MEK162 and LEE011 administration, correct with supplements or appropriate therapy as soon as possible, and repeat electrolytes until documented as normal. • Review concomitant medication usage for the potential to inhibit CYP3A4 and/or to prolong the QT interval. • Check compliance with correct dose and administration of LGX818 and MEK162 and LEE011.	
Vascular disorders	
Hypertension	
Grade 1	Maintain dose level of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm)
Grade 2	Interrupt dosing until recovery to G1 with proper therapy and monitoring – Re-initiate study drugs at same dose level. **If recurs at G2, interrupt study drugs until recovery to G1 and then re-initiate at next lower dose level.**
Grade 3 (requiring more than one drug or more intensive therapy than previously)	Interrupt dosing of LGX818 and MEK162 (and LEE011 in triple-combination arm), until resolved to Grade ≤ 1, then ↓ 1 dose level* of LGX818 and MEK162 (and LEE011 in triple-combination arm)
Grade 4 (life-threatening)	Discontinue patient from study drug treatment.

Recommended Dose Modifications for (dual) LGX818 and MEK162 or (triple) LGX818 and MEK162 and LEE011 combination study treatment	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
Eye disorders	
Retinal events	
Grade 1	Maintain dose level of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm) and increase frequency of ophthalmic monitoring to at least every 14 days (see also Section 6.2.6.2).
Grade 2	Maintain dose level of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm) and increase frequency of ophthalmic monitoring to at least weekly (see also Section 6.2.6.2). Refer the patient to a retinal specialist within one week for further evaluation. - If resolved to Grade ≤ 1 in ≤ 21 days, then maintain dose level of MEK162 and LGX818 (and LEE011 in patients treated in triple-combination arm) - If not resolved to Grade ≤ 1 in ≤ 21 days, then ↓ 1 dose level* of MEK162 and LGX818 (and maintain dose of LEE011 in patients treated in triple-combination arm). - At any time if symptoms worsen, or persist with the same severity for more than 7 days, reduce 1 dose level[f] of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm).
Grade 3	Interrupt dosing of LGX818 and MEK162, (and LEE011 if applicable) until recovery to Grade 1. Re-initiate study drugs at next lower dose level. If recurs at Grade 3, discontinue patient from study. - If resolved to Grade ≤ 1 in ≤ 21 days, then ↓ 1 dose level* of MEK162 and LGX818 (and maintain dose level of LEE011 in patients treated in triple-combination arm) - If not resolved to Grade ≤ 1 in ≤ 21 days, then discontinue patient from study drug treatment and refer the patient to an ophthalmologist for monitoring.
Grade 4 (retinopathy)	Discontinue patient from study drug treatment and refer the patient to an ophthalmologist for monitoring.[g]
Note: Results and images of ophthalmic examinations must be made available upon request. This includes scans/images of OCTs	
Retinal vein occlusion (RVO)[h]	
Any grade	Discontinue patient from study drug treatment and refer the patient to an ophthalmologist for monitoring.
Note: Results and images of ophthalmic examinations should be made available upon request.	

Recommended Dose Modifications for (dual) LGX818 and MEK162 or (triple) LGX818 and MEK162 and LEE011 combination study treatment	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
Other eye events (i.e. retinal detachment)	
Grades 1 or 2	Maintain dose level of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm) and increase frequency of ophthalmic monitoring to at least every 14 days. At any time if symptoms worsen, or persist with the same severity for more than 7 days, reduce 1 dose level of LGX818 and MEK162.[c]
Grade 3	Interrupt dosing of LGX818 and MEK162 (and maintain dose level of LEE011 in patients treated in triple-combination arm) and refer patient to ophthalmologist monitoring within one week.[g] - If resolved to Grade ≤ 1 in ≤ 21 days, reduce 1 dose level[h] of LGX818 and MEK162 - If not resolved to Grade ≤ 1 in > 21 days, discontinue patient from study drug treatment and refer the patient to an ophthalmologist for monitoring.[h]
Grade 4	Discontinue patient from study drug treatment and refer the patient to an ophthalmologist for monitoring.[g]
Skin and subcutaneous tissue disorders	
Rash / hand foot skin reaction (HFSR) / photosensitivity / Toxic Epidermal Necrolysis (TEN)	
Grade 1	Maintain dose level of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm), but consider initiating appropriate skin toxicity therapy (See Appendix 3).
Grade 2	Maintain dose level of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm), but initiate/intensify appropriate skin toxicity therapy.
Grade 3 despite skin toxicity therapy	Interrupt dosing of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm), until resolved to Grade ≤ 1 then: - If resolved in ≤ 7 days, ↓ 1 dose level* of LGX818 and MEK162 (and LEE011 in triple-combination arm) - If not resolved after > 7 days, discontinue patient from study drug treatment.
Grade 4 despite skin toxicity therapy	Discontinue patient from study drug treatment.

Recommended Dose Modifications for (dual) LGX818 and MEK162 or (triple) LGX818 and MEK162 and LEE011 combination study treatment	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
Respiratory, thoracic and mediastinal disorders	
ILD/Pneumonitis	Maintain dose level of LGX818; adjust dose of MEK162 (and LEE011 in patients treated in triple-combination arm) according to Grade below
Grade 1	No dose interruption or adjustment of MEK162 (or LEE011 in patients treated in triple-combination arm) is required. Initiate appropriate medical therapy and monitor as clinically indicated
Grade 2	Interrupt dosing of MEK162 (and LEE011 in patients treated in triple-combination arm) for ≤ 21 days. -If resolved to Grade ≤ 1 in ≤ 21 days, reduce 1 dose level[h] of MEK162 (and LEE011 in patients treated in triple-combination arm), performing an individualized benefit-risk assessment -If not resolved to Grade ≤ 1 in ≤ 21 days, then discontinue patient from study drug treatment. If Grade 2 recurs, discontinue patient from study drug treatment
Grade 3/4	Discontinue patient from study drug treatment
General disorders and administration site conditions	
Fatigue	
Grades 1 or 2	Maintain dose level of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm)
Grade 3	Interrupt dosing of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm) until resolved to Grade ≤ 1, then: - If resolved in ≤ 7 days, maintain dose level of LGX818 and MEK162 (and LEE011 in triple-combination arm) - If not resolved after > 7 days, then ↓ 1 dose level* of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm)
Edema	
Grades 1 or 2	Maintain dose level of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm)

Recommended Dose Modifications for (dual) LGX818 and MEK162 or (triple) LGX818 and MEK162 and LEE011 combination study treatment	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
Grade 3	Interrupt dosing of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm) until resolved to Grade ≤ 1, then: - If resolved in ≤ 14 days, then ↓ 1 dose level* of MEK162 and maintain dose of LGX818 (and LEE011 in patients treated in triple-combination arm) - If not resolved after > 14 days, then discontinue patient from study drug treatment.
Other adverse events	
Grades 1 or 2	Maintain dose level of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm)
Grade 3	Interrupt dosing of LGX818 and MEK162 (and LEE011 in patients treated in triple-combination arm) until resolved to Grade ≤ 1, then ↓ 1 dose level* of LGX818 and MEK162 (and LEE011 in triple-combination arm)
Grade 4	Discontinue patient from study drug treatment.

[a] All dose modifications should be based on the worst preceding toxicity.

[b] Not CTCAE grading

[c] Dose reduction below 50 mg QD for LGX818, and below 15 mg BID for MEK162 is not allowed.

[d] All patients with ALT or AST >5.0x ULN and total bilirubin > 1.5x ULN in the absence of cholestasis must immediately be withdrawn from study treatment and every attempt should be made to carry out the **liver event follow-up assessments** as described below in Section 6.3.3.
If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when omit dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment either at the same dose or at one dose lower if meeting a criterion for dose reduction

[e] "Cholestasis" defined as: ALP elevation (>2.0 x ULN and R value (ALT/ALP in x ULN) ,2.0) in patients without bone metastasis, or elevation of ALP liver function in patients with bone metastasis.

[f] All values refer to the average of triplicate measurements.

[g] Ophthalmic monitoring mandated for retinal event, posterior uveitis, RVO: further evaluation with specialized retinal imaging (e.g. ocular coherence tomography, angiography).

[h] Except: 1) lymphopenia unless clinically significant, 2) occurrence of KA and/or cutaneous SCC, 3) alkaline phosphatase, 4) AEs not considered clinically significant like alopecia study drug-related fever, electrolyte abnormalities (including K, NA, Cl, HCO_3, Mg, Ca, PO_4).

* ↓ 1 dose level refers to: next lower previously tested dose level of LGX818 and LEE011 and the next lower dose level of MEK162 (please see Table 6-1 and Table 6-2).

Recommended Dose Modifications for (dual) LGX818 and MEK162 or (triple) LGX818 and MEK162 and LEE011 combination study treatment	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**

** Confounding factors and/or alternative causes for increased transaminases should be excluded before dose interruption/reduction. They include but are not limited to: concomitant medications, herbal preparations or dietary supplements, infection, hepato-biliary disorder or obstruction, new or progressive liver metastasis, and alcohol intake.

6.3.3 Additional follow-up for hepatic toxicities in patients receiving LEE011

Hepatic toxicity monitoring includes the following LFTs: albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2 x ULN), alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher) and GGT. For patients with Gilbert Syndrome: total and direct bilirubin must be monitored, intensified monitoring applies to changes in direct bilirubin only.

Close observation is recommended in case of AST, ALT, and/or bilirubin increase requiring dose interruption, which involves:

- Repeating liver enzyme and serum bilirubin tests **two or three times weekly**. Frequency of re-testing can decrease to once a week or less if abnormalities stabilize or return to normal values.
- Obtaining a more detailed history of current symptoms.
- Obtaining a more detailed history of prior and/or concurrent diseases, including history of any pre-existing liver conditions or risk factors.
- Obtaining a history of concomitant drug use (including non-prescription medications, herbal and dietary supplements), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; hepatotropic virus infections (CMV, EBV or HSV); autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).
- Considering gastroenterology or hepatology consultations.
- Assessing cardiovascular dysfunction or impaired liver oxygenation, including hypotension or right heart failure as possible etiologies for liver dysfunction.
- Considering a liver biopsy, as clinically indicated to assess pathological change and degree of potential liver injury.

6.4 Concomitant medications

6.4.1 Permitted concomitant therapy

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug combination. All medications (other than study drugs) and significant non-drug therapies (including herbal medicines, physical therapy and blood transfusions) administered during the study must be listed on the Concomitant medications/Significant non-drug therapies eCRF.

Patients taking concomitant medication chronically should be maintained on the same dose and dose schedule throughout the study period, as medically feasible. The days of full PK blood sampling should be representative of the other study days with regard to the use of the chronically administered concomitant medications. However, if a concomitant medication is used intermittently during the study, this medication should be avoided on the days of full PK sampling, if medically feasible.

The use of bisphosphonates regardless of indication is allowed for the LGX818 and MEK162 dual combination (prophylactic treatment is not allowed for bisphosphonates with LEE011) provided patients have been on stable doses for at least 2 weeks prior to study entry. Stable doses should be maintained during the treatment period. Patients requiring initiation of bisphosphonates during the course of the study should be discontinued due to progressive disease unless disease progression can be completely ruled out and this is clearly documented in the patients' source documentation.

Chronic dosing of corticosteroids such as dexamethasone and prednisone is known to lead to induction of CYP3A enzymes, thereby potentially increasing the risk of reducing drug exposure for CYP3A substrates to subtherapeutic levels. The following forms of corticosteroid treatment are permitted:

- Topical applications (e.g. rash), inhaled sprays (e.g. obstructive airway diseases), eye drops, or local injections (e.g., intra-articular);
- A short duration (< 5 days) of systemic corticosteroids ≤ to the anti-inflammatory potency of 4 mg dexamethasone (e.g., for chronic obstructive pulmonary disease, or as an antiemetic).

Refer to the LGX818 Investigator's Brochure, MEK162 Investigator's Brochure and LEE011 Investigator's Brochure as applicable for information on possible interactions with other drugs.

Approved Covid-19 vaccines are permitted, including those under an EUA. The timing of COVID-19 vaccine administration is at the investigator's discretion. The administration of a COVID-19 vaccine would be recorded as a concomitant medication and standard AE collection and reporting processes would be followed.

6.4.2 Permitted concomitant therapy requiring caution and/or action for LGX818 and MEK162

LGX818 is a reversible inhibitor of CYP1A2, CYP2B6, CYP2C8/9, CYP2D6, CYP3A4, and UGT1A1. It is also a time dependent inhibitor of CYP3A4. Permitted medications to be used with caution in this study include those that are sensitive substrates of CYP1A2, CYP2B6, CYP2C8/9, CYP2D6, CYP3A4, and UGT1A1, or those substrates that have a narrow therapeutic index (NTI).

There is a potential for LGX818 to induce CYP3A4 at concentrations >10-50 uM, which may reduce the effectiveness of hormonal contraception methods. Therefore, the use of at least one form of non-hormonal contraception will be needed during the participation in this study. Please see Section 5.3 exclusion criterion 10 for use of contraception methods required for this study.

LGX818 has been identified to be primarily metabolized by CYP3A4 *in vitro*. It is advised that LGX818 should be taken with caution when co-administered with moderate inhibitors of CYP3A4 or strong inducers of CYP3A4 (NB. strong systemic inhibitors of CYP3A4 are prohibited (please see Section 6.4.3).

In vitro data showed that both LGX818 and MEK162 are substrates of P-gp. Thus, the use of drugs that are known to inhibit or induce P-gp should be used with caution. LGX818 is a BCRP

and P-gp inhibitor. It is also a potent inhibitor of the renal transporters OAT1, OAT3 and OCT2 and the hepatic transporters OATP1B1 and OATP1B3. Therefore the co-administration of drugs that are known to be sensitive or NTI substrate of BCRP, P-gp, OAT1, OAT3, OCT2, OATP1B1, and OATP1B3 should be used with caution.

MEK162 is a substrate for many CYP isoforms, in particular CYP1A2 and CYP2C19. The risk of metabolic interaction caused by an effect on an individual isoform is therefore minimized. Nevertheless, caution should be used in patients receiving concomitant treatment with other drugs that are either potent inhibitors or inducers of these enzymes.

Patients receiving such medications above must be carefully monitored for potentiating of toxicity due to any individual concomitant medication, and may require dose titration of the drug substance. Investigators should use caution when prescribing co-medications, as clinical experience with these compounds in patients with cancer is often limited. Investigators should contact the Sponsor when they are unsure whether a drug should be prescribed to a patient in the clinical study. All concomitant medications and dietary supplements must be documented on the eCRFs. Please refer to Appendix 4 for a list of medications to be used with caution as mentioned above.

6.4.2.1 Additional permitted concomitant therapy requiring caution and/or action for addition of LEE011 in the triple combination

LEE01 is a moderate substrate of P-glycoprotein (P-gp). LEE011 is a weak reversible inhibitor of CYP1A2. It is recommended that substrates metabolized predominantly by CYP1A2 with a narrow therapeutic index be taken with caution. LEE011 was found to inhibit the mitoxantrone-resistant protein (MXR or BCRP), and human bile salt export pump (BSEP). Medications to be used with caution during triple-combination treatment with LEE011 in this study are listed below (see Appendix 4, as this list is not comprehensive and is only meant to be used as a guide. Please contact the medical monitor with any questions). These medications should be excluded from patient use if possible. If they must be given based on the investigator's judgment, then use with caution and consider a LEE011 interruption if the concomitant medication is only needed for a short time.

- Moderate inhibitors or inducers of CYP3A4/5 (may increase or decrease LEE011 exposure, respectively)
- Sensitive substrates of CYP3A4/5 that do not have narrow therapeutic index (LEE011 may increase exposure to these medications)
- Strong inhibitors of BSEP (based on *in vitro* data co-administration with LEE011 may lead to intrahepatic cholestasis)
- Medications that carry a possible risk for QT prolongation (may precipitate QT prolongation and TdP)
- Sensitive substrates of the renal transporters, MATE1, OCT2 and BCRP (has a potential to increase exposure to substrates of these transporters, although no animal or clinical data are available to support these statements)
- Strong inhibitors/inducers of P-gp.

6.4.3 Prohibited concomitant therapy dual and triple combination

- Other investigational therapies must not be used while the patient is on study treatment.
- Anticancer therapy (chemotherapy, biologic or radiation therapy, palliative radiotherapy covering > 25% of the bone marrow reserve, and surgery) other than the study treatment must not be given to patients while the patient is on study treatment. If such agents are required for a patient, then the patient must be withdrawn from the study.
- The concomitant use of strong systemic CYP3A4 inhibitors would likely significantly increase the exposure of LGX818 and thus should not be used during this study (please refer to Table 14-10 in Appendix 4 for a partial list of CYP3A4 inhibitors).

6.4.3.1 Additional prohibited concomitant therapy for addition of LEE011 in the triple combination

- Prophylactic treatment with bisphosphonates is not allowed with LEE011.
- Strong inhibitors or inducers of CYP3A4/5 (may significantly increase or decrease ribociclib exposure, respectively)
- Substrates of CYP3A4/5 with a narrow therapeutic index (LEE011 may increase exposure to these medications resulting in toxicity to these medications)
- Medications with a known risk for QT prolongation and/or TdP (may precipitate QT prolongation and TdP in combination with LEE011). See Table 14-12 and the LEE011 Investigator's Brochure for a complete list of agents that are known to cause QTc prolongation in humans.
- Other investigational and antineoplastic therapies
- Herbal preparations/medications that are strong inhibitors or inducers of CYP3A4/5. These include but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, black cohosh and ginseng. Patients should stop using all herbal medications and dietary supplements at least 7 days prior to first dose of study treatment.

See Appendix 4 for a partial list of CYP3A4 substrates or inducers.

6.5 Patient numbering, treatment assignment and randomization

6.5.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient has signed the Molecular pre-screening Informed Consent Form (if applicable) or Study Informed Consent Form and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by the Sponsor to the investigative site) with a sequential patient number suffixed to it, so that each subject is numbered uniquely across the entire database. Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be changed, even if the patient is re-screened.

If the patient fails screening for any reason, the reason will be entered into the Screening log eCRF.

6.5.2 Treatment assignment and randomization

The assignment of a patient to a particular cohort will be coordinated by the sponsor.

No randomization will be performed in this study.

6.6 Study drug supply

6.6.1 Study drug preparation and dispensation

The Investigator needs to instruct the patient to take the study drugs as per protocol. The investigational drugs to be used in this trial are:

- LGX818, supplied as capsules for oral use of dosage strengths of 10, 25, 50 and 100 mg.
- MEK162, supplied as film-coated tablets for oral use of dosage strength 15 mg.
- LEE011, supplied as capsules for oral use of dosage strength of 50 and 200 mg.

Other strengths might be made available during development of the study drugs if deemed necessary.

All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

As of protocol amendment 3, two new MEK162 tablet variants were introduced as described in the Amendment 3 rationale and Section 6.2.3:

- MEK162 smaller tablet
- new MEK162 tablet variant

Both new tablet variants are available in a 15 mg dosage strength.

6.6.2 Study drug packaging and labeling

LGX818 capsules, MEK162 tablets and LEE011 capsules are packaged in HDPE bottles with child resistant closures.

Study drug labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug but no information about the patient.

As of protocol amendment 3, the MEK162 smaller tablet and new MEK162 tablet variant as described in this protocol, will be distinguishable by the following naming on the study drug labels:

- MEK162 15mg_NVS FMI (refers to the MEK162 smaller tablet).
- MEK162 15mg_NVS CSF (refers to the new MEK162 tablet variant).

6.6.3 Drug supply and storage

Study drugs will be centrally supplied by the Sponsor or a Sponsor-designated CRO, and must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, the study drugs should be stored according to the instructions specified on the drug labels.

6.6.4 Study drug compliance and accountability

6.6.4.1 Study drug compliance

At the day of a scheduled visit to the clinic, the patient will take the study drugs under supervision of the Investigator or designee. The time of dose administration must be recorded in the Dose Administration Record eCRF. For all other study days, the patient will take the study drugs at home.

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

Patients will be instructed to write down the date and time of administration in a patient diary provided by the sponsor. The investigator or designee must check compliance and note any drug interruptions in the Dose Administration record page of the eCRFs.

6.6.4.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment (including Lot numbers) according to local institutional guidelines for drug accountability. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability to the Sponsor's monitor or to the Sponsor address provided in the investigator folder at each site.

6.6.5 Disposal and destruction

The drug supply can be returned to and destroyed by the clinical supply vendor, as appropriate. Study drug destruction at the investigational site will only be permitted if authorized by the Sponsor in a prior agreement and if permitted by local regulations.

7 Visit schedule and assessments

[Any language regarding the triple combination of LGX818/MEK162/LEE011 in this Section is <u>not</u> applicable to the USA and Singapore]

7.1 Study flow and visit schedule

Note: As of protocol amendment 10, all efficacy and safety assessments will be completed per local standard-of-care, or otherwise as clinically indicated. See Table 7-2.

Table 7-1 and Table 7-2 list all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's

source documentation. The table indicates which assessments produce data to be entered into the database (D) or remain in source documents only (S) ("Category" column).

All screening assessments must be completed within 14 days before the first dose, with the exception of pregnancy test, which must be performed within 72 hrs before the first dose. The Screening/baseline imaging assessments must be completed within 21 days before first dose of study treatment, except whole-body bone scans, if applicable, which can be performed within 6 weeks of study treatment start. For PK sampling, the samples may be obtained ± 1 day from the scheduled date (except for PK sampling on Cycle 1 Day 1) under the LGX818 QD or BID dosing schedule. In case QOD dosing would be introduced for LGX818, the PK sampling must be performed on the specified day of dosing. For all other on-treatment visits, there is a ± 3-day window on assessments to take into account scheduling over public or religious holidays if not explicitly specified otherwise. For on-study imaging assessments, a ± 7 day window is allowed, except for the tumor assessment on C1D28 which must be performed between week 3 and 4 after starting the study drug combination (C1D28 tumor assessment not applicable for Phase II parts). Patients who have been on the LGX818/MEK162 dual-combination and LGX/MEK162/LEE011 triple-combination treatment for ≥ 24 months (Cycle 25 Day 1 onwards) will be evaluated for all potential sites of tumor lesions every 8-12 weeks (± 7 days) until disease progression. Every effort must be made to follow the schedule outlined in Table 7-1 and Table 7-2.

Assessments which are indicated to be performed at Screening/baseline and on Cycle 1 Day 1, need only to be repeated at Cycle 1 Day 1 if Screening/baseline assessment was more than 3 days earlier.

Table 7-1 Visit evaluation schedule

	Category	Reference to Section	Molecular Pre-Screening	Screening /Baseline	Cycle 1							Cycle 2					Subsequent cycles			EOT	30-day safety FU[m]	Disease progression FU (Phase II only)	SEC[a]	Survival FU (Phase II only)
Visit Name			1	2	3	4	5	6	7	8		10	201	11	202		13	14		777			778	
Day of cycle				-14 to-1	1	2	8	15	16	22	28	1	8	15	22	28	1	15	28	≤14d from last dose				
Molecular pre-screening Informed Consent, if applicable	D	7.1.1 / 11.3	X																					
Documented BRAF mutation	D	7.1.1		X																				
Obtain Study Informed Consent	D	7.1.2 / 11.3		X																				
Demography	D	7.1.2.3	X[b]	X																				
Inclusion / Exclusion criteria	D	5.2 / 5.3		X																				
Relevant medical history/current medical conditions	D	7.1.2.3		X																				
Diagnosis and extent of cancer	D	7.1.2.3		X																				
Prior antineoplastic therapy	D	7.1.2.3		X																				
Prior/concomitant medications	D	7.1.2.3		X	CONTINUOUS																			

	Category	Reference to Section	Molecular Pre-Screening	Screening /Baseline	Cycle 1							Cycle 2					Subsequent cycles			EOT	30-day safety FU[m]	Disease progression FU (Phase II only)	SEC[a]	Survival FU (Phase II only)
Visit Name			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**		**10**	**201**	**11**	**202**		**13**	**14**		**777**			**778**	
Day of cycle				**-14 to-1**	**1**	**2**	**8**	**15**	**16**	**22**	**28**	**1**	**8**	**15**	**22**	**28**	**1**	**15**	**28**	**≤14d from last dose**				
Physical examination	S	7.2.2.1		X	X		X[c]	X		X[c]		X		X[c]			X	C3[c,d]		X				
Vital signs	D	7.2.2.2		X	X		X[c]	X		X[c]		X		X[c]			X	C3[c,d]		X				
Performance status (WHO)	D	7.2.2.3		X	X		X[c]	X				X		X[c]			X	C3[c,d]		X				
Height	D	7.2.2.4		X																				
Weight	D	7.2.2.4		X	X							X					X			X				
Hematology	D	7.2.2.5.1		X	X		X	X		X		X		X			X	C3		X				
Clinical chemistry	D	7.2.2.5.2		X	X		X	X		X		X		X			X	C3		X				
Additional LFT	D	7.2.2.5.2											X		X			C4						
Coagulation	D	7.2.2.5.3		X	X							X					X			X				
Urinalysis (and 24h urine collection if applicable)	D	7.2.2.5.4		X	X			X				X					X			X				
Pregnancy test	D	7.2.2.5.5		X								X					X			X				
Dermatologic evaluation	D	7.2.2.6		X													Day 1 of odd-numbered Cycles (C3, C5, etc.)			X				
Ophthalmologic examination	D	7.2.2.7		X				X				X		X			X[e]			X				
ECG 12-lead[f]	D	7.2.2.8.1/ 7.2.2.8.2		X	X			X				X		X			X			X				

	Category	Reference to Section	Molecular Pre-Screening	Screening /Baseline	Cycle 1							Cycle 2					Subsequent cycles			EOT	30-day safety FU[m]	Disease progression FU (Phase II only)	SEC[a]	Survival FU (Phase II only)
Visit Name			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**		**10**	**201**	**11**	**202**		**13**	**14**		**777**			**778**	
Day of cycle				**-14 to-1**	**1**	**2**	**8**	**15**	**16**	**22**	**28**	**1**	**8**	**15**	**22**	**28**	**1**	**15**	**28**	**≤14d from last dose**				
Cardiac imaging	D	7.2.2.8.3		X								X					C5, C8 C11[g]			X				
Tumor imaging assessments (RECIST 1.1)	D	7.2.1		X							X[c,h]					X	C4, C6 X[i]			X		X[j]		
Brain MRI/CT	D	7.2.1		X[k]																				
Phone calls for Disease progression FU (if applicable)	S	7.2.1																				X (monthly)		
Adverse events	D	8	X (procedure-related SAEs only)	CONTINUOUS																				

	Category	Reference to Section	Molecular Pre-Screening	Screening /Baseline	Cycle 1							Cycle 2					Subsequent cycles			EOT	30-day safety FU[m]	Disease progression FU (Phase II only)	SEC[a]	Survival FU (Phase II only)
Visit Name			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**		**10**	**201**	**11**	**202**		**13**	**14**		**777**			**778**	
Day of cycle				**-14 to-1**	**1**	**2**	**8**	**15**	**16**	**22**	**28**	**1**	**8**	**15**	**22**	**28**	**1**	**15**	**28**	**≤14d from last dose**				
LGX818 administration	D	6.1.1 / 6.6			CONTINUOUS																			
MEK162 administration	D	6.1.1 / 6.6			CONTINUOUS																			
LEE011 administration (only for triple combination)	D	6.1.1 / 6.6			3 weeks on, 1 week off schedule (once daily for 21 days followed by a 7-day rest [28-day cycle]).																			
Blood for PK (up to cycle 10) – not for PhII arm 1 unless if required	D	7.2.3			X	X		X	X			X					X							
Archival tumor sample (paraffin block/slides) with an accompanying pathology report	D	7.2.4.1		X																				
Fresh tumor sample from biopsy/resection	D	7.2.4.1	X (if needed)	X[l]					X											X (at relapse)		X (at relapse)		

	Category	Reference to Section	Molecular Pre-Screening	Screening /Baseline	Cycle 1							Cycle 2					Subsequent cycles			EOT	30-day safety FU[m]	Disease progression FU (Phase II only)	SEC[a]	Survival FU (Phase II only)
Visit Name			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**		**10**	**201**	**11**	**202**		**13**	**14**		**777**			**778**	
Day of cycle				**-14 to-1**	**1**	**2**	**8**	**15**	**16**	**22**	**28**	**1**	**8**	**15**	**22**	**28**	**1**	**15**	**28**	**≤14d from last dose**				
Fresh skin biopsy (only applicable for those patients from whom fresh tumor sample is collected)	D	7.2.4.2		X					X											X (at relapse)		X (at relapse)		
Blood for genetic analysis	D	7.2.4.3							X (or any other visit)															
Phone calls for survival follow-up (every 3 months)	S	7.1.5																				X		X
Antineoplastic therapies since discontinuation of study treatment	D	7.1.5																		X	X	X		X
End of study evaluation	D	7.1.5																					X[a]	

	Category	Reference to Section	Molecular Pre-Screening	Screening /Baseline	Cycle 1							Cycle 2					Subsequent cycles			EOT	30-day safety FU[m]	Disease progression FU (Phase II only)	SEC[a]	Survival FU (Phase II only)
Visit Name			1	2	3	4	5	6	7	8		10	201	11	202		13	14		777			778	
Day of cycle				-14 to-1	1	2	8	15	16	22	28	1	8	15	22	28	1	15	28	≤14d from last dose				

a. SEC eCRF should be completed once the 30-day safety follow-up period is completed for the Phase Ib patients and for those Phase II patients who have progressed during study treatment. For patients enrolled in the Phase II parts who discontinue study treatment for any reason other than disease progression, the SEC eCRF should be completed upon progression, the initiation of subsequent anticancer therapies or death.

b. For only those patients who have signed the molecular pre-screening IC; does not have to be repeated at Screening for these patients.

c. Not applicable for patients enrolled in the Phase II parts of the study.

d. C3=only during Cycle 3

e. Patients who have been on the LGX818/MEK162 dual-combination and LGX818/MEK162/LEE011 triple-combination treatment for ≥ 24 months (Cycle 25 Day 1 onward) without a retinal AE should be evaluated for visual acuity at each scheduled patient visit and at the End of Treatment visit. A full ophthalmic examination is required if clinically indicated and at the End of Treatment visit.

f. All ECGs should be performed either before blood sample collection or at least 0.5 hours after blood sample collection.

g. Day 1 of every third cycle until Cycle 11 (i.e. Day 1 of Cycle 5, 8 and 11) and Day 1 of every fourth Cycle thereafter (i.e. Day 1 of Cycle 15, 19 etc.).

h. Should be performed between week 3 and 4 of Cycle 1.

i. Patients who have been on either combination treatment for ≥ 24 months (Cycle 25 Day 1 onward) will have CT/MRI scans every 8-12 weeks (± 7 days).

j. Patients who have been on either combination treatment for ≥ 24 months (Cycle 25 Day 1 onward) and then discontinue study treatment for any reason other than disease progression will have CT/MRI scans every 8-12 weeks (± 7 days).

k. Applicable only for patients enrolled in the triple-combination part of the study.

l. Fresh sample should only be collected at Screening/baseline if insufficient fresh tumor tissue was collected during local molecular pre-screening. Fresh tumor samples are mandatory for all patients in Phase II of the study at Screening/Baseline, although archival tissue is acceptable in some cases, (refer to Section 7.2.4.1.1).

m. Following the 30-day follow-up, when clinically appropriate, it is recommended patients be monitored with physical examinations, dermatological examinations, and chest CT scans for cutaneous and non-cutaneous secondary malignancies for up to 6 months after the last encorafenib dose or until initiation of another antineoplastic therapy.

Table 7-2 Visit evaluation schedule for patients as of Amendment 10

Procedure or Assessment[a]	As of Amendment 10						
	Category	Protocol Section	Treatment		EOT	30-day safety FU	Study Evaluation Completion
			Per local standard-of-care (Recommended every 4 weeks)	Recommended every 8-12 weeks			
Physical examination[b]	S	7.2.2.1	X		X		
Vital signs / weight	D	7.2.2.2	X		X		
Performance Status (WHO)	D	7.2.2.3	X		X		
Single ECG 12-lead	D	7.2.2.8.1/ 7.2.2.8.2		X	X		
Hematology	D	7.2.2.5.1	X		X		
Clinical chemistry	D	7.2.2.5.2	X		X		
Coagulation	D	7.2.2.5.3	X		X		
Dipstick Urinalysis[c]	D	7.2.2.5.4	X[c]		X		
Pregnancy test[d]	D	7.2.2.5.5	X		X		
Cardiac imaging[e]	D	7.2.2.8.3		as clinically indicated	X		
Visual acuity[f]	D	7.2.2.7	X		X		
Ophthalmologic examination[f]	D	7.2.2.7		as clinically indicated	X		
Dermatologic examination[b]	D	7.2.2.6			X		
LGX818/MEK162 (Dual combination patients)- Dispense and/or assess compliance	D	6.1.1 / 6.6	X				
LGX818/MEK162/LEE011 (Triple combination patients) - Dispense and/or assess compliance	D	6.1.1 / 6.6	X				
Adverse events	D	8	X		X	X	
Concomitant medications	D	7.1.2.3	X		X	X	
Tumor imaging assessments (RECIST 1.1)	D	7.2.1	Per institutional standar-of-care				
End of study evaluation[g]	D	7.1.5					X

Procedure or Assessment[a]	As of Amendment 10						
	Category	Protocol Section	Treatment		EOT	30-day safety FU	Study Evaluation Completion
			Per local standard-of-care (Recommended every 4 weeks)	Recommended every 8-12 weeks			

[a.] The minimally required procedures/assessments are indicated; these or any additional procedures/assessments can be repeated more frequently per standard-of-care or if clinically indicated.

[b.] Following the 30-day Safety Follow-up, when clinically appropriate, it is recommended patients be monitored with physical examinations, dermatological examinations, and chest CT scans for cutaneous and non-cutaneous secondary malignancies for up to 6 months after the last LGX818 dose or until initiation of another antineoplastic therapy.

[c.] To be conducted if clinically indicated.

[d.] Local urine test for women of childbearing potential only.

[e.] Assessed by ECHO or MUGA. The same method should be used throughout the study. Patients who develop signs/symptoms of CHF at any point during the study are required to have an evaluation by ECHO or MUGA.

[f.] Patients who have been on the LGX818/MEK162 dual combination and LGX818/MEK162/LEE011 triple combination treatment for ≥ 24 months (Cycle 25 Day 1 onward) without a retinal AE should be evaluated for visual acuity per local standard-of-care (recommended every 4 weeks) and at the End of Treatment visit. A full ophthalmic examination is required if clinically indicated and at the End of Treatment visit.

[g.] SEC eCRF should be completed once the 30-day safety follow-up period is completed or 30 days after treatment discontinuation.

7.1.1 Molecular Pre-screening assessments

Potential eligible patients must have documentation on the BRAF V600 mutational status of their disease. For patients considered for enrollment in this study, whose BRAF mutational status is unknown, archival or fresh tumor tissue should be provided to a local laboratory to identify the presence of a BRAF V600 mutation (a V600E mutation, or any other BRAF V600 mutation) prior to start of screening.

Patients who have a tumor which is not routinely screened for a BRAF mutation at a local laboratory, will be asked to sign and date an IRB/IEC approved Molecular pre-screening Informed Consent Form before the collection of the fresh tumor tissue or use of archival tumor tissue. A copy must be given to the patient or to the person signing the form.

If confirmed that the patient's tumor harbors a BRAF V600 mutation the patient will be allowed to sign the Study Informed Consent Form and start screening.

7.1.2 Screening

The Study IRB/IEC approved Informed Consent Form (ICF) must be signed and dated before any screening procedures are performed (procedures which are part of the clinical routine during the initial diagnostic work-up of the patient may be performed before obtaining the ICF). A copy of the ICF must be given to the patient or to the person signing the form. The Investigator or designee must record the date when the study informed consent was signed in the medical records of the patient.

Patients will be evaluated against study inclusion and exclusion criteria and safety assessments. For details of assessments, refer to Table 7-1. All Screening/baseline imaging scans must be completed within 21 days prior to the first dose of study treatment. All other screening assessments must be completed within 14 days prior to the first dose.

7.1.2.1 Eligibility screening

When the patient is considered eligible for study treatment, the Investigator should complete the Patient Registration Form and send it to the Sponsor. The allocation of patients to treatment cohorts will be handled by the Sponsor.

7.1.2.2 Information to be collected on molecular pre- screening and screening failures

Patients who sign an ICF but fail to be started on study treatment for any reason will be considered a screen failure. Both patients who sign a Molecular pre-screening ICF and are considered ineligible after molecular pre-screening, as well as patients who are found not eligible after signing the Study ICF, will be considered as screening failures and data will be handled in the same manner.

For all screening failures, the only information collected on the eCRF will be the Screening Log and the Demography pages.

7.1.2.3 Patient demographics and other baseline characteristics

Data to be collected will include general patient demographics, relevant medical history and current medical conditions, prior concomitant medications, diagnosis and extent of tumor, baseline tumor mutation status and details of prior anti-neoplastic treatments.

7.1.3 Treatment period

Note: As of protocol amendment 10, all efficacy and safety assessments will be completed per local standard-of-care practice, or otherwise as clinically indicated. See Table 7-2.

During the treatment period, the patient must follow the Investigators instructions with regards to contraception, concomitant medications, and dosing regimen (see Section 6.1.1 for dosing regimen guidelines). There is no fixed treatment duration; patients may continue treatment with the LGX818 and MEK162 dual combination or LGX818 and MEK162 and LEE011 triple combination until disease progression, unacceptable toxicity occurs that precludes any further treatment and/or treatment is discontinued at the discretion of the investigator or by patient refusal (withdrawal of consent).

If a patient remains on study although the patient required a dose interruption of > 21 days, because the patient had experienced objective evidence of clinical benefit and in the opinion of the investigator it is in the best interest of the patient to remain on study (see also Section 6.3.2), then this decision and report of a discussion with the sponsor, must be reported in the source documentation and in a comment in the eCRF.

If a patient remains on study although the patient's disease progressed (see also Section 6.1.5), then this decision and documentation of a discussion with the sponsor, must be reported in the source documentation and as an investigator comment in the eCRF.

For details of the frequency of the visits and assessments during the treatment period, refer to Table 7-1 and Table 7-2.

7.1.4 End of treatment visit, including premature withdrawal and study completion visit

Note: As of protocol amendment 10, patients will be considered to have completed the study after the 30-day safety evaluation or 30 days after treatment discontinuation, whichever is earlier. Post-treatment disease progression follow-up (if applicable) and/or survival follow-up (including documentation of subsequent antineoplastic therapies) will no longer be performed for any patient in the Phase II part of the study; see Table 7-2.

Patients who discontinue study treatment should be scheduled for an End of Treatment (EOT) visit as soon as possible and within 14 days after the last study drug dose, at which time all of the assessments listed for the EOT visit will be performed. For patients who had to interrupt study treatment for more than 14 days and then permanently discontinue study treatment without restarting, the EOT visit should be scheduled as soon as possible after the decision of discontinuation. An EOT eCRF page should be completed, giving the date and primary reason for stopping the study treatment. At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 30 days following the last dose of study treatment.

Patients who discontinue study treatment should also return for 30-day safety FU (see Section 7.1.5.1), Disease progression FU (if applicable, see Section 7.1.5.2) and survival FU (only for Phase II patients, see Section 7.1.5.3) assessments at the visits according to Table 7-1 and Table 7-2 and should not be considered withdrawn from the study. If patients refuse to return for these visits or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to obtain the FU information.

If a patient discontinues study treatment, but continues study assessments in the FU period, the patient remains on study until such time as he/she completes protocol criteria for ending study assessments. At that time, the reason for study completion should be recorded on the Study Evaluation Completion (SEC) eCRF page.

The SEC eCRF page records the end of study for every individual patient and should be completed for all patients enrolled in the Phase Ib part and those patients enrolled in the Phase II part who have progressed during study treatment, once the 30-day safety follow-up period is completed. For patients enrolled in the Phase II part who discontinue study treatment for any reason other than disease progression, the SEC eCRF should be completed upon progression or the initiation of subsequent anticancer therapies or death. Note: the survival FU assessments do continue beyond the SEC for all patients enrolled in the Phase II part.

7.1.4.1 Criteria for premature patient withdrawal

Patients **may** voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time. Patients may be withdrawn from the study if any of the following occur:

- Unacceptable AE(s), or failure to tolerate study treatment
- Delay in dosing > 21 consecutive days
- Pregnancy of the patient
- Patient withdrew consent
- Lost to follow-up
- Disease progression
- Initiation of new cancer therapy

7.1.4.2 Replacement policy

Dose Escalation (Phase Ib) part: Patients will not be replaced on study. However, if a patient is considered as non-evaluable for the DDS, enrollment of a new patient to the current cohort will be considered if there is less than the required number of evaluable patients. Enrollment of new patients may be considered until at least the minimum number (3) or at most the maximum number (6) of evaluable patients is achieved within the cohort (Section 10.8). Minimum and maximum numbers of evaluable patients per cohort are defined in Section 6.2.4.2.

Phase II part: During the Phase II part no replacement will be needed.

7.1.5 Follow-up period

Patients lost to follow-up should be recorded as such on the eCRF. For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

7.1.5.1 30-day safety follow-up period

All patients must have safety evaluations for 30 days after the last dose of study treatment. Information related to AEs (including concomitant medication taken for ongoing AEs) and ongoing anti-neoplastic treatments will be collected for 30 days after the last dose of study drug. All AEs suspected to be related to study treatment should be followed up weekly, or as clinically indicated, until resolution or stabilization.

7.1.5.2 Disease progression follow-up period

Note: As of protocol amendment 10, no post-treatment disease progression follow-up will be performed.

Patients enrolled in the Phase II part of the study who discontinue study treatment for any reason other than disease progression will be followed up monthly via a phone call and will have CT/MRI scans every 8 weeks (± 7 days) as detailed in Table 7-1 and Section 7.2.1, until disease progression or the initiation of subsequent anticancer therapies, or death, or until all patients have completed SEC, or have been lost to follow-up or withdrew consent, whichever occurs first.

Patients who have been on the LGX818/MEK162 dual-combination or LGX818/MEK162/LEE011 triple-combination treatment for ≥ 24 months (Cycle 25 Day 1 onward) and then discontinue study treatment for any reason other than disease progression will be followed up by CT/MRI scans every 8-12 weeks (± 7 days) as detailed in Table 7-1 and Section 7.2.1, until disease progression, death, removal of consent to follow, the initiation of subsequent anticancer therapies or until End of Study (see Section 4.3), whichever occurs first.

7.1.5.3 Survival follow-up period

Note: As of protocol amendment 10, no survival or subsequent antineoplastic therapy information will be collected.

All patients enrolled in the Phase II part of the study will be followed for survival every 3 months per phone call until death, or until all patients have completed SEC, or have been lost to follow-up or withdrew consent, whichever occurs first. Possible newly started antineoplastic therapies during this FU period must be recorded on the Antineoplastic therapy since discontinuation eCRF.

7.2 Assessment types

7.2.1 Efficacy assessments

Tumor response will be evaluated locally by the investigator according to the guideline based on RECIST version 1.1 (see Appendix 1). Each subject will be evaluated for all potential sites of tumor lesions at Screening/baseline, at the end of Cycle 1 (not applicable for patients enrolled

in the Phase II part of the study) and Cycle 2 and then every 8 weeks (2 cycles) thereafter during the study treatment until disease progression. Screening/baseline imaging assessments may be performed within 21 days of treatment start, except whole-body bone scans, if applicable, which can be performed within 6 weeks of treatment start. On-study tumor assessments have a ± 7 day window, except for the tumor assessment on C1D28 which must be performed between week 3 and 4 after starting the study drug combination. Patients who have been on the LGX818/MEK162 dual- or triple-combination treatment for ≥ 24 months (Cycle 25 Day 1 onward) will be evaluated for all potential sites of tumor lesions every 8-12 weeks (± 7 days) until disease progression.

There will be a tumor assessment at End of Treatment (± 3 days) if the patient discontinues for any reason other than disease progression and the last tumor assessment has been performed > 21 days prior to this day. Subjects included in the Phase II part of the study, who discontinue study treatment due to another reason than disease progression, should be followed up monthly via a phone call and undergo tumor assessments every 8 weeks (± 7 days) until disease progression or initiation of subsequent anti-neoplastic therapy, or death, whichever occurs first (Section 7.1.5.2). Patients who have been on either dual- or triple-combination treatment for ≥ 24 months (Cycle 25 Day 1 onward) and then discontinue study treatment for any reason other than disease progression will have CT/MRI scans every 8-12 weeks (± 7 days).

At Screening/baseline the following should be performed:

- A CT scan with intravenous (i.v.) contrast of chest, abdomen and pelvis is required for all patients.
- In subjects with a history of asymptomatic brain metastases, a brain MRI or CT scan must be performed.
- In subjects participating in the triple-combination part of the study a brain MRI or CT with intravenous (i.v.) contrast scan to assess CNS disease must be performed. Contrast enhanced brain MRI is preferred, however, if MRI contrast is contraindicated, then brain MRI without contrast or brain CT with/without contrast is acceptable.
- If clinically indicated, a whole-body bone scan (i.e., if bone metastases are suspected or known at baseline) should be performed. Sites may use a whole-body bone imaging method per their local standard-of-care (e.g., Tc99m bone scan, NaF PET scan, or whole-body bone MRI). Skeletal lesions identified on a whole-body bone scan at baseline, which are not visible on the chest, abdomen and pelvis CT (or MRI) scan should be imaged at baseline using localized CT, MRI or x-ray.
- Color photography if skin lesions are present (it is recommended to include a ruler to estimate the size of the lesion).

Every effort must be made to assess each lesion that is measured at Screening/baseline by the same method throughout the study so that the comparison is consistent.

At all post-Screening/baseline assessments the following should be performed:

- All patients are required to undergo chest, abdomen and pelvis CT or MRI scans.
- Brain MRI or CT scan, if metastases were documented at baseline.
- Skeletal lesions identified at baseline should continue to be imaged at subsequent scheduled visits using localized CT, MRI or x-ray if not visible on the chest, abdomen and

pelvis CT or MRI scan. After baseline, whole-body bone scans need not be repeated, unless clinically indicated.

- Color photography of any skin lesions documented at baseline (it is recommended to include a ruler to estimate the size of the lesion).
- Additional tumor assessments (e.g. MRI or CT of the brain) may be performed if there is symptomatic evidence suggesting the possibility of disease progression based on clinical symptoms or physical exam at any time.

Criteria required for determining partial or complete response should be present for at least 4 weeks. All complete and partial responses must be confirmed by a second assessment at least 4 weeks later. Note: sites must make sure for patients enrolled in the Phase Ib part of the study that at least 4 weeks are scheduled between the tumor assessments on C1D28 and C2D28 to allow confirmation of response.

CT scans should be acquired with i.v. contrast. If a patient is known to have a medical contraindication to CT i.v. contrast agent or develops a contraindication during the study, a CT scan without i.v. contrast of the chest and MRI with i.v. contrast, if possible, of the abdomen and pelvis may be performed. A CT scan of the brain, preferably with i.v. contrast, may be performed if MRI is contra-indicated.

Chest x-ray or ultrasound should not be used for tumor response assessments in this study.

Any lesions that have been subjected to loco-regional therapies (e.g., radiotherapy, ablation, etc.) should not be considered measurable, unless they have clearly progressed since the therapy. Previously treated lesions that have not progressed should be considered non-measurable and therefore, assessed as non-target lesions.

While FDG-PET scans are not required for this study, sites may perform combined PET/CT scans per their local standard-of-care, provided the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of oral and intravenous contrast media. If acquired according to local standard-of-care, FDG-PET may be relied upon to document progressive disease in accordance with RECIST v1.1 (Appendix 1).

Each center should have a designated radiologist responsible for the interpretation of scans and response evaluations for study subjects. Preferably, a single radiologist should perform all evaluations for an individual subject.

7.2.2 Safety and tolerability assessments

Note: As of protocol amendment 10, safety assessments will be performed as indicated in Table 7-2.

Safety will be monitored by assessing the procedures listed below as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8. All safety assessments should be performed pre-dose unless specified otherwise.

7.2.2.1 Physical examination

Note: As of protocol amendment 10, physical examinations will be performed as outlined in Table 7-2.

A complete physical examination will be performed at Screening/baseline and will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, peripheral vascular system and neurologic system. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

A short physical exam (examination of general appearance) will be at all visits during treatment unless the investigator considers a complete physical examination is necessary.

Physical examinations will take place at the following visits irrespective of the time of dosing:

- Screening/Baseline
- Cycle 1 Days 1, 8, 15 and 22 (for Phase II: Cycle 1 Days 1 and 15)
- Cycles 2 and 3: at Day 1 and Day 15 (for Phase II: Cycles 2 and 3 at Day 1)
- Cycle 4 and Onwards: Day 1
- EOT

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 7Appendix 7Appendix 7Appendix 7Appendix 7) must be reported according to the processes in Section 8.1.1 and Appendix 7. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's eCRF.

7.2.2.2 Vital signs

Note: As of protocol amendment 10, vital signs will be performed as outlined in Table 7-2.

Vital signs include blood pressure, temperature and pulse measurements. After the patient has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated device (e.g. OMRON), with an appropriately sized cuff. The repeat sitting measurements will be made at 1- to 2-minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

Vital signs will take place pre-dose at:

- Screening/Baseline
- Cycle 1 Days 1, 8, 15 and 22 (for Phase II: Cycle 1 Days 1 and 15)
- Cycles 2 and 3: at Day 1 and Day 15 (for Phase II: Cycle 3 at Day 1)
- Cycle 4 and onwards: Day 1
- EOT

7.2.2.3 Performance status

Note: As of protocol amendment 10, WHO Performance Status will be performed as outlined in Table 7-2.

Assessment of WHO Performance Status (Table 7-3) will be performed at screening and regularly throughout the whole study period irrespective of the time of dosing:

- Screening/Baseline
- Cycle 1 Days 1, 8 and 15 (for Phase II: Cycle 1 Days 1 and 15)
- Cycles 2 and 3: Day 1 and Day 15 (for Phase II: Cycles 2 and 3 at Day 1)
- Cycle 4 and onwards: Day 1
- EOT

Performance status should be obtained on the scheduled day, even if study medication is being held.

Table 7-3 WHO performance status scale

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

7.2.2.4 Height and weight

Note: As of protocol amendment 10, weight information will be collected as outlined in Table 7-2.

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured.

Height information will be collected only at Screening/baseline. Weight information will be collected at Screening/baseline, Day 1 of each cycle and at EOT irrespective of dosing time.

7.2.2.5 Laboratory evaluations

Note: As of protocol amendment 10, laboratory evaluations will be performed as outlined in Table 7-2.

Sites will use their local laboratories for the analysis of all safety lab samples collected at the time points indicated in the Visit Schedule (Table 7-1 and Table 7-2). More frequent assessments may be performed if clinically indicated, or at the investigator's discretion, and these should be recorded on the Unscheduled Visit eCRFs.

Abnormal laboratory values that are clinically relevant (e.g., require an interruption or delay to study treatment, lead to clinical symptoms, or require therapeutic intervention) must be documented in the Adverse Event eCRF. If any abnormal laboratory value constitutes an AE, then these must be recorded on the Adverse Event eCRF.

The Sponsor will be provided with a copy of the site's local laboratory certification and tabulation of the normal ranges for each parameter required at study start and should be kept up to date on an ongoing basis. In addition, if at any time a patient has laboratory parameters obtained from a different outside laboratory, the Sponsor must be provided with a copy of the certification and a tabulation of the normal ranges for that laboratory.

7.2.2.5.1 Hematology

The following will be assessed:

WBC count plus differential (total neutrophil including bands, lymphocyte, monocyte, eosinophil, basophil and other counts), RBC count, hemoglobin, hematocrit and platelet count.

Hematology assessments will be performed pre-dose at:

- Screening/baseline
- Cycle 1 Days 1, 8, 15 and 22. (For Cycle 1 Day 1, before first dose unless screening samples were collected <72 hrs prior).
- Cycles 2 and 3: Day 1 and Day 15
- Cycles 4 and onwards: Day 1
- EOT

7.2.2.5.2 Clinical chemistry

The following will be assessed:

Sodium, potassium, chloride, bicarbonate, total calcium, inorganic phosphate, magnesium, urea or blood urea nitrogen (BUN), creatinine, uric acid, bilirubin (total, indirect and direct), AST, ALT, creatine phosphokinase (CPK) (if total CPK is elevated ≥ CTCAE Grade 2, then weekly measure isoenzymes in blood, and myoglobin in blood and urine until resolved to ≤ CTCAE Grade 1), albumin, total protein, alkaline phosphatase, lactate dehydrogenase (LDH), glucose, amylase, lipase.

The following do not need to be collected during Phase II: chloride, urea (BUN), and uric acid.

These parameters will be measured pre-dose at:

- Screening/baseline
- Cycle 1 Days 1, 8, 15 and 22. (For Cycle 1 Day 1, before first dose unless screening samples were collected <72 hrs prior).
- Cycles 2 and 3: Day 1 and Day 15
- Cycles 4 and onwards: Day 1
- EOT

Additional liver function test (LFT = AST, ALT, alkaline phosphatase and bilirubin (total, indirect and direct)) will be assessed at the following times:

- Cycle 2: Day 8 and Day 22
- Cycle 4: Day 15

Total cholesterol, triglycerides, HDL, and LDL (to be collected for Phase Ib only):

- Cycle 1 Day 1
- Cycle 2 Day 1 and Day 1 of every other subsequent cycle (C4D1, C6D1 etc.)
- EOT

TSH (free T4, and free T3 should also be measured only if clinically indicated) will be assessed at the following times (to be collected for the Phase Ib part of the protocol only):

- Cycle 1 Day 1
- Day 1 of every 3 months (Cycle 4, 7 etc)
- EOT

7.2.2.5.3 Coagulation

Coagulation profiles will include a prothrombin time (PT) or international normalized ratio (INR), activated partial thromboplastin time (aPTT), and fibrinogen

Coagulation profiles will be performed at:

- Screening/baseline
- Cycle 1 Day 1 before first dose, unless screening samples were collected <72 hrs prior
- Day 1 of all subsequent cycles
- EOT

7.2.2.5.4 Urinalysis

Urine color and appearance should be evaluated. A macroscopic urinalysis (dipstick or other equivalent method according to local practice), including bilirubin, ketones, leukocytes, protein, glucose, blood, and specific gravity should be performed.

Abnormal findings will be followed up with a microscopic evaluation and/or additional assessments as clinically indicated. A microscopic evaluation (WBC/HPF, RBC/HPF, and any other evaluations depending on macroscopic findings) need only be performed if the urinalysis result is abnormal (except for institutions where microscopic urinalysis is not available).

Urinalysis will be performed at:

- Screening/baseline
- Cycle 1 Days 1 and 15 (Day 1 before first dose, unless screening samples were collected <72 hrs prior)
- Day 1 of all subsequent cycles
- EOT

Note: If at Screening/baseline there is documentation of [+2] result or higher for protein from urinalysis, a 24-hour urine collection for total protein and measured creatinine clearance (CrCl) must be obtained. Whenever a 24-hour urine collection is performed, the total volume of urine must be recorded on the appropriate eCRF.

7.2.2.5.5 Pregnancy and assessments of fertility

All females of childbearing potential will have a serum pregnancy test ≤72 hrs before first dose of study drug and a urine or serum during study treatment (Day 1 of Cycle 2 and onwards) and at the End of Treatment visit.

A positive urine pregnancy test requires immediate interruption of study treatment until serum β-HCG is performed and found to be negative. If positive, the patient must be discontinued from the study.

7.2.2.6 Dermatologic evaluations

Note: As of protocol amendment 10, dermatologic evaluations will be performed as outlined in Table 7-2.

Skin evaluations will be performed by dermatologists at Screening/baseline, every 8 weeks thereafter (±1 week; Day 1 of Cycle 3, 5 etc.) and at the End of Treatment visit to look for the appearance of squamous cell carcinoma or keratoacanthomas. This assessment can be done pre- or post-dose.

In the occurrence of these lesions, the lesions should be removed and the patient must be treated as per institutional practice.

7.2.2.7 Ophthalmologic examination

Note: As of protocol amendment 10, ophthalmological evaluations will be performed as outlined in Table 7-2. Patients who have been on dual or triple combination treatment for ≥ 24 months (Cycle 25 Day 1 onward) without a retinal AE should be evaluated for visual acuity per local standard-of-care (recommended every 4 weeks) and at the EOT visit. A full ophthalmological examination is required if clinically indicated and at the EOT visit.

Full ophthalmological examination including slit lamp examination, visual acuity testing, visual field testing, tonometry (IOP), OCT and indirect fundoscopy (with dilation) with attention to retinal abnormalities (especially CSR and RVO), should be performed by an ophthalmologist at the following time points and as clinically indicated:

- Screening/baseline
- Cycle 1 Day 15
- Cycle 2 Days 1 and 15
- Day 1 of all subsequent Cycles*
- EOT

*Patients who have been on dual- or triple-combination treatment for ≥ 24 months (Cycle 25 Day 1 onward) without a retinal AE should be evaluated for visual acuity at each scheduled patient visit and at the End of Treatment visit. A full ophthalmic examination is required if clinically indicated and at the End of Treatment visit.

For patients with clinical suspicion of retinal changes additional assessments of fluorescein angiography and/or focal ERG (where feasible) are recommended and should be performed

upon the discretion of the treating physician. Any observed abnormalities and/or changes to Screening/baseline must be documented in the Adverse Event eCRF.

7.2.2.8 Cardiac assessments

Note: As of protocol amendment 10, cardiac assessments will be performed as outlined in Table 7-2.

7.2.2.8.1 Electrocardiogram (ECG) schedule for the dual combination

At Screening/baseline a standard 12 lead ECG (local assessment) will be performed to assess eligibility. Subsequent 12-lead ECGs are to be conducted at the following time points:

- Cycle 1 Days 1 and 15 predose
- Cycle 2 Days 1 and 15 predose
- Day 1 of all subsequent cycles predose
- EOT

For all patients, prior to the first administration of the LGX818 and MEK162 combination on Cycle 1 Day 1, three sequential 12 lead ECGs, separated by at least 5-10 minutes, must be performed. The average of the triplicate ECG measurements will serve as the patient's baseline value for post-dose comparisons. Single ECGs will be performed for the other pre-dose ECGs during the study at the indicated time points, at EOT and if clinically indicated.

7.2.2.8.2 Electrocardiogram (ECG) schedule for the triple combination

At Screening/baseline a standard 12 lead ECG (local assessment) will be performed to assess eligibility. Subsequent triplicate 12-lead ECGs are to be conducted at the following time points:

- Cycle 1 Days 1 and 15: pre-dose, 1.5 hrs (± 0.5 hr) and 4 hr (± 0.5 hr) post-dose
- Cycle 2 Day 1: pre-dose, 1.5 hrs (± 0.5 hr) and 4 hr (± 0.5 hr) post-dose
- Cycle 2 Day 15: pre-dose
- Day 1 of subsequent cycles: pre-dose
- EOT

All ECGs for patients treated with the triple study drug combination should be taken before a blood sample or at least 0.5 hours after a blood sample to avoid potential effects of blood-draw on ECG readout.

For any patients who had therapy interrupted due to QTcF ≥ 481 ms, ECGs should be repeated 7 days and 14 days after dose resumption (then as clinically indicated). For all patients experiencing a grade 3 QTcF interval prolongation, hypokalemia, hypomagnesaemia and oxygenation status should be monitored.

All ECGs (except the screening ECG) for patients treated with either the dual or triple study drug combination will be independently reviewed by a central laboratory. Instructions for the collection and transmission of ECGs to the independent reviewer will be provided in the ECG Manual. Interpretation of the tracing must be made by a qualified physician and documented on the ECG eCRF page. Each ECG tracing print-out should be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept in the source

documents at the study site. Clinically significant abnoimalities present when the patient signed infonned consent should be reported on the relevant medical histoiy/cmTent medical conditions eCRF page. Clinically significant findings must be discussed with the Sponsor's Medical Monitor prior to enrolling the patient in the study. New or worsened clinically significant findings occmTing after infoimed consent must be recorded on the AE eCRF page.

7.2.2.8.3 Cardiac imaging - MUGA (multiple gated acquisition) scan or echocardiogram

- The left ventricular heait function will be evaluated by ECHO or MUGA at Screening/baseline, during the study on Day 1 of Cycle 2, Day 1 of eveiy third cycle until Cycle 11 (i.e. Day 1 of Cycle 5, 8 and 11) and Day 1 of every fomth Cycle thereafter (i.e. Day 1 of Cycle 15, 19 etc.), at the End of Treatment visit and if clinically indicated iiTespective of the time of dosing. The same procedure should be used throughout the study.

7.2.3 Pharmacokinetics

The blood sampling regiinens for deteimining the phaimacokineticsof MEK162 and its priinaiy active metabolite AR00426032, LGX818, and LEE0ll and its metabolite LEQ803 after oral administration of the dual or triple combination as applicable, ai·e given in Table 7-3 (dose escalation) and Table 7-4 (dual-combination Phase II aims 2 and 3, and aim 1 ifrequii·ed as per instruction from Sponsor/ triple-combination Phase II aim A). Blood samples for LGX818, MEK162/AR00426032 and LEE011/LEQ803 (as applicable) plasma concentr·ation measurements will be collected and evaluated on all patients enrolled in the dose escalation and on a selected number of patients in the dual-combination Phase II anns 2 and 3 (and aim 1 if requii·ed as per instruction from the Sponsor for assessment of the potential iinpact of demographic differences (e.g. Japanese vs Caucasian) and triple- combination Phase II aim A, paits of the study.

fu addition to LGX818, MEK162/AR00426032 and LEE011/LE 803 anal ses., CCI

[redacted]

Plasma samples remaining from the analysis may be retained by the Sponsor for additional investigations (e.g. long teim stability, reproducibility).

A detailed description of the planned phaimacokinetic analyses is given in Section 10.5.3.

7.2.3.1 Pharmacokinetic blood sample collection and handling

7.2.3.1.1 Blood collection plan

Dose Escalation: From all patients tr·eated in the dose escalation part, blood for full phaimacokinetic profiling of LGX818 and MEKl62, and LEE011 if applicable will be collected on Cycle 1 Days 1 and 15 (including a 24 hr post dose sample on the following day; see Table 7-4). Additionally, pre-dose samples will be collected on Day 1 of Cycle 2 through Cycle 10.

Dual combination Phase II arm 1: No PK sampling will be performed for patients enrolled in this arm. The exception to this is for newly enrolled patients in which an assessment of the potential impact of demographic differences on the PK of the LGX818 and MEK162 combination may be made, if required as per instruction from the Sponsor.

Dual combination Phase II arms 2 and 3: From the first 10 patients in each arm, and if required as per instruction from the Sponsor, from additional patients in which an assessment of the potential impact of demographic differences on the PK of the LGX818 and MEK162 combination may be made. Blood for pharmacokinetic profiling of LGX818 and MEK162 will be collected on Cycle 1 Days 1 and 15 (including a 24 hr post dose sample on the following day; see Table 7-4) to study the CCI of the study drug dual combination. The 4- and 6-hour post-dose samples collected during dose escalation are replaced with a 5-hour post-dose sample for these patients to collect less blood from the patients but still cover the PK profile of the study drugs. Additionally, pre-dose samples will be collected on Day 1 of Cycle 2 through Cycle 10 for those patients.

PK blood sample collection time points will remain the same if the dosing schedule of LGX818 would change to a BID and/or QOD dosing schedule.

Triple-combination Phase II arm A: From the first 10 patients, blood for pharmacokinetic profiling of LGX818 and MEK162 and LEE011 will be collected on Cycle 1 Days 1 and 15 (including a 24 hr post dose sample on the following day; see Table 7-4) to study the CCI of the study drug triple combination. Additionally, pre-dose samples will be collected on Day 1 of Cycle 2 through Cycle 10 for those patients.

For all patients from whom PK samples are collected (either treated with the dual or triple combination), exact dates and clock times of drug administration and actual PK blood draw will be recorded on the appropriate eCRF. Any sampling problems (e.g. patient took study drug before draw took place) must be noted in the comments section of the eCRF and on appropriate source documentation. The time of the last meal should be recorded on PK sampling days Cycle 1 Days 1 and 15 on the appropriate eCRF.

If vomiting or diarrhea occurs within 4 hrs following study drugs administration on the days of full PK blood sampling, the exact time (using the 24-h clock) of any vomiting or diarrhea episode should be recorded in a separate section of the eCRF in addition to recording this on the AE eCRF.

Complete instructions for sample collection, processing, handling and shipment will be provided in the [CMEK162X2110 Laboratory Manual].

Table 7-4 Schedule of blood sample collections for PK in dose escalation

Cycle	Day	PK collection No. LGX818	PK Sample No LGX818	PK collection No. MEK162	PK sample No. MEK162	PK collection No. LEE011[a]	PK sample No. LEE011[a]	Scheduled time relative to dosing
1	1	101	101	201	201	501	501	Pre-dose*
1	1	101	102	201	202	501	502	0.5 hr post dose
1	1	101	103	201	203	501	503	1.5 hr post dose
1	1	101	104	201	204	501	504	2.5 hr post dose
1	1	101	105	201	205	501	505	4 hr post dose

Cycle	Day	PK collection No. LGX818	PK Sample No LGX818	PK collection No. MEK162	PK sample No. MEK162	PK collection No. LEE011[a]	PK sample No. LEE011[a]	Scheduled time relative to dosing
1	1	101	106	201	206	501	506	6 hr post dose
1	1	101	107	201	207	501	507	8 hr post dose
1	2	102	108	202	208	502	508	24 hr post dose immediately prior to dosing on C1D2
1	15	103	109	203	209	503	509	Pre-dose*
1	15	103	110	203	210	503	510	0.5 hr post dose
1	15	103	111	203	211	503	511	1.5 hr post dose
1	15	103	112	203	212	503	512	2.5 hr post dose
1	15	103	113	203	213	503	513	4 hr post dose
1	15	103	114	203	214	503	514	6 hr post dose
1	15	103	115	203	215	503	515	8 hr post dose
1	16	104	116	204	216	504	516	24 hr post dose immediately prior to dosing on C1D16**
2	1	105	117	205	217	505	517	Pre-dose*
3	1	106	118	206	218	506	518	Pre-dose*
4	1	107	119	207	219	507	519	Pre-dose*
5	1	108	120	208	220	508	520	Pre-dose*
6	1	109	121	209	221	509	521	Pre-dose*
7	1	110	122	210	222	510	522	Pre-dose*
8	1	111	123	211	223	511	523	Pre-dose*
9	1	112	124	212	224	512	524	Pre-dose*
10***	1	113	125	213	225	513	525	Pre-dose*
NA	NA	NA	1001+	NA	2001+	NA	5001+	Unscheduled****

*Collect PK sample immediately prior to the start of oral study drug combination (LGX818 and MEK162 or LGX818 and MEK162 and LEE011) administration.
**Schedule PK collection together with collection fresh tumor and skin biopsy (if applicable). If it is not possible to collect the tumor and skin biopsy on C1D16, then an additional unscheduled pre-dose PK sample should be collected on the day fresh tumor biopsy and skin biopsy is collected. For patients for who a fresh skin/tumor biopsy is not collected, the C1D16 PK sample should be collected on the scheduled time point and day. The PK sample at this time point should be collected prior to the collection of the blood for genetic analysis sample.
*** Pre-dose PK samples will be collected up to Cycle 10 only.
****Applies only to samples collected before effective date of Protocol Amendment Version 09. Unscheduled PK samples will be uniquely, sequentially numbered 1001, 1002 etc. for LGX818 and 2001, 2002 etc for MEK162 and 5001, 5002 etc for LEE011.
[a] only for patients treated with the triple study drug combination.

Table 7-5 Schedule of blood sample collections for PK in dual-combination Phase II arms 2 and 3, (and arm 1 if required[a]) / triple-combination Phase II arm A

Cycle	Day	PK collection No. LGX818	PK Sample No LGX818	PK collection No. MEK162	PK sample No. MEK162	PK collection No. LEE011[b]	PK sample No. LEE011[b]	Scheduled time relative to dosing
1	1	301	301	401	401	601	601	Pre-dose*
1	1	301	302	401	402	601	602	0.5 hr post-dose

Cycle	Day	PK collection No. LGX818	PK Sample No LGX818	PK collection No. MEK162	PK sample No. MEK162	PK collection No. LEE011[b]	PK sample No. LEE011[b]	Scheduled time relative to dosing
1	1	301	303	401	403	601	603	1.5 hr post dose
1	1	301	304	401	404	601	604	2.5 hr post dose
1	1	301	305	401	405	601	605	5 hr post dose
1	1	301	306	401	406	601	606	8 hr post dose
1	2	302	307	402	407	602	607	24 hr post dose immediately prior to dosing on C1D2
1	15	303	308	403	408	603	608	Pre-dose*
1	15	303	309	403	409	603	609	0.5 hr post-dose
1	15	303	310	403	410	603	610	1.5 hr post dose
1	15	303	311	403	411	603	611	2.5 hr post dose
1	15	303	312	403	412	603	612	5 hr post dose
1	15	303	313	403	413	603	613	8 hr post dose
1	16	304	314	404	414	604	614	24 hr post dose immediately prior to dosing on C1D16**
2	1	305	315	405	415	605	615	Pre-dose*
3	1	306	316	406	416	606	616	Pre-dose*
4	1	307	317	407	417	607	617	Pre-dose*
5	1	308	318	408	418	608	618	Pre-dose*
6	1	309	319	409	419	609	619	Pre-dose*
7	1	310	320	410	420	610	620	Pre-dose*
8	1	311	321	411	421	611	621	Pre-dose*
9	1	312	322	412	422	612	622	Pre-dose*
10***	1	313	323	413	423	613	623	Pre-dose*
NA	NA	NA	3001+	NA	4001+	NA	6001+	Unscheduled****

[a] Only for newly enrolled patients in which an assessment of the potential impact of demographic differences on the PK of the LGX818 and MEK162 combination may be made, if this assessment is required.
[b] Only for patients treated with the triple study drug combination.
*Collect PK sample immediately prior to the start of oral study drug combination (LGX818 and MEK162 or LGX818 and MEK162 and LEE011) administration.
**Schedule PK collection together with collection fresh tumor and skin biopsy. If it is not possible to collect the tumor and skin biopsy on C1D16, then an additional unscheduled pre-dose PK sample should be collected on the day fresh tumor biopsy and skin biopsy is collected. The PK sample at this time point should be collected prior to the collection of the blood for genetic analysis sample.
*** Pre-dose PK samples will be collected up to Cycle 10 only.
**** Applies only to samples collected before effective date of Protocol Amendment Version 09. Unscheduled PK samples will be uniquely, sequentially numbered 3001, 3002 etc. for LGX818 and 4001, 4002 etc for MEK162 and 6001, 6002 etc for LEE011.

7.2.3.2 Analytical method

For all samples collected, one tube will be shipped to each analytical lab for analysis. Refer to the [CMEK162X2110 Laboratory Manual] for detailed instructions for the collection, handling, and shipping of samples.

Plasma LGX818 concentrations will be measured at the Sponsor or designated CRO using a validated liquid chromatography-tandem mass spectrometiy (LC/MS/MS) assay. The lower limit of quantitation (LLOQ) is cmTently 1.0 ng/mL.

Plasma concenti·ations of MEK162 and its metabolite, AR00426032, will be measured by the Sponsor (or designated CRO using a validated LC/MS/MS assay with an LLOQ of 5.0 ng/mL.

Plasma concentl'ations of LEE0ll and its metabolite, LEQ803 will be measured (only applicable for ti·iple combination) at the Sponsor or at a designated CRO using a validated liquid chromatography-tandem mass specti·ometiy assay (LC/MS/MS). The lower limit of quantitation (LLOQ) is cmTently 1.0 ng/mL.

7.2.4 Biomarkers

Note: As of protocol amendment 10, biomarker samples at time of relapse will no longer be collected.

As outlined in Table 7-6, tumor, samples will be collected before and/or during ti·eatmentwith the LGX818 andMEK162 orLGX818 andMEK162 andLEE0l 1 dual and ti·iple combination, res, ectivel, to investi_ate the effect of the dm _at the molecular andcellular level

CCI

Table 7-6 Biomarker sample collection schedule

Visit	Details
Tumor **Biopsy Samples**	
Screening/baseline	Phase Ib: A fresh tumor biopsy at Screening/baseline is highly recommended if accessible, and required from at least one patient of each dose level". Phase II: A fresh tumor biopsy at Screening/baseline is mandatory for all patients, however archival tissue is acceptable in some cases, please see Section 7.2.4.1.1.
Cycle 1 Day 16 (+ 5 days..)	A fresh on-treatment tumor biopsy is highly recommended, if accessible and if a fresh tumor biopsy was collected at Screening/baseline, at C1D16 (+ 5 days..) before the patients receive their morning dose on that day. This biopsy is required from at least one patient of each dose level during the dose escalation, and from at least 15 metastatic melanoma patients each enrolled in Phase II arm 2 and 3 dual combination and in Phase II arm A triple combination, and at least 6 metastatic CRC patients • enrolled in Phase II arm1 dual combination. .. For scheduling purposes the biopsy can be taken 5 days after the specified time point or earlier during Cycle 1 at the discretion of the investigator on Day 8 (always pre-morning dose on the scheduled day and always paired with a pre-dose PK sample (except for Phase II arm 1 dual combination if no PK is collected)).
At time of relapse	If feasible according to the investigator, collection of a fresh tumor biopsy is strongly encouraged upon patient relapse (irrespective of whether a fresh tumor biopsy was collected at Screening/Baseline or on-treatment). This sample will be used to investigate changes in pathway signaling and potential mechanisms of resistance. The sample should be collected while the patient is still on study treatment or as soon as possible after study treatment discontinuation. For Phase II patients who are followed for disease progression after study treatment discontinuation, a fresh tumor biopsy should only be collected if the patient relapses within 2 months of study drugs discontinuation.
Archival tumor sample with an accompanying pathology report, at Screening/baseline	Requested from all patients and required for those in the Phase Ib and II parts not providing a fresh tumor biopsy sample. Sample should be a paraffin embedded block (preferred) or a representative number of slides as described in the (CMEK162X2110 Laboratory Manual].
•evaluable paired tumor biopsies (pre and on-treatment (i.e. Screening/baseline and C1D16 + 5 days, or C1D8))	
CCI [redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	

7.2.4.1 Biomarker assessments in tumor

7.2.4.1.1 Screening/baseline tumor sample

Representative tumor tissue (archival and/or fresh tumor sample) will be required from all patients at Screening/baseline. For patients enrolled in the Phase II paii of the study, a fresh tumor biopsy at Screening/baseline is mandato1y for all patients, unless sufficient fresh tumor tissue was collected dming local moleculai· pre-screening which can be submitted to the Sponsor-designated laborato1y at Screening (please refer to [CMEK162X2110 Laborato1y Manual] for details on collection, handling and shipment). If a tumor biopsy was collected after the last anti-neoplastic treatment within 2 months prior to study enrollment, the archival tissue of this tumor biopsy will be acceptable for enrollment instead of the fresh tumor biopsy. This sample will be used to investigate the of molecules in addition to BRAF that ai·e relevant to RAF/MEK./ERK and PI3K/AKT signaling pathways, (e.g. NRAS, PTEN, c-Kit, PIK3CA, etc.), to investigate the PTEN protein expression (IHC) and to potentially identify other predictive markers of efficacy. In addition, these samples are planned to be used for assessment of other genetic abnonnalities in the RAF/MEK./ERK and EGFR/PI3K/AKT signaling pathways, other pathways that may interact with the RAF/MEK./ERK and EGFR/PI3K/AKT signaling pathways, or ai·e thought to be important in cancer.

CCI

[redacted]

CCI

[redacted]

CCI [redacted]

7.2.4.1.4 Collection of tumor biopsies

Two biopsy passes must be obtained for all fresh tumor biopsies. The processing is described in Table 7-7. Detailed instructions for the collection, handling, and shipment of samples are outlined in the [CMEK162X2110 Laboratory Manual].

Table 7-7 Processing requirements for fresh tumor biopsy samples

Tumor fragment number	Processing requirements	
1	Formalin-fixed paraffin- embedded (FFPE)	To be processed/embedded together
2	Formalin-fixed paraffin- embedded (FFPE)	

CCI [redacted]

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CCI

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7.2.5 Other assessments

No additional tests will be perfo1med on patients entered into this study.

8 Safety monitoring and reporting

8.1 Adverse events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Section 14.7, Appendix 7.

AEs will be repo1ied by the patient (or, when appropriate, by a caregiver, Slmogate, or the patient's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, doclllllenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate infonnation both to detennine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the patient to discontinue the study treatment.

Each patient will be questioned about the occmTence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up info1mation in an expedited fashion.

8.1.1 Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each patient begins from the time the patient provides informed consent, which is obtained before the patient's paiiicipation in the study (ie, before undergoing anystudy related procedure and/or receiving study treatment), through and including a minimllll of 30 calendar days, except as indicated below, after the last administration of the study treatment.

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For patients who are screen failures, the active collection period ends when screen failure status is dete1mined.

If the patient withdraws from the study and also withdraws consent for the collection of future info1mation, the active collection period ends when consent is withdrawn.

If a patient definitively discontinues or temporarily discontinues study treatment because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Repo1i Fo1m.

Investigators ai·e not obligated to actively seek AEs or SAEs after the patient has concluded study pa1iicipation. However, if the investigator learns of any SAE, including a death, at any time after a patient has completed the study, and he/she considers the event to be reasonably

related to the study treatment, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

Patients who sign the molecular pre-screening ICF

For patients who sign the molecular pre-screening ICF (see Section 4.1 and Section 7.1.1), AEs which occur after signature of this consent will only be captured if they meet the definition of serious as outlined in Section 14.7.2 and are associated with study related procedures (e.g. an invasive procedure such as biopsy). Once the study ICF is signed, all AEs per the descriptions below will be captured in the AE eCRF.

Patients who sign the study ICF

For patients whose BRAF mutational status is known and sign the study ICF, AEs that begin or worsen after informed consent should be recorded in the AE eCRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History eCRF. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected though a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-4)
2. Its duration (start and end dates)
3. Its relationship to the study treatment (reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy taken (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event eCRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary)

of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

8.1.1.1 Reporting SAEs to Pfizer Safety

All SAEs occurring in a patient during the active collection period as described in Section 8.1.1. are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Section 14.7, Appendix 7. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

If a patient begins a new anticancer therapy, SAEs occurring during the above indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening treatment. Note that a switch to a commercially available version of the study treatment is considered as a new anticancer therapy for the purposes of SAE reporting.

8.1.1.2 Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a patient during the active collection period, which begins after obtaining informed consent as described in Section 11.3, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the patient.

If a patient begins a new anticancer therapy, the recording period for nonserious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above indicated active collection period. Note that a switch to a commercially available version of the study treatment is considered as a new anticancer therapy for the purposes of SAE reporting.

8.1.2 Methods of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 14.7, Appendix 7.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.1.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up.

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses,

must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Section 14.7, Appendix 7.

8.1.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.1.5 Exposure During Pregnancy or Breastfeeding and Occupational Exposure

Exposure to the study treatment under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.1.5.1 Exposure During Pregnancy

An EDP occurs if:

- A female patient is found to be pregnant while receiving or after discontinuing study treatment.
- A male patient who is receiving or has discontinued study treatment exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study treatment due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study treatment by ingestion.
    - A male family member or healthcare provider who has been exposed to the study treatment by ingestion then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a patient or a patient's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study treatment and until 30 days after last dose.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the patient enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study treatment.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case by case basis (e.g., follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the patient with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the patient was given the Pregnant Partner Release of Information Form to provide to his partner.

8.1.5.2 Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female patient is found to be breastfeeding while receiving or after discontinuing study treatment.
- A female is found to be breastfeeding while being exposed or having been exposed to study treatment (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study treatment by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the patient enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (e.g., vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.1.5.3 Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study treatment, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial patient's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the CT SAE Report Form. Since the information does not pertain to a patient enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.1.6 Cardiovascular and Death Events

Cardiovascular events are to be managed per the dose modification guidelines in Section 6.3. Additionally, cardiovascular events will be reported per AE and SAE reporting guidelines and ECG criteria, as detailed in Section 8.1 and Section 14.7, Appendix 7 and Section 7.2.2.8, respectively. AEs and SAEs that result in death are to be reported per the reporting guidelines as outlined in Section 8.1 and Section 14.7, Appendix 7.

8.1.7 Disease-Related Events and/or Disease Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.1.8 Adverse Events of Special Interest

Not applicable.

8.1.8.1 Lack of Efficacy

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

8.1.9 Medical Device Deficiencies

Not applicable.

8.1.10 Medication Errors

Medication errors may result from the administration or consumption of the study treatment by the wrong patient, or at the wrong time, or at the wrong dosage strength.

Exposures to the study treatment under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the AE CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	Only if associated with an AE or SAE	Only if associated with an SAE

Medication errors include:

- Medication errors involving patient exposure to the study treatment;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study patient.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

If applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

8.2 Treatment Overdose

There is no known antidote for an overdose of either LGX818, MEK162 or LEE011. Supportive measures should be instituted.

In the event of an overdose, the investigator/treating physician should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the patient for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of study treatment (whichever is longer). Closely monitor the patient for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE**.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Sponsor Medical Monitor based on the clinical evaluation of the patient.

8.3 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator Brochure. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.4 Data Monitoring Committee

A Data Monitoring Committee (DMC) will not be in place for this trial. Instead, the Sponsor will convene a joint teleconference with the participating Investigators of the dose escalation at the end of each treatment cohort. At the dose escalation teleconference the clinical course (available safety information including both DLTs and all ≥ CTCAE Grade 2 toxicity data during Cycle 1, PK and PD data as appropriate) for each patient in the current dose cohort will be described in detail. Updated safety data on other ongoing patients, including data in later cycles, will be discussed as well.

Dose escalation decisions will be based on a clinical synthesis of all relevant available data and not solely on DLT information. Selection of the actual dose for the next cohort of patients will be guided by the BLRM (with EWOC) recommendation, and a medical review of available relevant clinical, PK, PD and laboratory data. The parties i.e. study Investigators and the Sponsor, must reach a consensus on whether to declare MTD, escalate the dose any further, or whether to de-escalate and/or expand recruitment into particular cohorts. The Sponsor will prepare minutes from these meetings and circulate them to all concerned (Section 6.2.4.2.1).

9 Data collection and management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Sponsor personnel (or designated CRO) will review the protocol and eCRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on eCRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. The Sponsor's monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

The designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

PK and biomarker (blood and tissue) samples drawn during the course of the study will be collected from the Investigator sites and analyzed by a Sponsor-assigned laboratory or contracted central labs. ECG data (except the screening/baseline ECG) collected during the study will be reviewed and processed centrally by a specialist CRO. Designated investigational site staff will enter the information required by the protocol into the appropriate eCRF (and/or designated laboratory requisition forms that are printed on 2 or 3-part, non-carbon-required paper). Field monitors will review the eCRFs and laboratory paper requisition forms for accuracy and completeness and instruct site personnel to make any required corrections or

additions. One copy of the requisition form will be forwarded to each analytical laboratory with the respective sample(s) by the field monitor or by the designated investigational site staff; and one copy will be retained at the investigational site.

9.4 Database management and quality control

Sponsor personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Biomarker and PK samples and ECG (except screening/baseline) will be processed centrally, and the results for these will be sent electronically to the Sponsor (or a designated CRO).

After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

[Any language regarding the triple combination of LGX818/MEK162/LEE011 in this Section is <u>not</u> applicable to the USA and Singapore]

Data will be analyzed by the Sponsor and/or designated CRO. Any data analysis carried out independently by the investigator must be submitted to the Sponsor before publication or presentation.

It is planned that the data from participating centers in this protocol will be combined, so that an adequate number of patients will be available for analysis. Data will be summarized with respect to demographic and baseline characteristics, efficacy and safety observations and measurements and all relevant PK and PD measurements.

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

An initial clinical study report (CSR) will be presented based on the Ph Ib/II patients' data from the dual study drug combination. The cut-off for reporting will be either LPFV + 18 months or when 80% of the patients treated with the dual study drug combination can be assessed for PFS, whichever occurs first.

Additional data for any patients continuing to receive the LGX818 and MEK162 dual combination past the cut off point for the initial reporting, as allowed by the protocol, and the Phase Ib/II patients' data from the LGX818 and MEK162 and LEE011 triple combination will be summarized in a final CSR that will be prepared when all patients have completed or discontinued from the study.

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

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

Screen failure patients are those who signed the informed consent, but never started the study treatment for any reason. For these patients, the eCRF data collected, Section 7.1.2.2, will not be included in any analysis, but will be reported in the CSR as separate listings.

10.1 Analysis sets

10.1.1 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.

10.1.2 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, where treatment received is defined as:

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

10.1.3 Dose-Determining Set

The dose-determining set (DDS) includes all 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.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively for all patients in the FAS.

10.3 Treatments (study treatment, concomitant therapies, compliance)

10.3.1 Study treatment

The actual dose and duration in days of LGX818 and MEK162 and LEE011 treatment as well as the dose intensity (computed as the ratio of actual dose received and actual duration) and the relative dose intensity (computed as the ratio of dose intensity and planned dose received/planned duration), will be listed and summarized by means of descriptive statistics. The summary data will be presented for each treatment cycle individually, as well as for all study days as a single category. The daily doses of LGX818, MEK162, and LEE011 for each patient will be summarized using descriptive statistics (e.g. mean, median, and modal doses). The FAS will be used. For patients who switch to the new MEK162 tablet variants, dose intensity will be calculated based on the bioavailability ratio between the original and new MEK162 tablet variants if the new and old variants are not similar. Details will be provided in report analysis plan (RAP).

10.3.2 Concomitant therapies

Concomitant medications and significant non-drug therapies prior to and after the start of the study drug treatment will be listed by patient and summarized by ATC (Anatomical therapeutic chemical classification system) term by means of contingency tables.

10.3.3 Compliance

Compliance to the protocol will be assessed by the number and proportion of patients with protocol deviations. These will be identified prior to database lock and will be listed and summarized.

10.4 Primary objective

Phase Ib

The primary purpose of the Phase Ib part of the study is to estimate the MTD(s) and/or RP2D(s) of the LGX818 and MEK162 dual combination and MTD(s) and/or RP2D(s) of LGX818 and MEK162 and LEE011 triple combination in patients with solid tumors harboring a BRAF V600 mutation (see Section 3). The corresponding method of analysis is an adaptive Bayesian logistic regression model (BLRM) guided by the escalation with overdose control (EWOC) principle (Babb 1998).

Phase II

The primary purpose of the Phase II part of the study is to assess the efficacy of the RP2D(s) of the dual combination of LGX818 and MEK162 combination in patients with metastatic BRAF

V600 mutant mCRC (arm 1), in patients with metastatic BRAF V600 mutant melanoma who have progressed after prior treatment with selective BRAF inhibitor (arm 2) and in patients with metastatic BRAF V600 mutant melanoma who are naïve to prior treatment with selective BRAF inhibitor (arm 3). The primary purpose of the Phase II part of triple combination of LGX818 and MEK162 and LEE011 is to assess the efficacy of the RP2D(s) in patients with metastatic BRAF V600 mutant melanoma who are naïve to prior treatment with selective BRAF inhibitor (arm A).

10.4.1 Variable

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 dose-determining set. This probability is estimated by the model in Section 10.4.2. 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.

Phase II

Dual combination (LGX818 and MEK162)

For arm 1, the primary variable is the Disease Control Rate (DCR) at week 16. DCR is defined as the proportion of patients with a best overall response of complete response (CR), partial response (PR) or stable disease (SD). Estimation of the true DCR in this part of the study will be based upon observed DCR for patients in the FAS. The true DCR is estimated using a Bayesian design. The primary analysis of the DCR will be based on the local review of overall lesion responses.

For arms 2 and 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 in this part of the study will be based upon observed ORR for patients in the FAS. The true ORR is estimated using a Bayesian design. 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), defined as the proportion of patients with a best overall response of complete response (CR) or partial response (PR). Estimation of the true ORR in this part of the study will be based upon observed ORR for patients in the FAS. The true ORR is estimated using a Bayesian design. The Primary analysis of the ORR will be based on the local review of overall lesion responses.

10.4.2 Statistical hypothesis, model, and method of analysis

10.4.2.1 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. While developing dual combination (LGX818 and MEK162) all information available about the dose-DLT relationship of the single agents LGX818 (i.e., from [LGX818X2101] study on both the capsule and micro-emulsion formulations) and MEK162 [ARRAY-162-111 study] will be summarized in prior distributions, based on a meta-analytical predictive approach to properly down-weight the information. 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. Three week on 1 week off DLT data from [CLEE011X2101] will be summarized in prior distributions based on a meta-analytical predictive approach to properly down-weight the information.

The 5-parameter BLRM for 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 $\pi_2(d_2)$ the probability of a DLT if MEK162 is given as a single agent at dose d_2. The dose-response relationship is then modeled as:

$\text{LGX818: } \text{logit}(\pi 1(d1)) = \log(\alpha 1) + \beta 1 \log(d1/d1^*)$

$\text{MEK162 original tablet: } \text{logit}(\pi 2(d2)) = \log(\alpha 2) + \beta 2 \log(d2/d2^*)$

$\text{Odds}(\pi 12(d1,d2))) = \pi 12(d1,d2)/(1- \pi 12(d1,d2))$

$= \exp(\eta 12(d_1/d_1^*)(d_2/d_2^*))(\pi 1(d1)+ \pi 2(d2) - \pi 1(d1)\pi 2(d2))/((1- \pi 1(d1))(1- \pi 2(d2))),$

where

- $\text{logit}(\pi_{.}(d_{.})) = \log[\pi_{.}(d_{.})/\{1- \pi_{.}(d_{.})\}]$, $\pi(d)$ is the probability of a DLT at dose d,
- $\pi 12(d1,d2)$ 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 original tablet respectively,
- $\alpha_1, \alpha_2, \beta_1, \beta_2 > 0$ and $-\infty < \eta_{12} < \infty$ is a scalar. With η_{12} the interaction term between LGX818 and MEK162 original tablet.

For further details on the statistical model including the prior specification for the model parameters refer to Appendix 5.

The 5-parameter BLRM for 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 $\pi_3(d_3)$ 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:

LGX818: $\text{logit}(\pi 1(d1)) = \log(\alpha 1) + \beta 1 \log(d1/d1^*)$

MEK162 smaller tablet/ new tablet variant: $\text{logit}(\pi 3(d3)) = \log(\alpha 3) + \beta 3 \log(d3/d3^*)$

$\text{Odds}(\pi 13(d1,d3))) = \pi 13(d1,d3)/(1- \pi 13(d1,d3))$

$= \exp(\eta 13(d_1/d_1^*)(d_3/d_3^*)))(\pi 1(d1)+ \pi 3(d3) - \pi 1(d1)\pi 3(d3))/((1- \pi 1(d1))(1- \pi 3(d3))),$

where

- $\text{logit}(\pi(d)) = \log[\pi(d)/\{1- \pi(d)\}]$, $\pi(d)$ is the probability of a DLT at dose d,
- $\pi 13(d1,d3)$ is the probability of a DLT given the combination doses
- $d_1^* = 100$mg and d_3^* are the reference doses of LGX818 and MEK162 respectively. The value of d_3^* will be determined prior to first DETC for the MEK162 smaller tablet/ new tablet variant.
- $\alpha_1, \alpha_3, \beta_1, \beta_3 > 0$ and $-\infty < \eta^{13} < \infty$ is a scalar. With η^{13} the interaction term between LGX818 and MEK162 smaller tablet/new tablet variant.

For further details on the statistical model including the prior specification for the model parameters refer to Appendix 5.

The 10-parameter BLRM

The 10-parameter BLRM is formulated in the following way: Let $\lambda 1(d1)$ be the probability of DLT if LGX818 is given as a single agent at QD dose d1, $\lambda 2(d2)$ the probability of DLT if MEK162 is given as a single agent at BID dose d2, and $\lambda 3(d3)$ the probability of DLT if LEE011 is given as a single agent at 3 week on 1 week off dose of d3.

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

LGX818: $\text{logit}(\pi 1(d1)) = \log(\alpha 1) + \beta 1 \log(d1/d1^*)$

MEK162: $\text{logit}(\pi 2(d2)) = \log(\alpha 2) + \beta 2 \log(d2/d2^*)$

LEE011: $\text{logit}(\pi 4(d4)) = \log(\alpha 4) + \beta 3 \log(d4/d4^*)$

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

$\text{Odds}(\pi 12(d1,d2))) = \pi 12(d1,d2)/(1- \pi 12(d1,d2))$

$= \exp(\eta 12(d_1/d_1^*)(d_2/d_2^*))(\pi 1(d1)+ \pi 2(d2) - \pi 1(d1)\pi 2(d2))/((1- \pi 1(d1))(1- \pi 2(d2))),$

$\text{Odds}(\pi 14(d1,d4))) = \pi 14(d1,d4)/(1- \pi 14(d1,d4))$

$= \exp(\eta 14(d_1/d_1^*)(d_4/d_4^*)))(\pi 1(d1)+ \pi 4(d4) - \pi 1(d1)\pi 4(d4))/((1- \pi 1(d1))(1- \pi 4(d4))),$

$\text{Odds}(\pi 24(d2,d4))) = \pi 24(d2,d4)/(1- \pi 24(d2,d4))$

$= \exp(\eta 24(d_4/d_4^*)(d_2/d_2^*)))(\pi 2(d2)+ \pi 4(d4) – \pi 2(d2)\pi 4(d4))/((1- \pi 2(d2))(1- \pi 4(d4))),$

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

$\text{Odds}(\pi 124(d1, d2,d4))) = \pi 124 (d1, d2,d4)/(1- \pi 124(d1,d2,d4))$

= exp(η124(d1/d1*)(d2/d2*)(d4/d4*)+ η12(d1/d1*)(d2/d2*)+ η14(d1/d1*)(d4/d4*)+ η24(d2/d2*)(d4/d4*))(π1(d1)+ π2(d2)+ π4(d4) – π1(d1)π2(d2)-π1(d1)π4(d4)-π2(d2)π4(d4)+ π1(d1)π2(d2) π4(d4))/((1- π1(d1))(1- π2(d2))(1- π4(d4))),

where logit(π.(d.)) = log[π.(d.)/{1- π.(d.)}], d1* = 100mg (QD), d2* = 60mg (BID) and d4* = 400mg (3 week on 1 week off) are the reference doses of LGX818, MEK162 and LEE011 respectively, α1, α2, α4, β1, β2 , β4> 0 and -∞ < ζ12, ζ13, ζ23, ζ124 < ∞ are constants.

For further details on the statistical model including the prior specification for the model parameters refer to Appendix 6.

Dose recommendation

Dose recommendation will be based on posterior summaries including the mean, median, standard deviation, 95%- credible interval, and the probability that the true DLT rate for each dose combination lies in one of the following categories:

- [0%, 16%) under-dosing
- [16%, 35%) targeted toxicity
- [35%, 100%] excessive toxicity

Following the principle of EWOC, after each cohort of patients the dose combination recommended by the BLRM is the one with the highest posterior probability of DLT in the target interval [16%, 35%) among the doses fulfilling the overdose criterion that there is less than 25% chance of excessive toxicity.

In addition, the maximum inter-cohort combined dose escalation across the 2 combination partners is limited to 100%, where 100% refers to the sum of the relative escalation for each of the combination partners, e.g. 100% and 0% increase for LGX818 and MEK162 respectively, 0% and 100% increase for LGX818 and MEK162 respectively, etc.

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.

10.4.2.2 Phase II

Efficacy will be assessed using the local CT/MRI assessments evaluated under RECIST version 1.1, Appendix 1. The Best Overall Response (BOR) for each patient and individual lesion measurements will be listed. The (BOR) is the best response recorded from the start of the treatment until disease progression. Based on patients' BOR during study, the Objective Response Rate (ORR) and the Disease control Rate (DCR) are then calculated.

The ORR is defined as the proportion of patients with a best overall response of Complete Response (CR) or Partial Response (PR). The DCR is defined as CR or PR or Stable Disease (SD).

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.

Arm 1 dual combination: patients with metastatic BRAF V600 mutant mCRC

A Bayesian design will be used in order to estimate the true DCR. Inferential statements will be based on the uncertainty of this quantity. For a Bayesian design it is required to specify a prior distribution for the parameter of interest, in this case DCR.

For the current study, the prior clinical assumption for a MEK inhibitor in BRAF V600 mutant mCRC at pre-specified dose-levels will be used in order to derive a minimally informative unimodal Beta prior distribution that reflects the level of uncertainty around the DCR before starting the current trial. At completion of the study, this prior distribution will be updated with all the data available in this part of the study.

Once updated, the distribution summarizes the probability that the true DCR at the dose of the LGX818 and MEK162 combination used in the Phase II lies in the following categories:

- [0, 20%) unacceptable efficacy
- [20%, 30%) limited efficacy
- [30%, 40%) moderate efficacy
- [40%, 100%] clinically relevant efficacy

If the observed DCR is equal or greater than 30% (i.e. 9 or more patients with BOR of SD, PR or CR), then this will be considered as evidence of clinically relevant anti-tumor efficacy of the LGX818 and MEK162 combination in BRAF V600 mutant mCRC. Note that for a sample size of 28, if at least 9 patients with DCR are observed, then the true DCR has posterior risk of being in the unacceptable efficacy category of less than 10% (Section 10.8)**.** If the observed DCR is less than 20% then inactivity will be declared.

A minimally informative Beta prior distribution of the true DCR is derived as follows: **a priori** it is assumed that the true mean of the DCR equals 30%. A true DCR of 30% is the midpoint between limited and moderate efficacy and serves as a compromise between a skeptical view assuming the treatment has only limited efficacy and an optimistic view assuming the treatment has moderate efficacy.

The parameters of the minimally informative Beta prior distribution of the DCR are then derived noting that $b = 1$ *and* $a/(a+b) = 0.30$ i.e. $a = 0.428$ and $b = 1$

Arm 2 dual combination: patients with metastatic BRAF V600 mutant melanoma who have progressed after prior treatment with selective BRAF inhibitor

A Bayesian design will be used in order to estimate the true ORR. Inferential statements will be based on the uncertainty of this quantity. For a Bayesian design it is required to specify a prior distribution for the parameter of interest, in this case ORR:

For the current study, the prior clinical assumption for a MEK inhibitor in BRAF V600 mutant melanoma at pre-specified dose-levels will be used in order to derive a minimally informative unimodal Beta prior distribution that reflects the level of uncertainty around the ORR before starting the current trial. At completion of the study, this prior distribution will be updated with all the data available in this part of the study.

Once updated, the distribution summarizes the probability that the true ORR at the dose of the LGX818 and MEK162 combination used in the Phase II lies in the following categories:

- [0, 10%) unacceptable efficacy
- [10%,15%) limited efficacy
- [15%, 20%) moderate efficacy
- [20%, 100%] clinically relevant efficacy

If the observed ORR is equal or greater than 15% (i.e. 7 or more patients with BOR of PR or CR), then this will be considered as evidence of clinically relevant anti-tumor efficacy of the LGX818 and MEK162 combination in BRAF V600 mutant melanoma. Note that for a sample size of 41, if at least 7 responses (CR or PR) are observed, then the true ORR has posterior risk of being in the unacceptable efficacy category of less than 10% (Section 10.8). If the observed ORR is less than 10% then inactivity will be declared.

A minimally informative Beta prior distribution of the true ORR is derived as follows: **a priori** it is assumed that the true mean of the ORR equals 15%. A true ORR of 15% is the midpoint between limited and moderate efficacy and serves as a compromise between a skeptical view assuming the treatment has only limited efficacy and an optimistic view assuming the treatment has moderate efficacy.

The parameters of the minimally informative Beta prior distribution of the ORR are then derived noting that $b = 1$ *and* $a/(a+b) = 0.15$ i.e. $a = 0.176$ and $b = 1$

Arm 3 dual combination / Arm A triple combination: patients with metastatic BRAF V600 mutant melanoma who are naïve to prior treatment with selective BRAF inhibitor

A Bayesian design will also be used in order to estimate the true ORR in these populations. Inferential statements will be based on the uncertainty of this quantity. For a Bayesian design it is required to specify a prior distribution for the parameter of interest, in this case ORR:

For the current study, a minimally informative unimodal Beta prior distribution (Neuenschwander et al 2008) is developed for ORR. The prior distribution reflects the level of uncertainty around the ORR before starting the current trial. At completion of the study, this prior distribution will be updated with all the data available in this part of the study.

Once updated, the distribution summarizes the probability that the true ORR at the dose of the dual combination (LGX818 and MEK162) and triple combination (LGX818 and MEK162 and LEE011) used in the Phase II lies in the following categories:

- [0, 30%) unacceptable efficacy
- [30%, 40%) limited efficacy
- [40%, 50%) moderate efficacy
- [50%, 100%] clinically significant efficacy

If the observed ORR is equal to or greater than 40% (i.e. 16 or more patients with BOR of PR or CR for a sample size of 40), then this will be considered as evidence of clinically relevant anti-tumor efficacy of the dual combination (LGX818 and MEK162) or triple combination (LGX818 and MEK162 and LEE011) in BRAF V600 mutant melanoma patients who have not

been previously treated with selective BRAF inhibitor. Note that for a sample size of 40, if at least 16 responses (CR or PR) are observed, then the hue ORR has posterior risk of being in the unacceptable efficacy catego1y of less than 10% (Section 10.8). If the observed ORR is less than 30% then inactivity will be declared. A minimally infonnative Beta prior dish·ibution of the h11e ORR is derived as follows: **a priori** it is assumed that the h11e mean of the ORR equals 40%. A hue ORR of 40% is the midpoint between limited and moderate efficacy and serves as a compromise between a skeptical view assuming the h·eatment has only limited efficacy and an optimistic view assuming the h·eatinent has moderate efficacy.

The parameters of the minimally infonnative Beta prior dish·ibution of the ORR are then derived noting that b=l and a/(a+b)=0.4 i.e. a=0.67 and b=l.

Re-assessment of the MTD/RP2D

A re-assessment of the dual-combination MTD/RP2D will be perfonned (using dual-combination data only) after at least 10 patients in the Phase II paii (aim 1 + aim 2 + aim 3) of the study have been h'eated for at least one cycle. A re-assessment of the h'iple-combination MTD/RP2D will be perfo1med after at least 10 patients in the Phase II paii of the study have been h·eated with the h·iple combination for at least one cycle. The BLRM will be re-nm to confnm that the cmTent dose combination still satisfies the overdose criteria for the model. If this combination fails to satisfy the criteria, a change to the doses lmder study will be made subject to the BLRM recommendation. If different RP2Ds ai·e used for ann 1, aim 2 and aim 3, respectively, then the above re-assessment will be done by RP2D rather than combining the aims.

Emollment in the Phase II anns will not be inte1n1pted due to this re-assessment of the MTD/RP2D.

10.4.3 Handling of missing values/censoring/discontinuations

Patients who are ineligible for the DDS may be replaced as described in Section 7.1.4.2. Continuing events (e.g. AEs, concomitant medication, etc) will be summarized using the data cut-off date as the date of completion, with an indication within listings that the event is continuing. For patients who discontinue the study with ongoing events, the discontinuation date will be used as the completion date of the event with the appropriate censoring as described in the above pai·agraph.

Patients for whom no best overall response can be assessed at the time of the primaiy analysis will be h·eated as h·eatinent failmes.

The reason for discontinuation from study will be smnmai·ized and listed, along with dates of first and last study dmg h'eatinent, dmation of exposme to study dmg h'eatment and date of discontinuation for each patient.

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

10.4.4 Supportive analyses

[redacted]

If deemed necessary, a sensitivity analysis will be performed using central imaging assessments according to RECIST v1.1 (see Appendix 1, Section 14.1). The same method of analysis as for the primary analysis will be used, using the FAS.

10.5 Secondary objectives

10.5.1 Efficacy

Phase Ib. A secondary objective of the Phase Ib is to assess preliminary clinical anti-tumor activity of the combination in patients with BRAF V600-dependent advanced solid tumors. For all efficacy analyses the FAS will be used.

Anti-tumor activity will be assessed using the Investigator imaging assessments under RECIST version 1.1, Appendix 1. The Best Overall Response (BOR) for each patient and individual lesion measurements will be listed. The (BOR) is the best response recorded from the start of the treatment until disease progression. ORR will be estimated for this patient population. TTR and DOR will be assessed if at least one responder is observed.

Phase II. Local imaging assessments will be used for all Phase II efficacy assessments of tumor activity. The FAS will be used.

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. Kaplan-Meier estimates with confidence intervals for median survival and survival probabilities for specific time points will be presented.

The secondary endpoint progression-free survival (PFS) will be analyzed using Kaplan-Meier estimates (including plots) with 95% confidence interval for median survival. If a patient has not had an event, he/she will be censored at the date of last adequate response assessment. PFS is defined as the number of days from the first day of treatment to the date of the first documented progression of disease or date of death, whichever occurs first. PFS will be summarized by arm.

Kaplan-Meier estimates based on all responders with 95% confidence intervals will be presented for the secondary endpoint duration of overall response (DOR). This analysis based on responders will be used as a descriptive analysis. DOR is the time between the date of first documented response (CR or PR) and the date of documented progression or censoring. Censoring will occur at the last adequate tumor assessment date at which continued response is documented.

The secondary endpoint time to response (TTR) is the time between the date of first treatment administration and the first documented response (CR or PR). Patients who did not achieve a confirmed PR or CR will be censored at the last adequate tumor assessment date when they did not progress, or at maximum follow-up (i.e. FPFV to LPLV used for analysis) when they had an event for PFS.

If deemed necessary, analyses of TTR and DOR as described above, will be performed using central imaging assessments (RECIST v1.1). FAS will be applied.

10.5.2 Safety

For all safety analyses, the safety set will be used, unless otherwise specified. The assessment of safety will be based mainly on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges. All individual safety data reported in the clinical data base will be listed by patient and dose level.

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

- pre-treatment period: from day of patient's informed consent signature to the day before first dose of study treatment.
- on-treatment period: from day of first dose of study treatment to 30 days after last dose of study medication.
- post-treatment period: starting at day 31 after last dose of study treatment.

10.5.2.1 Adverse events

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by primary system organ class, severity based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, type of adverse event, and relationship to the study drug by dose level on the pool of patients recruited during the dose escalation part of the study as well as on the complete pool of patients (including dose escalation and Phase II parts). Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by primary system organ class, type of adverse event, and dose level.

DLTs will be listed and their incidence summarized by primary system organ class, worst grade based on the CTCAE version 4.03, type of adverse event, and by dose level in the dose escalation part. The dose-determining set will be used for these summaries.

Details of analysis to be performed are given in the Reporting and Analysis Plan (RAP).

10.5.2.2 Laboratory abnormalities

All laboratory values will be converted into SI units and the severity grade calculated using CTCAE, version 4.03. Parameters for which a grading does not exist will be classified into low/normal/high group by means of laboratory normal ranges.

For each laboratory test (e.g. hematology, biochemistry etc) a listing of laboratory values will be provided by laboratory parameter, patient, and dose level. The frequency of notable laboratory abnormalities (i.e., newly occurring CTC grade 3 or 4 laboratory toxicities) will be displayed by parameter, cycle and dose level. Similarly, the frequency of all laboratory abnormalities will be displayed by parameter, worst CTCAE grade experienced and dose level. A separate listing will display notable laboratory abnormalities.

Laboratory data will be summarized by presenting grade shift tables for those parameters for which CTCAE allows classification. All remaining data will be summarized by presenting shift tables based on normal ranges.

Laboratory data will be also be displayed by presenting summary statistics of raw data and change from baseline values (means, medians, standard deviations, ranges).

10.5.2.3 Other Safety data

Any other safety information collected will be listed and notable values will be flagged. Any statistical tests performed to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration. Additionally, the following outputs will be produced:

ECG

- shift table baseline to worst on-treatment result for overall assessments
- listing of ECG evaluations for all patients with at least one abnormality.

Vital signs

- shift table baseline to worst on-treatment result
- table with descriptive statistics at baseline, one or several post-baseline time points and change from baseline to this/these post-baseline time points.

Ocular

- Listing of ocular assessment for all patients with at least one abnormality will be presented.

10.5.2.4 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. Cumulative dose, dose intensity and relative dose intensity of MEK162, LGX818 and LEE011 will be listed by patient and summarized. Categories for relative dose intensity of the combination MEK162, LGX818 and LEE011 will be specified as < 0.5, ≥ 0.5 - < 0.75, ≥ 0.75 - < 0.9, ≥ 0.9 - < 1.1 and ≥ 1.1. The number and proportion of patients within each category will be presented.

10.5.3 Pharmacokinetics

A secondary objective of this study is to determine the single and multiple dose pharmacokinetic profile of the dual combination (MEK162 and LGX818), and the triple combination (LGX818 and MEK162 and LEE011).

For plasma LGX818, the LLOQ is 1.0 ng/mL, for MEK162 is 5.0 ng/mL and LEE011 is 1.0 ng/mL. All concentrations below the LLOQ or missing data will be labeled as such in the concentration data listings. Concentrations below the LLOQ will be treated as zero in summary statistics. The parameters displayed on Table 10-1 will be estimated and reported.

Descriptive graphical plots of individual and mean plasma concentration (per treatment) along with its time course will be generated. Further graphical exploratory analyses will be carried out if deemed appropriate. Pharmacokinetic parameters for each dose cohort will be analyzed by descriptive statistics, including the mean, SD, CV% or median (range). Since t_{max} is generally evaluated by a non-parametric method, median values and ranges will be given for this parameter.

Assessment of dose-proportionality, inter- and intra-individual variability and steady-state attainment will be conducted. If appropriate, an analysis of variance (ANOVA) will be performed on log-transformed AUCs and C_{max} using a linear mixed effect model to assess day effect.

Details of PK analysis presented will be given in the Reporting and Analysis Plan. Any other exploratory analysis will be conducted if necessary.

Table 10-1 PK parameters

Variable	Definition
C_{max}	Maximum observed plasma concentration after drug administration [mass x volume^{-1}]
$C_{max,ss}$	Maximum observed plasma concentration during a dosing interval at steady state [mass x volume^{-1}]
C_{trough}	Measured concentration at the end of a dosing interval at steady state (taken directly before next administration) [mass x volume^{-1}]
t_{max}	Time to reach C_{max} [time]
$t_{max,ss}$	Time to reach C_{max} at steady state [time]
AUC_{tau}	Area under the concentration-time curve during a dosing interval [mass x time x volume^{-1}]
AUC_{inf}	Area under the concentration-time curve from time zero to infinity with extrapolation of the terminal phase [mass x time x volume^{-1}]
$AUC_{tau,ss}$	Area under the concentration-time curve during a dosing interval at steady state [mass x time x volume^{-1}]
$t_{1/2}$	Elimination half-life associated with the terminal slope (λ_z) of a semi logarithmic concentration-time curve [time]
CL/F	Apparent total plasma clearance of drug after oral administration [volume x time^{-1}]
V/F	Apparent volume of distribution [volume]
R_A	Accumulation ratio calculated as $AUC_{tau,ss}/AUC_{tau,dose1}$

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).

10.5.3.1 Data handling principles

10.5.3.1.1 Analysis sets

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

10.5.3.1.2 Basic tables, figures and listings

Descriptive statistics (mean, standard deviation, CV% or median (range)) will be presented for all parameters for each dose cohort. When a geometric mean is presented, it will be stated as such. CL/F will be assessed for MEK162, LGX818 and LEE011, as applicable, and only median values and ranges will be given for t_{max}.

Descriptive graphical plots of individual plasma concentration by time will be generated, as will mean concentration time profiles for MEK162, LGX818 and LEE011, as applicable. Further graphical exploratory analyses will be carried out if deemed appropriate.

10.5.3.1.3 Advanced data analysis methods

CCI

[redacted]

10.5.4 Biomarkers

10.5.4.1 Outline of the data analysis

As a project standard, only patient pre-selection and PD markers collected in the clinical database will be analyzed by the Sponsor. Since this clinical trial was not designed to address specific hypotheses related to patient pre-selection or PD markers, the analysis of this data should be viewed as explorato1y and hypotheses generating. Analytical results from such analyses may be used to generate additional hypotheses that must then be verified with data derived from subsequent clinical trials. No adjustment for multiple comparisons is planned.

If the number of samples is inadequate to perfonn a rigorous data analysis, then the available data will only be listed. Additional analyses that may be perfo1med after the completion of the end-of-study clinical study repo1t 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 patient pre-selection or PD markers generated from samples collected during the study but analyzed after the database lock and completion of the clinical study repo1t. The data analysis will be described in an addendum of the RAP or in a stand-alone analysis plan document, as appropriate.

10.5.4.2 Data handling principles

All measurements below their respective LLOQs or missing data will be labeled as such in the concentration data listings. Measurements below the LLOQ will be treated as zero in summaiy statistics. Change from baseline analyses will only be perfonned on patients with measurable sainples and pre- and post-treatment time points.

10.5.4.3 Data analysis principles

10.5.4.3.1 Analysis sets

The FAS will be used for all analyses. The number of patients with measureable samples will be identified in the summaries and relevant propo1tions will be calculated against this number of patients.

10.5.4.3.2 Basic tables, figures and listings

To characterize baseline molecular status of molecules relevant to RAF/MEKIMAPK and EGFR/PI3K./AKT signaling in tumor tissue in the Phase II parts of the study, baseline molecular status (mutation/amplification/expression) in tumor tissue of potential predictive markers (BRAF, HRAS, KRAS, NRAS, PTEN, cKIT, PIK3CA, MAP2Kl, MAP2K2, ARAF, c-MET, RAFI, EGFR) will be summarized by patient group. All biomarker assessments obtained from the full complement of fresh pre- and post-treatment paired tumor/skin biopsies collected in the trial will be listed by patient and time point and summarized using descriptive statistics by time point.

All biomarker assessments only collected at baseline will be listed by patient and summarized using descriptive statistics.

All biomarker assessments obtained from tumor samples from patients with disease progression will be listed by biomarker and by patient.

10.5.4.3.3 Advanced analysis methods

CCI [redacted]

10.5.5 Resource utilization

Not applicable.

10.5.6 Patient-reported outcomes

Not applicable.

CCI [redacted]

10.7 Interim analysis

An interim analysis for futility will be perfo1med in the phase II BRAF V600 mutant mCRC aim (dual-combination ann 1), when 14 patients (50% of the total sample size) have completed 4 cycles of treatment. As mentioned in Section 10.8, study results ai·e successful if 9 responses ai·e observed at the end of the trial. At the interim analysis, if the predictive probability of success is < 13%, i.e. if less than 3 responses (DCR at week 16) are observed, this study ai·m will be stopped for futility.

10.8 Sample size calculation

Phase lb

Dose escalation: Cohorts of 3 to 6 evaluable patients will be emolled in the dose escalation pait including at least six patients at the MTD/RP2D level, as described in Section 6.2.4.

Multiple cohorts may be sequentially enrolled to the same dose level. Additional cohorts of 1 to 6 patients may be enrolled at any dose level below the estimated MTD/RP2D for further elaboration of safety and PK parameters as required. At least 18 patients are expected to be treated in the dual-combination dose-escalation part of the study, for the model to have reasonable operating characteristics relating to its MTD recommendation (see Appendix 5 for details). At least 12 patients are expected to be treated in the triple-combination dose- escalation part of the study.

Phase II

Arm 1 dual combination: Based on the prior distribution and decision rules described in Section 10.4, it was explored how likely it is to wrongly declare activity given the true DCR = 20%, and how likely it is to correctly declare activity given the true DCR = 40%, when 28 patients are evaluated.

- If the true DCR = 20%, the probability to wrongly declare activity (i.e. seeing at least 9 patients with SD or better) is 9.0%.
- If the true DCR = 40%, the probability to correctly declare activity (i.e. seeing at least 9 patients with SD or better) is 85.2%.

If 9 out of 28 patients have at least SD or better, then the posterior risk of the true DCR being in the unacceptable category is 7.0%.

Note: if the interim analysis is performed, the probability to correctly declare activity if the true DCR = 40% is 82.3%.

Arm 2 dual combination: Based on the prior distribution and decision rules described in Section 10.4, it was explored how likely it is to wrongly declare activity given the true ORR = 10%, and how likely it is to correctly declare activity given the true ORR = 20%, when 41 patients are evaluated:

- If the true ORR = 10%, the probability to wrongly declare activity (i.e. seeing at least 7 responses) is 11.0%.
- If the true ORR = 20%, the probability to correctly declare activity (i.e. seeing at least 7 responses) is 73.9%.

If 7 out of 41 patients have PR or CR, then the posterior risk of the true ORR being in the unacceptable category is 9.8%.

Arm 3 dual combination / Arm A triple combination: Based on the prior distribution and decision rules described in Section 10.4, it was explored how likely it is to wrongly declare activity given the true ORR = 30%, and how likely it is to correctly declare activity given the true ORR = 50%, when 40 patients are evaluated:

- If the true ORR=30%, the probability of wrongly declaring at least moderate efficacy (i.e. at least 16 responses) is 11.5%.
- If the true ORR=50%, the probability of correctly declaring at least moderate efficacy (i.e. seeing at least 16 responses) is 92.3%.

If 16 out of 40 patients have PR or CR, then the posterior risk of the true ORR being in the unacceptable category is 9.0%.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to the Sponsor before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to the Sponsor's monitors, auditors, Sponsor Clinical Quality Assurance representatives, designated agents of the Sponsor, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their eCRFs.

The Sponsor will provide investigators in a separate document with a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by the Sponsor before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Sponsor's monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

For this study, the following ICFs apply:

- Molecular pre-screening consent form (if applicable)
- Study consent form; one for dual study treatment combination and one for triple study treatment combination [the ICF for triple study treatment combination (LGX818 / MEK162 / LEE011) is not applicable for the USA and Singapore].

11.4 Discontinuation of the study

The Sponsor reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.4.

11.5 Publication of study protocol and results

The Sponsor assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

11.6 Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bonafide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

11.7 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in an Array BioPharma-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept

at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines

11.8 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to the Sponsor. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.9 Audits and inspections

Source data/documents must be available to inspections by the Sponsor or designee or Health Authorities.

11.10 Financial disclosures

Financial disclosures should be provided by study personnel who is directly involved in the treatment or evaluation of patients at the site - prior to study start.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact the Sponsor or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by the Sponsor and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the Sponsor, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the Sponsor should be notified of this action and the IRB/IEC/REB at the study site should be informed within 10 working days.

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14 Appendices

14.1 Appendix 1 - Response Evaluation Criteria in Solid Tumors (RECIST 1.1) Harmonization of Efficacy Analysis of Solid Tumor Studies

This document is based on Novartis implementation guidelines version 3.

Glossary

CR	Complete response
CRF	Case Report Form
CT	Computed tomography
DFS	Disease-free survival
eCRF	Electronic Case Report Form
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
FPFV	First patient first visit
GBM	Glioblastoma multiforme
LPLV	Last patient last visit
MRI	Magnetic resonance imaging
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
RAP	Report Analysis Preparation
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Stable disease
SOD	Sum of Diameter
TTF	Time to treatment failure
TTP	Time to progression
UNK	Unknown

14.1.1 Introduction

The purpose of this document is to provide the working definitions and rules necessary for a consistent and efficient analysis of efficacy for oncology studies in solid tumors. This document is based on the RECIST criteria for tumor responses (Therasse 2000) and the revised RECIST guidelines (version 1.1) (Eisenhauer 2009).

This document will not address the use of RECIST 1.1 for glioblastoma multiforme (GBM).

The efficacy assessments described in Section 14.1.2 and the definition of best response in Section 14.1.17 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 14.1.18 is summarizing the “time to event” variables and rules which are mainly derived from internal discussions and regulatory consultations, as the RECIST criteria do not define these variables in detail. Section 14.1.28 of this guideline describes data handling and programming rules. This section is to be referred to in the analysis plan(s) to provide further details needed for programming.

14.1.2 Efficacy assessments

Tumor evaluations are made based on RECIST criteria for tumor responses (Therasse 2000) and the revised RECIST guidelines (version 1.1) (Eisenhauer 2009).

The assessment schedule for tumor assessments is described in Section 7.2.1 of the protocol. Frequency of tumor re-evaluation while on treatment should be adapted to the type and schedule of treatment, and the type of tumor treated.

It is assumed that all information which is considered for assessment of the tumor is captured in the RECIST eCRF, i.e. not merged from several sources.

14.1.3 Definitions

14.1.4 Disease measurability

In order to evaluate tumors throughout a study definitions of measurability are required in order to classify lesions appropriately at baseline. In defining measurability a distinction also needs to be made between nodal lesions (pathological lymph nodes) and non-nodal lesions.

- **Measurable disease** - the presence of at least one measurable nodal or non-nodal lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

For patients without measurable disease see Section 14.1.26.

Measurable lesions (both nodal and non-nodal)

- Measurable non-nodal - As a rule of thumb, the minimum size of a measurable non-nodal target lesion at baseline should be no less than double the slice thickness or 10mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components, that can be evaluated by CT/MRI, can be considered as measurable lesions.
- Measurable nodal lesions (i.e. lymph nodes) - Lymph nodes ≥15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring ≥10mm and <15mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at baseline, regardless of the slice thickness, are normal and not considered indicative of disease.
- Non-measurable lesions - all other lesions are considered non-measurable, including small lesions (longest diameter <10 mm with CT scan or pathological lymph nodes with ≥ 10 to < 15 mm short axis), e.g., blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions.

If any lesion should be handled differently, this must be clearly stated and justified in the protocol, e.g. tumor lesions that are situated in a previously irradiated area might or might not be considered measurable, and the conditions under which such lesions should be considered must be defined in the protocol when appropriate.

14.1.5 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations (e.g. in Phase III studies where PFS is the primary endpoint). However, it is recommended that patients be excluded from trials where the main focus is on the ORR. Guidance on how patients with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in Section 14.1.26.

14.1.6 Methods of tumor measurement - general guidelines

The following considerations are to be made when evaluating the tumor:

- All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- If different window for baseline assessments is allowed in the protocol this must be justified in the protocol.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.
- For optimal evaluation of patients the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If at baseline a patient is known to be allergic to CT contrast or develops allergy during the trial, the following change in imaging modality will be accepted for follow-up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.
- A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change in methodology will result by default in a UNK overall lesion response assessment. However another response assessment than the calculated UNK response may be accepted from the Investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.

If head and neck tumors and those of extremities are evaluated in the study, please specify the methods in detail in the protocol.

- **FDG-PET**: can complement CT scans in assessing progression (particularly possible for ‘new’ disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - No FDG-PET at baseline with a positive FDG-PET at follow-up:

- If the positive FDG-PET at follow-up coITesponds to a new site of disease confinned by CT, this is PD.
- If the positive FDG-PET at follow-up is not confnmed as a new site of disease on CT, additional follow-up CT are needed to dete1mine if there is tiuly progression occuITing at that Site (if so, the date of PD will be the date of the initial abnonnal CT scan).
- If the positive FDG-PET at follow-up coITesponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- **Chest x-ray:** Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and smTounded by aerated lung. However, CT is preferable.
- **Ultrasound:** When the prirna1y endpoint of the study is objective response evaluation, ulti·asound should not be used to measure tmnor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. Ulti·asound might also be useful to confinn the complete disappearance of superficial lesions usually assessed by clinical examination.
- **Endoscopy and laparoscopy:** The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expe1iise that may only be available in some centers. Therefore, the utilization of such techniques for objective tmnor response should be resti·icted to validation pmposes in specialized centers. However, such techniques can be useful in confnming complete pathological response when biopsies are obtained.
- CCI

CCI

If tmnor markers are used in the study for the response assessment, the criteria must be clearly stated in the protocol and the presence of abno1mality in tmnor markers be entered in the eCRF page for RECIST evaluations (see also Section 14.1.8).

- **Cytology and histology:** Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after ti·eatment to differentiate between residual benign lesions and residual malignant lesions in tmnor types such as ge1m cell tmnors). Cytologic confnmation of neoplastic nature of any effusion that appears or worsens during h'eatment is required when the measurable tmnor has met the criteria for response or stable disease. Under such circUlllStances, the cytologic examination of the fluid collected will pennit differentiation between response and stable disease (an effusion may be a side effect of the ti·eatment) or progressive disease (if the neoplastic origin of the fluid is confnmed).

When pathological response is being used, the protocol must clearly state details on how pathological responses are documented.

- **Clinical examination**: Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

If the protocol is considering specific symptoms as objective signs of clinical progression, e.g. bone pain or GI bleeding, then the criteria for clear worsening of these non-measurable 'lesions' indicative of PD should be clearly specified in the protocol. In that case, the protocol should clearly specify that additional criteria are used to complement RECIST criteria.

14.1.7 Baseline documentation of target and non-target lesions

For the evaluation of lesions at baseline and throughout the study, the lesions are classified at baseline as either target or non-target lesions:

- **Target lesions**: All measurable lesions (nodal and non-nodal) up to a maximum of five lesions in total (and a maximum of two lesions per organ), representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). Each target lesion must be uniquely and sequentially numbered on the CRF (even if it resides in the same organ).

Minimum target lesion size at baseline

- **Non-nodal target**: Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination) should be at least 10mm in longest diameter. See Section 14.1.4.
- **Nodal target**: See Section 14.1.4.

A sum of diameters (long axis for non-nodal lesions, short axis for nodal) for all target lesions will be calculated and reported as the baseline sum of diameters (SOD). The baseline sum of diameters will be used as reference by which to characterize the objective tumor response. Each target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

- **Non-target lesions**: All other lesions are considered non-target lesions, i.e. lesions not fulfilling the criteria for target lesions at baseline. Presence or absence or worsening of non-target lesions should be assessed throughout the study; measurements of these lesions are not required. Multiple non-target lesions involved in the same organ can be assessed as a group and recorded as a single item (i.e. multiple liver metastasis). Each non-target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

If the protocol is considering specific symptoms for assessment of the tumor, e.g. bone pain or GI bleeding, then these symptoms are to be entered as non-target lesions with either presence or absence or as a new lesion (based on protocol specified criteria). In that case, the protocol should clearly specify that additional criteria are used to complement RECIST criteria.

For cancers which are known to metastasize in bone, the protocol should specify if and how bone lesions should be handled, e.g. if they are not identified only at baseline and end of study by scintigram but also followed throughout the study by bone X-ray or CT scan.

14.1.8 Follow-up evaluation of target and non-target lesions

To assess tumor response, the sum of diameter for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for the target (Table 14-1) and non-target lesions (Table 14-2) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 14-3) as well as the presence or absence of new lesions.

If tumor markers are used as non-target lesions to evaluate response, please specify criteria for CR, SD and PD in the protocol, e.g. CR='Normalization of tumor marker level', PD='Elevation of tumor markers to certain level', SD='Not qualifying for CR or PD'. These criteria are indication and study specific. In that case, the protocol should clearly specify that additional criteria are used to complement RECIST criteria.

14.1.9 Follow-up & recording of lesions

At each visit and for each lesion the actual date of the scan or procedure which was used for the evaluation of each specific lesion should be recorded. This applies to target and non-target lesions as well as new lesions that are detected. At the assessment visit all of the separate lesion evaluation data are examined by the Investigator in order to derive the overall visit response. Therefore all such data applicable to a particular visit should be associated with the same assessment number.

14.1.10 Non-nodal lesions

Following treatment, lesions may have longest diameter measurements smaller than the image reconstruction interval. Lesions smaller than twice the reconstruction interval are subject to substantial "partial volume" effects (i.e., size may be underestimated because of the distance of the cut from the longest diameter; such lesions may appear to have responded or progressed on subsequent examinations, when, in fact, they remain the same size).

If the lesion has completely disappeared, the lesion size should be reported as 0 mm.

When a tumor does not disappear completely and shrinks to less than the slice thickness a default value should be assigned depending on the slice thickness. With 5 mm contiguous slice thickness, the default value will be 5 mm. Similarly, for a 7 mm slice thickness, the default value will be 7 mm. Actual measurement should be given for all lesions larger than the default value.

In other cases where the lesion cannot be reliably measured for reasons other than its size (e.g., borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

14.1.11 Nodal lesions

A nodal lesion less than 10 mm in size by short axis is considered normal. Lymph nodes are not expected to disappear completely, so a "non-zero size" will always persist.

If a nodal lesion shrinks to less than the slice thickness a default value should be assigned depending on the slice thickness. With 5 mm contiguous slice thickness, the default value will be 5 mm. Similarly, for a 7 mm slice thickness, the default value will be 7 mm. Actual measurement should be given for all lesions larger than the default value.

However, once a target nodal lesion shrinks to less than 10 mm in its short axis, it will be considered normal for response purpose determination. The lymph node measurements will continue to be recorded to allow the values to be included in the sum of diameters for target lesions, which may be required subsequently for response determination.

14.1.12 Determination of target lesion response

Table 14-1 Response criteria for target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm [1]
Partial Response (PR):	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm[2].
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD.
Unknown (UNK)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline.[3]

[1.] SOD for CR may not be zero when nodal lesions are part of target lesions
[2.] Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10mm in size. In this case, the target lesion response is CR
[3.] Methodology change See Section 14.1.6

Notes on target lesion response

Reappearance of lesions: If the lesion appears at the same anatomical location where a target lesion had previously disappeared, it is advised that the time point of lesion disappearance (i.e., the "0 mm" recording) be re-evaluated to make sure that the lesion was not actually present and/or not visualized for technical reasons in this previous assessment. If it is not possible to change the 0 value, then the Investigator/radiologist has to decide between the following three possibilities:

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as progressive disease
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the CRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 14-1 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline). Proper documentation should be available to support this decision.

- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.
- **Missing measurements**: In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is 100mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit is 140mm (with data for 2 other lesions missing) then a PD should be assigned. However, in other cases where a PD cannot definitely be attributed the target lesion response would be UNK.
- **Nodal lesion decrease to normal size**: When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size they should still have a measurement recorded on scans. This measurement should be reported even when the nodes are normal in order not to overstate progression should it be based on increase in the size of nodes.
- **Lesions split**: In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.
- **Lesions coalesced**: Conversely, it is also possible that two or more lesions which were distinctly separate at baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the "merged lesion" should be used when calculating the sum of diameters for target lesions. On the case report form, the diameter of the "merged lesion" should be recorded for the size of one of the original lesions while a size of "0"mm should be entered for the remaining lesion numbers which have coalesced.
- The **measurements for nodal lesions**, even if less than 10mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.
    - Since lesions less than 10mm are considered normal a CR for target lesion response should be assigned when nodal target lesions shrink to less than 10mm and all non-nodal target lesions have disappeared.
    - Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
    - Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion "reappears" or if the absolute sum of the remaining nodal target lesions increases by at least 5mm **and** at least one of those remaining lesions are at least 10mm in size. i.e. if the short axis of a remaining nodal target lesion increases from 5 mm to 10 mm or from 7 mm to 12.5 mm this is called PD, but if it increases from 7 mm to 10 mm it does not qualify for PD.

When both nodal and non-nodal lesions are still present there may be rare occasions when a PD for target lesion response is primarily due to increases in size of nodal lesions but where the target lymph nodes are still all less than 10mm in size. This kind of rare anomaly is acceptable since otherwise the rules for determining target lesion response would become too complex.

14.1.13 Determination of non-target lesion response

Table 14-2 Response criteria for non-target lesions

Response Criteria	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions. In addition, all lymph nodes assigned a non-target lesions must be non-pathological in size (< 10 mm short axis)
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions.[1]
Incomplete Response/ Stable Disease (SD):	Neither CR nor PD
Unknown (UNK)	Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a different method than baseline.

[1.] Although a clear progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the treating physician does prevail and the progression status should be confirmed later on by the review panel (or study chair).

Notes on non-target lesion response

- The response for non-target lesions is **CR** only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e. < 10mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e. ≥ 10 mm) the response can only be '**Incomplete response/Stable disease**' unless any of the lesions was not assessed (in which case response is **UNK**) or there is unequivocal progression of the non-target lesions (in which case response is **PD**).
- **Unequivocal progression**: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. Even in cases where there is no measurable disease at baseline, in order for a PD to be assigned on the basis of non-target lesions the increase in the extent of the disease must be substantial. In studies where the overall non-target lesion response is not recorded but instead the individual status of individual lesions (Absent, Present or Worsened) is determined, if there is unequivocal progression of non-target lesions then at least one of the non-target lesions must be assigned a status of "Worsened". Similarly, an individual non-target lesion should only be assigned a "Worsened" status if there is unequivocal progression of non-target lesions overall.
- Where possible, similar rules to those described in Section 14.1.12 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

14.1.14 New lesions

The appearance of a new lesion is always associated with Progressive Disease (PD) and has to be recorded as a new lesion in the New Lesion CRF page.

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion1
- If new disease is observed in a region which was **not scanned at baseline** or where the particular baseline scan is not available for some reason then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment (see Section 14.1.15).
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ≥ 10mm for the first time in the study plus 5mm absolute increase.

FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 14.1.6.

14.1.15 Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table 14-3.

Table 14-3 Overall lesion response at each assessment

Target lesions	Non-target lesions	New Lesions	Overall lesion response
CR	CR	No	CR[1]
CR	Incomplete response/SD[3]	No	PR
CR, PR, SD	UNK	No	UNK
PR	Non-PD and not UNK	No	PR[1]
SD	Non-PD and not UNK	No	SD[1, 2]
UNK	Non-PD or UNK	No	UNK[1]
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

This overall lesion response also applies when there are no non-target lesions identified at baseline.
[1.] Once confirmed PR was achieved, all these assessments are considered PR.
[2.] As defined in Section 14.1.8

If there are no baseline scans taken at all at baseline then the overall lesion response at each assessment should be considered Unknown (UNK).

If the evaluation of any of the target or non-target lesions identified at baseline could not be made during follow-up, the overall status must be 'unknown' unless progression was seen.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

14.1.16 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 14.1.26 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

14.1.17 Best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

The best overall response will usually be determined from response assessments undertaken while on treatment. However, if any assessments occur after treatment withdrawal the protocol should specifically describe if these will be included in the determination of best overall response and/or whether these additional assessments will be required for sensitivity or supportive analyses. As a default, any assessments taken more than 28 days after the last dose of study therapy will not be included in the best overall response derivation. If any alternative cancer therapy is taken while on study any subsequent assessments would ordinarily be excluded from the best overall response determination. If response assessments taken after withdrawal from study treatment and/or alternative therapy are to be included in the main endpoint determination then this should be described and justified in the protocol.

Where a study requires a response PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met.

Longer intervals may also be appropriate. However, this must be clearly stated in the protocol. The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

- For non-randomized trials where response is the primary endpoint, confirmation is needed.
- For trials intended to support accelerated approval, confirmation is needed.
- For all other trials, confirmation of response may be considered optional.

The best overall response for each patient is determined from the sequence of overall (lesion) responses according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required

- SD = at least one SD assessment (or better) > 6 weeks after randomization/start of treatment (and not qualifying for CR or PR).

The protocol should state if randomization or start of treatment is used as start date (baseline). This is then used in all definitions.

If a different minimum follow-up period is required to classify for overall response= 'stable disease', this must be specified in the protocol.

- PD = progression ≤ 12 weeks after randomization/ start of treatment (and not qualifying for CR, PR or SD).

If PD in a different follow-up period is considered overall response='progressive disease', this must be specified in the protocol.

The protocol should state if discontinuation due to 'Disease progression' or death due to study indication is considered PD even if this was not accompanied by documentation of PD based on tumor measurements. This depends on Phase of the study and the primary endpoint (e.g. Phase III studies in which progression-free survival is primary endpoint should consider only documented PD, whereas Phase I and II studies may consider all clinical deteriorations PD). The following sentence therefore is only applicable if this is specified in the protocol:

- Patients with symptoms of rapidly progressing disease without radiologic evidence will be classified as progression only when clear evidence of clinical deterioration is documented and/or patient discontinued due to 'Disease progression' or death due to study indication.
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks)

Overall lesion responses of CR must stay the same until progression sets in, with the exception of a UNK status. A patient who had a CR cannot subsequently have a lower status other than a PD, e.g. PR or SD, as this would imply a progression based on one or more lesions reappearing, in which case the status would become a PD.

Once an overall lesion response of PR is observed (which may have to be a confirmed PR depending on the study) this assignment must stay the same or improve over time until progression sets in, with the exception of an UNK status. However, in studies where confirmation of response is required, if a patient has a single PR (≥30% reduction of tumor burden compared to baseline) at one assessment, followed by a <30% reduction from baseline at the next assessment (but not ≥20% increase from previous smallest sum), the objective status at that assessment should be SD. Once a confirmed PR was seen, the overall lesion response should be considered PR (or UNK) until progression is documented or the lesions totally disappear in which case a CR assignment is applicable. In studies where confirmation of response is not required after a single PR the overall lesion response should still be considered PR (or UNK) until progression is documented or the lesion totally disappears in which case a CR assignment is applicable.

Example: In a case where confirmation of response is required the sum of lesion diameters is 20 cm at baseline and then 14 cm - 15 cm - 14 cm - 16 cm - 16 cm at the subsequent visits. Assuming that non-target lesions did not progress, the overall lesion response would be PR - SD - PR - PR - PR. The second assessment with 14 cm confirms the PR for this patient. All

subsequent assessments are considered PR even if tumor measurements decrease only by 20% compared to baseline (20 cm to 16 cm) at the following assessments.

If the patient progressed but continues study medication, further assessments are not considered for the determination of best overall response.

Note: these cases may be described as a separate finding in the Clinical Study Report but not included in the best overall response rate.

The best overall response for a patient is always calculated, based on the sequence of overall lesion responses. However, the overall lesion response at a given assessment may be provided from different sources:

- Investigator overall lesion response
- Central Blinded Review overall lesion response
- Calculated overall lesion response (based on measurements from either Investigator or Central Review)

The primary analysis of the best overall response will be based on the sequence of Investigator/central blinded review/calculated (Investigator)/calculated (central) overall lesion responses.

Specify which determination of best overall response will be considered primary (and delete the other terms in the text). If a central blinded review is used (e.g. in an open-label study in which response is the primary endpoint), the best overall response evaluated by the central blinded review will always be considered the primary response.

Based on the patients' best overall response during the study, the following rates are then calculated:

Overall response rate (ORR) is the proportion of patients with a best overall response of CR or PR. This is also referred to as 'Objective response rate' in some protocols or publications.

Disease control rate (DCR) is the proportion of patients with a best overall response of CR or PR or SD.

Another approach is to summarize the progression rate at a certain time point after baseline. In this case, the following definition is used:

Early progression rate (EPR) is the proportion of patients with progressive disease within 8 weeks of the start of treatment.

The protocol should define populations for which these will be calculated. The timepoint for EPR is study specific. EPR is used for the multinomial designs of (Dent and Zee 2001) and counts all patients who at the specified assessment (in this example the assessment would be at 8 weeks ± window) do not have an overall lesion response of SD, PR or CR. Patients with an unknown (UNK) assessment at that time point and no PD before, will not be counted as early progressors in the analysis but may be included in the denominator of the EPR rate, depending on the analysis population used. Similarly when examining overall response and disease control, patients with a best overall response assessment of unknown (UNK) will not be regarded as "responders" but may be included in the denominator for ORR and DCR calculation depending on the analysis population (e.g. populations based on an ITT approach).

14.1.18 Time to event variables

The protocol should state which of the following variables is used in that study.

14.1.19 Progression-free survival

Usually in all Oncology studies, patients are followed for tumor progression after discontinuation of study medication for reasons other than progression or death. If this is not used, e.g. in Phase I or II studies, this should be clearly stated in the protocol. Note that randomized trials (preferably blinded) are recommended where PFS is to be the primary endpoint.

Progression-free survival (PFS) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of last adequate tumor assessment.

14.1.20 Overall survival

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

Overall survival (OS) is defined as the time from date of randomization/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.

14.1.21 Time to progression

Some studies might consider only death related to underlying cancer as an event which indicates progression. In this case the variable "Time to progression" might be used. TTP is defined as PFS except for death unrelated to underlying cancer.

Time to progression (TTP) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to underlying cancer. If a patient has not had an event, time to progression is censored at the date of last adequate tumor assessment.

14.1.22 Time to treatment failure

This endpoint is often appropriate in studies of advanced disease where early discontinuation is typically related to intolerance of the study drug. In some protocols, time to treatment failure may be considered as a sensitivity analysis for time to progression. The list of discontinuation reasons to be considered or not as treatment failure may be adapted according to the specificities of the study or the disease.

Time to treatment failure (TTF) is the time from date of randomization/start of treatment to the earliest of date of progression, date of death due to any cause, or date of discontinuation due to reasons other than 'Protocol violation' or 'Administrative problems'. The time to treatment

failure for patients who did not experience treatment failure will be censored at last adequate tumor assessment.

14.1.23 Duration of response

The analysis following variables should be performed with much caution when restricted to responders since treatment bias could have been introduces. There have been reports where a treatment with a significantly higher response rate had a significantly shorter duration of response but where this probably primarily reflected selection bias which is explained as follows: It is postulated that there are two groups of patients: a good risk group and a poor risk group. Good risk patients tend to get into response readily (and relatively quickly) and tend to remain in response after they have a response. Poor risk patients tend to be difficult to induce a response, may have a longer time to respond, and tend to relapse quickly when they do respond. Potent agents induce a response in both good risk and poor risk patients. Less potent agents induce a response mainly in good risk patients only. This is described in more detail by (Morgan 1988).

It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a responders only descriptive analysis is presented. An analysis of responders should only be performed to provide descriptive statistics and even then interpreted with caution by evaluating the results in the context of the observed response rates... If an inferential comparison between treatments is required this should only be performed on all patients (i.e. not restricting to “responders” only) using appropriate statistical methods such as the techniques described in (Ellis 2008). It should also be stated in the protocol if duration of response is to be calculated in addition for unconfirmed response.

For summary statistics on “responders” only the following definitions are appropriate. (Specific definitions for an all-patient analysis of these endpoints are not appropriate since the status of patients throughout the study is usually taken into account in the analysis).

Duration of overall response (CR or PR): For patients with a CR or PR (which may have to be confirmed the start date is the date of first documented response (CR or PR) and the end date and censoring is defined the same as that for time to progression.

The following two durations might be calculated in addition for a large Phase III study in which a reasonable number of responders is seen.

Duration of overall complete response (CR): For patients with a CR (which may have to be confirmed) the start date is the date of first documented CR and the end date and censoring is defined the same as that for time to progression.

Duration of stable disease (CR/PR/SD): For patients with a CR or PR (which may have to be confirmed) or an SD the start and end date as well as censoring is defined the same as that for time to progression.

14.1.24 Time to response

Time to overall response (CR or PR) is the time between date of randomization/start of treatment until first documented response (CR or PR). The response may need to be confirmed

depending on the type of study and its importance. Where the response needs to be confirmed then time to response is the time to the first CR or PR observed.

Although an analysis on the full population is preferred a descriptive analysis may be performed on the "responders" subset only, in which case the results should be interpreted with caution and in the context of the overall response rates, since the same kind of selection bias may be introduced as described for duration of response in Section 14.1.23. It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a responders only descriptive analysis is presented. Where an inferential statistical comparison is required then all patients should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all patients, patients who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

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

Time to overall complete response (CR) is the time between dates of randomization/start of treatment until first documented CR. Similar analysis considerations including (if appropriate) censoring rules apply for this endpoint described for the time to overall response endpoint.

Indicate in the protocol whether a subgroup analysis of responders only will be performed in addition to the full population analysis (which should be included as default).

14.1.25 Definition of start and end dates for time to event variables

Assessment date

For each assessment (i.e. evaluation number), the **assessment date** is calculated as the latest of all measurement dates (e.g. X-ray, CT-scan) if the overall lesion response at that assessment is CR/PR/SD/UNK. Otherwise - if overall lesion response is progression - the assessment date is calculated as the earliest date of all measurement dates at that evaluation number.

Start dates

State in the protocol if date of randomization or date of start of treatment is to be used for all definitions. For randomized studies specify exactly where the randomization date comes from, e.g. from IVRS, or if start of treatment is used as randomization date. For non-randomized studies please specify which treatment start date is taken if more than one treatment is to be given.

For all "time to event" variables, other than the duration of responses, the randomization/ date of treatment start will be used as the start date.

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

- Date of first documented response is the assessment date of the first overall lesion response of CR (for duration of overall complete response) or CR / PR (for duration of overall response) respectively, when this status is later confirmed.

End dates

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

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

If applicable, if patients who discontinued due to 'Disease progression' are considered to be PD solely based on clinical deterioration, then add the following in the protocol:

When there is no documentation of radiologic evidence of progression, and the patient discontinued for 'Disease progression' due to documented clinical deterioration of disease, the date of discontinuation is used as date of progression.

- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of CR, PR or SD which was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate tumor assessment plus the protocol specified time interval for assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 14.1.26).

Example (if protocol defined schedule of assessments is 3 months): tumor assessments at baseline - 3 months - 6 months - missing - missing - PD. Date of next scheduled assessment would then corresponds to 9 months.

- Date of discontinuation is the date of the EOT visit.
- Date of last contact is defined as the last date the patient was known to be alive. This corresponds to the latest date for either the visit date, lab sample date or tumor assessment date. If available, the last contact date from that survival follow-up page is used. If no survival follow-up is available, the date of discontinuation is used as last contact date.

In comparative studies with long follow-up period and therefore extended visit schedule, it may be useful to collect the survival status at a pre-specified cut-off within a limited timeframe for all patients with no documented death. In this case, this requires a contact to be made with the patient or with any reliable source of information on the patient's status, but not requiring a specific visit to be scheduled

- Date of secondary anti-cancer therapy is defined as the start date of any additional (secondary) antineoplastic therapy or surgery.

If this is applicable for the study, it should be specified in the protocol if new cancer therapy is considered an event or endpoints are censored.

14.1.26 Handling of patients with non-measurable disease only at baseline

It is possible that patients with just non-measurable disease present at baseline are entered into the study, either because of a protocol violation or by design (e.g. Phase III studies with PFS as the primary endpoint). In such cases the handling of response data requires special consideration with respect to inclusion in any analysis of endpoints based on the overall response evaluations.

The protocol should state clearly whether patients with non-measurable disease only at baseline will be allowed into the study. If patients with non-measurable disease only are allowed to be enrolled then the statistical section should describe clearly how data from these patients will be incorporated into the primary analysis and main analyses of the key secondary endpoints. In studies where presence or otherwise of measurable disease is expected to have a relatively large impact on the primary endpoint, this factor can even be considered as a stratification factor in the randomization process.

It is recommended that any patients with only non-measurable disease at baseline should be included in the main (ITT) analysis of each of these endpoints.

For studies which specifically exclude patients with non-measurable disease only at baseline the pre-specified analysis plan should describe how to handle data from these types of patients if they are enrolled by error. It is recommended for these types of studies that patients with non-measurable disease identified through the local site evaluation be included in the list of protocol violations. However, decisions on exclusion from a per protocol analysis should relate to whether the patient has measurable disease according to the primary data source. For example, if the primary data source is from a central independent review then patients with non-measurable disease only according to this central review should be excluded from the relevant per protocol analyses.

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also be incorporated in an appropriate manner. The overall response for patients with measurable disease is derived slightly differently according to Table 14-4.

Table 14-4 Overall lesion response at each assessment: patients with non-target disease only

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

[1] As defined in Section 14.1.8

In general, the **non-CR/non-PD response** for these patients is considered equivalent to an SD response in endpoint determination. In summary tables for best overall response patients with

just non-measurable disease may be highlighted in an appropriate fashion e.g. in particular by displaying the specific numbers with the non-CR/non-PD category.

In considering how to incorporate data from these patients into the analysis the importance to each endpoint of being able to identify a PR and/or to determine the occurrence and timing of progression needs to be taken into account.

For ORR it is recommended that the main (ITT) analysis includes data from patients with only non-measurable disease at baseline, handling patients with a best response of CR as "responders" with respect to ORR and all other patients as "non-responders". Study teams may also want to perform sensitivity analyses excluding patients from the analysis of ORR (e.g. possibly as part of a per-protocol type analysis). Similar considerations should be given to other endpoints which rely on a clear distinction being made between a PR and an SD response.

For PFS, it is again recommended that the main ITT analyses on these endpoints include all patients with just non-measurable disease at baseline, with possible sensitivity analyses which exclude these particular patients. Endpoints such as PFS which are reliant on the determination and/or timing of progression can incorporate data from patients

14.1.27 Sensitivity analyses

This section outlines the possible event and censoring dates for progression, as well is addressing the issues of missing tumor assessments during the study. For instance, if one or more assessment visits are missed prior to the progression event, to what date should the progression event be assigned? And should progression event be ignored if it occurred after a long period of a patient being lost to follow-up? It is important that the protocol and analysis plan specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed.

Based on definitions outlined in Section 14.1.25, and using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics April 2005) as a reference, the following analyses can be considered:

Table 14-5 Options for event dates used in PFS, TTP, duration of response

Situation		Options for end-date (progression or censoring?)[1] (1) = default unless specified differently in the protocol or analysis plan	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment[3]	Censored
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[2]	Progressed Progressed
C1	Progression or death after **exactly one** missing assessment	(1) Date of progression (or death) (2) Date of next scheduled assessment[2]	Progressed Progressed
C2	Progression or death after **two or more** missing assessments	(1) Date of last adequate assessment[2] (2) Date of next scheduled assessment[2] (3) Date of progression (or death)	Censored Progressed Progressed
D	No progression	(1) Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on Investigator claim	(1) N/A (2) Date of discontinuation (visit date at which clinical progression was determined)	Ignored Progressed

Situation		Options for end-date (progression or censoring?)[1] (1) = default unless specified differently in the protocol or analysis plan	Outcome
F	New anticancer therapy given	(1) Date of last adequate assessment (2) Date of secondary anti-cancer therapy (3) Date of secondary anti-cancer therapy (4) N/A	Censored Censored Event Ignored
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP and duration of response)
1=Definitions can be found in Section 14.1.25. 2=After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 14.1.25 3=The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.			

The primary analysis and the sensitivity analyses must be specified in the protocol. Clearly define if and why options (1) are not used for situations C, E and (if applicable) F.

Situations C (C1 and C2): Progression or death after one or more missing assessments: The primary analysis is usually using options (1) for situations C1 and C2, i.e.

- (C1) taking the actual progression or death date, in the case of only one missing assessment.
- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments.

In the case of two or missing assessments (situation C2), option (3) may be considered jointly with option (1) in situation C1 as sensitivity analysis. A variant of this sensitivity analysis consists of backdating the date of event to the next scheduled assessment as proposed with option (2) in situations C1 and C2.

Situation E: Treatment discontinuation due to 'Disease progression' without documented progression: By default, option (1) is used for situation E as patients without documented PD should be followed for progression after discontinuation of treatment. However, option (2) may be used as sensitivity analysis. If progression is claimed based on clinical deterioration instead of tumor assessment by e.g. CT-scan, option (2) may be used for indications with high early progression rate or difficulties to assess the tumor due to clinical deterioration.

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1), i.e. censoring at last adequate assessment may be used as a default in this case.

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g. by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 14-5 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

- **Date of previous scheduled assessment (from baseline)** is the date when a tumor assessment would have taken place, if the protocol assessment scheme was strictly followed from baseline, immediately before or on the date of the last adequate tumor assessment.

In addition, analyses could be repeated using the Investigators' assessments of response rather than the calculated response. The need for these types of sensitivity analyses will depend on the individual requirements for the specific study and disease area and have to be specified in the protocol or RAP documentation.

14.1.28 Data handling and programming rules

The following section should be used as guidance for development of the protocol, data handling procedures or programming requirements (e.g. on incomplete dates).

14.1.29 Study/project specific decisions

For each study (or project) various issues need to be addressed and specified in the protocol or RAP documentation. Any deviations from protocol must be discussed and defined at the latest in the RAP documentation.

The proposed primary analysis and potential sensitivity analyses should be discussed and agreed with the health authorities and documented in the protocol (or at the latest in the RAP documentation before database lock).

14.1.30 Treatment and study completion CRFs

If study drug is discontinued, the **EOT Page** is to be completed with a visit date reflecting the date the discontinuation decision was made, and with the 'Last known date patient took study drug' and one of the following reasons:

- AE(s)
- Abnormal laboratory value(s)
- Abnormal test procedure results(s)
- Protocol violation
- Patient withdrew consent
- Lost to follow-up
- Administrative problems
- Death
- Disease progression
- Treatment duration completed as per protocol (optional, to be used if only a fixed number of cycles is given)

For reasons other than progression (and death) it should be checked if this was not in fact progression (especially reasons AEs, Abnormal laboratory value (s), Abnormal test procedure result and patient withdrew consent). Also it should be checked if patient withdrew consent because of safety issues, in which case reasons AEs, Abnormal laboratory value (s), Abnormal

test procedure result should be used. In such cases where the reason for discontinuation is AE, the AE CRF page must be consistent with the EOT reason provided

All patients who discontinued study drug will be followed for post a treatment evaluation until progression or until a new anticancer therapy is initiated. Patients who discontinued study drug for reasons other than documented progression, death or lost to follow-up will be followed for progression thereafter (patients who withdrew consent might not be followed with regular tumor assessments at the study site, but should ideally be followed until progression outside the study site). Ideally, all patients who discontinued study drug for progression without documented progression will still be followed with regular tumor assessments (e.g. in case of central radiology review).If patient withdraws consent, it must be clearly stated if patient is also withdrawing consent from post treatment evaluations and/or post treatment follow-up assessments. During that evaluation period, usually only tumor measurements (and/or response status) and survival data are collected. In some protocols, the subsequent anti-cancer therapies may also be recorded.

14.1.31 Study evaluation completion

At the end of the study evaluation period, the **study evaluation completion page** is filled out with the following options:

- Patient withdrew consent
- Lost to follow-up
- Administrative problems (when follow-up for progression has met protocol required events, e.g. follow-up stopped at certain number of events or certain time)
- Death
- New cancer therapy (optional, to be used when follow-up for progression is stopped in this case)
- Disease progression

Thereafter, patients will be followed for survival using the survival follow-up pages. If information on death becomes available for patients who were lost to follow-up or withdrew consent, this may also be entered in the database. The reason for death must be documented (and will be coded using MedDRA); it must be also stated if death was due to ‘Study indication’ or ‘Other’ reason.

In comparative studies with long follow-up period and therefore extended visit schedule, it may be useful to collect the survival status at a pre-specified cut-off within a limited timeframe for all patients with no documented death. In this case, this requires a contact to be made with the patient or with any reliable source of information on the patient’s status, but not requiring a specific visit to be scheduled.

Until the specified cut-off point has been reached, the goal is to collect tumor assessments until disease progression for all patients regardless of whether the patients are still receiving study drug. If patients are not followed for progression, e.g. in a Phase I or II study mainly evaluating safety, the evaluation is completed when study drug is completed (in this case only the first completion page is used).

14.1.32 Medical validation of programmed overall lesion response

As RECIST is very strict regarding measurement methods (i.e. any assessment with more or less sensitive method than the one used to assess the lesion at baseline is considered UNK) and not available evaluations (i.e. if any target or non-target lesion was not evaluated the whole overall lesion response is UNK unless remaining lesions qualified for PD), these UNK assessments may be re-evaluated by clinicians at the Sponsor or designee or by external experts. In addition, data review reports will be available to identify assessments for which the Investigators' opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the Investigator response assessment will never be overruled.

If the Sponsor or designee elect to invalidate an evaluation of overall lesion response upon internal or external review of the data, the calculated overall lesion response at that specific assessment is to be kept in a dataset. This must be clearly documented in the RAP documentation and agreed before database lock. This dataset should be created and stored as part of the 'raw' data.

Any discontinuation due to 'Disease progression' without documentation of progression by RECIST criteria should be carefully reviewed. Only patients with documented deterioration of symptoms indicative of progression of disease should have this reason for discontinuation of treatment or study evaluation.

14.1.33 Programming rules

The following should be used for programming of efficacy results:

14.1.34 Calculation of 'time to event' variables

Time to event = end date - start date + 1 (in days)

When no post-baseline tumor assessments are available, the date of randomization/start of treatment will be used as end date (duration = 1 day) when time is to be censored at last tumor assessment, i.e. time to event variables can never be negative.

14.1.35 Incomplete assessment dates

All investigation dates (e.g. X-ray, CT scan) must be completed with day, month and year.

If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and assessment date is calculated as outlined in Section 14.1.25). If all measurement dates have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

14.1.36 Incomplete dates for last contact or death

All dates must be completed with day, month and year. If the day is missing, the 15th of the month will be used for incomplete death dates or dates of last contact.

14.1.37 Non target lesion response

If no non-target lesions are identified at baseline (and therefore not followed throughout the study), the non-target lesion response at each assessment will be considered 'not applicable (NA)'.

14.1.38 Study/project specific programming

The standard analysis programs need to be adapted for each study/project.

14.1.39 Censoring reason

In order to summarize the various reasons for censoring, the following categories will be calculated for each time to event variable based on the treatment completion page, the study evaluation completion page and the survival page.

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up
- For PFS and TTP (and therefore duration of responses) the following censoring reasons are possible:
- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see Table 14-5)
- Death due to reason other than underlying cancer (only used for TTP and duration of response)
- New cancer therapy added (optional; only if the protocol specified that PFS/TTP will be censored at that date)

*Adequate assessment is defined in Section 14.1.25. This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor assessments prior to the cut-off date. The following clarifications concerning this reason should also be noted:-

- This may be when there has been a definite decision to stop evaluation (e.g. reason='Administrative problems' on study evaluation completion page), when patients are not followed for progression after treatment completion or when only UNK assessments are available just prior to data cut-off).

- The reason "Adequate assessment no longer available" also prevails in situations when another censoring reason (e.g. withdrawal of consent, loss to follow-up or alternative anti-cancer therapy) has occurred more than the specified period following the last adequate assessment.
- This reason will also be used for censor in case of no baseline assessment.

14.1.40 References (available upon request)

Dent S, Zee B, Dancey J, et al (2001) Application of a new multinomial phase II stopping rule using response and early progression. J Clin Oncol; 19(3): 785-91.

Eisenhauer EA, Therasse P, Bogaerts J, et al (2009) New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer; 45(2): 228-47.

Ellis S, Carroll KJ, Pemberton K (2008) Analysis of duration of response in oncology trials. Contemp Clin Trials; 29(4): 456-65.

FDA Guidelines: 2005 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005.

FDA Guidelines: 2007 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007.

Morgan TM (1988) Analysis of duration of response: a problem of oncology trials. Control Clin Trials; 9(1): 11-8.

Therasse P, Arbuck SG, Eisenhauer EA, et al (2000) New Guidelines to Evaluate the Response to Treatment in Solid Tumors. J Natl Cancer Inst; 92(3): 205-16.

14.2 Appendix 2 - The 2009 American Joint Committee on Cancer (AJCC) staging system

Table 14-6 The 2009 American Joint Committee on Cancer (AJCC) staging system for malignant melanoma

Stage	Primary tumour (pT)	Lymph nodes (N)	Metastases (M)
IA	< 1 mm, no ulceration,		
	mitoses < 1 mm)2		
IB	< 1 mm, with ulceration or		
	mitoses ‡1mm)2[a]		
	1Æ01-2 mm, no ulceration		
IIA	1Æ01-2 mm, with ulceration		
	2Æ01-4 mm, no ulceration		
IIB	2Æ01-4 mm, with ulceration		
	> 4 mm, no ulceration		
IIC	> 4 mm, with ulceration		
IIIA	Any Breslow thickness,	Micrometastases	
	no ulceration	1-3 nodes	
IIIB	Any Breslow thickness,	Micrometastases	
	with ulceration	1-3 nodes	
	Any Breslow	1-3 palpable	
	thickness, no ulceration	metastatic nodes	
	Any Breslow thickness,	No nodes, but in-transit	
	no ulceration	or satellite metastasis⁄es	
IIIC	Any Breslow thickness,	Up to three palpable	
	with ulceration	lymph nodes	
	Any Breslow thickness,	Four or more nodes or matted	
	with or without ulceration	nodes or in-transit disease	
		+ lymph nodes	
	Any Breslow thickness,	No nodes, but in-transit or	
	with ulceration	satellite metastasis⁄es	
IV, M1a			Skin, subcutaneous or
			distant nodal disease
IV, M1b			Lung metastases
IV, M1c			All other sites or any other sites of metastases
			with raised lactate dehydrogenase

[a] In the rare circumstances where mitotic count cannot be accurately determined, a Clark level of invasion of either IV or V can be used to define T1b melanoma. Every patient with melanoma should be accurately staged using the AJCC system; this may include performing a sentinel lymph node biopsy when this is recommended by the Specialist Skin Cancer Multidisciplinary Team. Staging should be updated following relapse.

14.3 Appendix 3 - Guidelines for the treatment of study drug combination induced skin toxicity

[Any language regarding the triple combination of LGX818/MEK162/LEE011 in this Section is <u>not</u> applicable to the USA and Singapore]

14.3.1 Rash

Skin disorder/rash has been observed in the ongoing studies of single-agent LGX818 and MEK162 and thus is recognized as a potential overlapping toxicity associated with the concurrent use of both compounds. The majority of these events were CTCAE Grade 1 or 2, but also dose-limiting as Grade 3 at the 80mg BID dose for MEK162.

The results of the STEPP study (Mitchell 2009; Piperdi 2009) support the use of pre-emptive skin treatment for patients at risk of treatment induced skin toxicity. In this study, the pre-emptive skin treatment regimen reduced the incidence of specific CTCAE Grade ≥ 2 skin toxicity by more than 50% as compared to the group who received only reactive skin toxicity treatment. In this study, patients will not initially receive prophylactic treatment for skin toxicity during Cycle 1. However, prophylactic treatment for skin toxicity may be introduced in subsequent cycles of treatment and in new patients if at least one patient has experienced CTCAE Grade 3 or greater skin toxicity, or if at least two patients have experienced such toxicities that are CTCAE Grade ≥ 2. Prophylactic supportive therapy for skin toxicity (i.e. initiated 24 hrs prior to study drug combination) including skin moisturizers, sunscreen (PABA free, SPF ≥ 15, UVA/UVB protection), topical steroid (1% hydrocortisone cream), and doxycycline (100 mg BID) may be initiated in all patients at the dose levels where these toxicities have been observed and may be advised to all further patients. Effective medications also include antihistamines, topical corticosteroids and low-dose systemic corticosteroids (the latter should be used with caution due to the increased risk of hyperglycemia).

The treatment algorithm is as follows:

Mild Rash (CTCAE Grade 1)

- Treatment with LGX818 and MEK162 or LGX818 and MEK162 and LEE011 should be maintained at the current dose.
- Topical hydrocortisone (1% or 2.5% cream) for macular rash and/or topical clindamycin (1%) for pustular rash is recommended.
- The patient should be reassessed after 2 weeks.

Moderate Rash (CTCAE Grade 2)

- Treatment with LGX818 and MEK162 or LGX818 and MEK162 and LEE011 should be maintained at the current dose, and the rash should be closely monitored for change in severity.
- Doxycycline or minocycline are not recommended due to phototoxicity and should be replaced with oxytetracycline or lymecycline. However, if doxycycline or minocycline are used, precaution measurements should be taken (i.e., avoid direct exposure on sun, use of sunglasses, sunscreen, ect.). The recommendation is: topical clindamycin (1%) plus either

hydrocortisone (2.5% cream) or pimecrolimus (1% cream) plus oxytetracycline (500 mg twice daily) or lymecycline (408 mg QD).

Severe Rash (CTCAE Grade 3-4)

CTCAE Grade 3

- The dose of LGX818 and MEK162 or LGX818 and MEK162 and LEE011 should be omitted until resolved to CTCAE Grade ≤ 1, in line with protocol recommendations, and the rash should be closely monitored for any change in severity.
- In addition to the interventions recommended for moderate rash, prednisolone may be given (with caution due to risk of hyperglycemia) as a reducing dose regimen (25 mg for 7 days, subsequently decreasing the dose by 5 mg/day every day to 0).
- If skin toxicity CTCAE Grade 3 is not resolved within 7 days, discontinue patient from study drug treatment.

CTCAE Grade 4

- If skin toxicity CTCAE Grade 4 occurs the dose of LGX818 and MEK162 or LGX818 and MEK162 and LEE011 should be omitted and patients discontinued from study drug treatment.

Table 14-7 Treatment of skin toxicity

Mild Rash (Grade 1) Dry Skin Nail changes Pruritus Desquamation Acneiform	Topical hydrocortisone 1% or 2.5% and/or Clindamycin 1% gel
Moderate Rash (Grade 2) Dry Skin Nail changes Pruritus Desquamation Acneiform	Topical clindamycin (1%) plus either hydrocortisone (2.5% cream) or pimecrolimus (1% cream) plus oxytetracycline (500 mg twice daily) or lymecycline (408 mg QD).
Severe Rash (Grade 3-4) Dry Skin Nail changes Pruritus Desquamation Acneiform	Hydrocortisone 2.5% cream or Clindamycin 1% gel or Pimecrolimus 1% cream plus oxytetracycline (500 mg twice daily) or lymecycline (408 mg QD) plus prednisolone (with caution due to risk of hyperglycemia) (25 mg for 7 days, decreasing the dose by 5 mg/day every day).
Adapted from Thatcher 2009.	

14.3.2 Hand Foot Skin Reaction

As HFSR has been reported in some patients during LGX818 treatment, it is recommended that patients are educated prior to starting study treatment which activities to avoid and on supportive measures for prevention and/or management of HFSR. Recommendations are summarized below in Table 14-8. Furthermore, the patient should be treated at the first symptoms according the institutional standards of care. A visit at a podiatrist may also be recommended at the discretion of the investigator.

Table 14-8 Supportive care for the prevention and management of HFSR

Stage	Recommendations
Prior to treatment	Educate the patient about the early signs and symptoms of HFSR and discuss the importance of early reporting.
Prevention of HFSR	Monitor the patient for signs and symptoms of HFSR. Instruct the patient to: - Apply emollient cream regulary to hands and feet - Avoid skin irritants (e.g. perfumes, alcohol, harsh cleaning agents) - Wear cotton socks or gloves to bed to enhance the absorption of creams - Avoid tight, irritating or ill-fitting clothing and shoes[a] - Avoid the use of band aides or other types of adhesive bandages or tape - Avoid repetitive activity or staying in one position for long periods of time - Keep the skin uncovered when possible to minimize perspiration - Wear rubber gloves while doing dishes - Pat (do not rub) skin dry with towels - Avoid extremes of temperature, pressure and friction - Avoid performing mechanically stressful manual work - Minimise exposure to strong, direct sunlight - Elevate affected limbs
Treatment of HFSR	1) Ensure that patient follows treatment interruption or dosage reduction guidelines 2) Monitor the patient for progression/resolution of HFSR 3) Prescribe analgesics if necessary 4) Instruct the patient to: - Continue the use of prevention strategies - Cushion sore skin - Submerge hands and feet in cool water baths or apply cold compresses for relief
[a] Wear loose-fitting clothing made of soft, natural fabrics and shoes that are wide and comfortable. Avoid tight belts, panties and bras. This Table is adapted from (van Moos et al 2008).	

14.3.3 References (available upon request)

Mitchell EP, Lacouture M, Shearer H (2009) Final STEPP results of prophylacatic versus reactive skin toxicity (ST) treatment (tx) for panitumumab (pmab)-related ST in patients (pts) with metastatic colorectal cancer (mCRC). J Clin Oncol; 27:18s, (suppl; abstr CRA4027).

Van Moos R, Thuerlimann B, Chair M , et al (2008) Pegylated liposomal doxorubicin-associated hand-foot syndrome: Recommendations of an international panel of experts. Eur J Cancer; 1016: 1-10.

Piperdi B, Mitchell EP, Lacouture M, et at (2009) STEPP, an open-label, randomized study of pre-emptive (P) versus reactive (R) skin toxicity (ST) treatment (tx) in metastatic colorectal cancer (mCRC) patients (pts) receiving panitumumab (pmab) + FOLFIRI or irinotecan-based (Iri) chemotherapy (CT) as second-line tx: Results by CT and *KRAS* status. ASCO 2009 Gastrointestinal Cancers Symposium. Poster presentation Abstract No: 394.

Thatcher N, Nicolson M, Groves RW, et al (2009) Expert Consensus on the Management of Erlotinib-Associated Cutaneous Toxicity in the U.K. Oncologist; 14(8): 840-7.

14.4 Appendix 4 - List of concomitant medications prohibited or to be used with caution for dual and triple combination

[Any language regarding the triple combination of LGX818/MEK162/LEE011 in this Section is <u>not</u> applicable to the USA and Singapore]

Table 14-9 Narrow therapeutic index substrates of CYP3A4*, CYP2B6, CYP2C9 prohibited or to be administered with caution

The information presented on sensitive and narrow TI substrates is a compilation of the University of Washington Drug-Drug Interaction (DDI) database and FDA DDI guidance. This list might not be exhaustive.

	Sensitive Substrates	**Narrow TI Substrates**
CYP1A2	Alosetron, duloxetine, melatonin, ramelteon, tacrine, tizanidine	Theophylline, tizanidine
CYP3A4*	budesonide, buspirone, eplerenone, eletriptan, felodipine, fluticasone, lovastatin, midazolam, saquinavir, sildenafil, simvastatin, triazolam, vardenafil	alfentanil, astemizole(a), cisapride(a), cyclosporine, diergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine(a)
CYP2B6	bupropion, efavirenz	Not Applicable
CYP2C9	NA	warfarin, phenytoin
Reproduced from fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm081177.htm#4* prohibited for patients treated with the triple combination		

Table 14-10 List of CYP inhibitors and inducers prohibited or to be used with caution

The information presented on inhibitors and inducers is a compilation of the University of Washington Drug-Drug Interaction (DDI) database and FDA DDI guidance. This list might not be exhaustive

Strong CYP3A4*,5,7 inhibitors (AUC > 5-fold increase)			
Itraconazole	Ketoconazole	Mibefradil	Nefazodone
Nelfinavir	Posaconazole	Ritonavir	Saquinavir
Telithromycin	Troleandomycin	Voriconazole	Boceprevir
Clarithromycin	conivaptan	indinavir	lopinavir
Grapefruit juice (citrus paradisi fruit juice)	telaprevir	cobicistat	
Moderate CYP3A4,5,7 inhibitors (AUC ≥ 2-fold increase and < 5-fold increase)			
Amprenavir	Atazanavir	Cimetidine	Ciprofloxacin
Diltiazem	dronedarone	Fluconazole	erythromycin
Imatinib	Schisandra Sphenanthera	Tofisopam	Verapamil
aprepitant	casopitant	cyclosporine	darunavir
fosamprenavir			
Strong & Moderate CYP3A4 inducers (AUC ≥ 2-fold increase)**			
Avasimide	Bosentan	Carbamazepine	Efavirenz
Etravirine	Modafenil	Nafcillin	Nevirapine
Phenobarbital	Phenytoin	Rifabutin	Rifampin (Rifampicin)
Ritonavir	St. John's wort	Talviraline	
Strong & Moderate CYP1A2 inhibitors (AUC ≥ 2-fold increase)			
Clinafloxacin	Enoxacin	Etintidine	Fluvoxamine
Idrocilamide	Methoxsalen	Mexiletine	Oltipraz
Oral contraceptives	Phenylpropanolamine	Pipemidic acid	Propranolol
Rofecoxib	Thiabendazole	Zafirlukast	Zileuton
CYP1A2 inducers			
Tobacco			
Strong & Moderate CYP2C19 inhibitors (AUC ≥ 2-fold increase)			
Fluconazole	Fluvoxamine	Fluoxetine	Moclobemide
Omeprazole	Ticlopidine	Voriconazole	
CYP2C19 inducers			
Rifampin			

This database of CYP inhibitors and inducers was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table, the University of Washington's Drug Interaction Database, and the FDA's "Guidance for Industry, Drug Interaction Studies."* prohibited for patients treated with the dual and triple combination
** prohibited for patients treated with the triple combination

Table 14-11 List of BCRP substrates, BSEP inhibitors, P-gp inhibitors/inducers, and MATE1/2, P-gp, OAT1, OAT3, OCT1, OCT2, OATP1B1 and OATP1B3 substrates to be used with caution

The information presented on transporter substrates, inducers and inhibitors is a compilation of the University of Washington Drug-Drug Interaction (DDI) database and FDA DDI guidance. This list might not be exhaustive.

Category	Drug Name
BCRP substrates	atorvastatin, daunorubicin, doxorubicin, ethinyl estradiol, hematoporphyrin, imatinib, methotrexate[6], mitoxantrone, pitavastatin[6], rosuvastatin[6], SN-38 (irinotecan), simvastatin, sulfasalazine, sofosbuvir[1], topotecan[1], sulfasalazine[1]
BSEP	Vinblastine
Strong BSEP inhibitors	Alectinib, atazanavir, bromocriptine, bosentan, clofaziminie, cerivastatin, fusidate, glibenclamide, glyburide, nefazadone, paritaprevir, pioglitazone, reserpine, rosiglitazone, sulindac, troglitazone (TGZ-sulfate), valinomycin
NTI substrates of P-gp[1]	digoxin, quinidine, paclitaxel, cyclosporine, sirolimus, tacrolimus, fentanyl, phenytoin
Substrates of P-gp (≥2X AUC change)[2]	aliskiren, ambrisentan, atorvastatin, atorvastatin acid, azithromycin, cerivastatin, colchicine, CP-481,715, cyclosporine, dabigatran, digoxin, docetaxel, domperidone, doxorubicin, fentanyl, fexofenadine, lapatinib, linezolid, loperamide, maraviroc, nevirapine, paclitaxel, proguanil, quinidine, ranolazine, ritonavir, saquinavir, simvastatin, sirolimus, sofosbuvir, tacrolimus, ticagrelor, voclosporin
Substrates of P-gp mentioned in US label[3]	afatinib, alfuzosin, aliskiren, alogliptin, ambrisentan, apixaban, apremilast, aprepitant, boceprevir, bosentan, carvedilol, carvedilol, caspofungin, ceritinib, citalopram, colchicine, cyclosporine, dabigatran, digoxin, doxepin, doxorubicin, eribulin, everolimus, fidaxomicin, fluvastatin, fosamprenavir, gatifloxacin, idelalisib, iloperidone, indacaterol, irbesartan, lacosamide, lapatinib, levetiracetam, levofloxacin, linagliptin, losartan, maraviroc, mirabegron, moxifloxacin, naloxegol, nateglinide, nintedanib, olodaterol, pantoprazole, paroxetine, pazopanib, posaconazole, pravastatin, quinine, ranolazine, riociguat, risperidone, rivaroxaban, saquinavir, silodosin, simeprevir, sirolimus, sitagliptin, sorafenib, telaprevir, tenofovir, ticagrelor, tipranavir, tolvaptan, topotecan, umeclidinium, valsartan, vardenafil, vincristine, voriconazole
P-gp inhibitors	alogliptin, amiodarone[4], azithromycin[4], canaglifozin, captopril[4], carvedilol[4], clarithromycin[4], conivaptan[4], cremophor RH40, curcumin, diltiazem[4], dronedarone[4], elacridar[4], erythromycin[4], felodipine[4], fluvoxamine[4], ginko[4,5], indinavir[4], indinavir/ritonavir[4], itraconazole[4], ketoconazole, lapatinib, lopinavir/ritonavir, mibefradil[4], milk thisle[4,5], mirabegron, nelfinavir[4], nifedipine[4], nitredipine[4], paroxetine[4], propafenone, quercetin.[4], quinidine[4], ranolazine[4], rifampin[4], ritonavir[4], sequinavir/ritonavir[4], *schisandra chinesis* extract[4,5], simepravir, St. John's wort extract[4,5], talinolol[4], telaprevir[4], telmisartan[4], ticagrelor[4], tipranavir/ritonavir[4], tolvaptan[4], valspodar, vandetanib, verapamil[4], voclosporin, Zosuquidar LY335979
P-gp Inducers	avasimibe, carbamazepine, efavirenz, genistein[2], phenytoin, quercetin[2], rifampin, St. Johns wort extract[5]
OCT1/2 substrates[7]	, Amantadine, , 6-beta-hydroxycortisol, carboplatin, cisplatin, cephalexin, cephradine, ipratropium, lamivudine, linagliptin, metformin, oxyplatin, oxybutynin, phenformin, picoplatin, pilsicainide, pindolol, ranitidine, sorafenib, tropisetron, trospium, umeclidinium, zidovudine
MATE1/2 substrates[3,8]	Acyclovir, cephalexin, cimetidine, fexofenadine, ganciclovir, glycopyrronium, metformin, pindolol, plisicainide, ranitidine, topotecan, varenicline
OAT1	Adefovir, captopril, furosemide, lamivudine, methotrexate, oseltamivir, tenofovir, zalcitabine, zidovudine
OAT3	Acyclovir, bumetanide, ciprofloxacin, famotidine, furosemide, methotrexate, zidovudine, oseltamivir acid, (the active metabolite of oseltamivir), penicillin G, pravastatin, rosuvastatin, sitagliptin

Category	Drug Name
OATP1B1 substrates	ambrisentan, anacetrapib asunaprevir, atorvastatin, atrasentan, benzylpenicillin, bosentan, bromociptine, caspofungin, cerivastatin, danoprevir, empangliflozin, enalapril, ezetimibe, fexofenadine, fimasartan, fluvastatin, maraviroc, methotrexate, olmesartan, pitavastatin, pravastatin, repaglinide, rifampicin, rosuvastatin, simvastatin acid, SN-38; temocapril, troglitazone, valsartan
OATP1B3 substrates	asunaprevir, atrasentan, bosentan, danoprevir, digoxin, docetaxel, empangliflozin, enalapril, erythromycin, fexofenadine, fluvastatin, imatinib, methotrexate, olmesartan, ouabain, paclitaxel, pitavastatin, pravastatin, rifampicin, rosuvastatin, telmisartan, SN-38; thyroxine (T4), valsartan

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[1] These drugs have both a narrow therapeutic index and an *in vivo* DDI outcome ascribed at least in part ascribed to P-gp (inhibition or induction) that exceeds a 20% change in AUC.

[2] These drugs have *in vivo* DDI outcomes (inhibition) which are ≥2x increase in AUC and are at least in part ascribed to P-gp.

[3] The US labels for these drugs have specific language on *in vivo* P-gp substrate status.

[4] Dual P-gp and CYP3A4 inhibitor

[5] Herbal medication.

[6] Have been shown to have DDI in vivo, others are reported as substrates *in vitro*.

[7] OCT1 and OCT2 share considerable substrate specificity.

[8] MATE1 and MATE2 share considerable substrate specificity.

Table 14-12 List of QT prolonging drugs

This list might not be exhaustive.

TdP Risk	Generic Name
Known[1]	Amiodarone, anagrelide, arsenic trioxide, astemizole, azithromycin, bepridil, chloroquine, cocaine, chlorpromazine, cilostazol, ciprofloxacin, cisapride, citalopram, clarithromycin, disopyramide, dofetilide, domperidone, donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, gatifloxacine, grepafloxacin, halofantrine, haloperidol, ibutilide, levofloxacin, levomethadyl, mesoridazine, methadone, moxifloxacin, ondansetron (i.v. only), oxaliplatin, papaverine HCl, pentamidine, pimozide, probucol, procainamide, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sparfloxacin, sulpiride, terfenadine, thioridazine, vandetanib
Possible[2]	Alfuzosin, apomorphine, aripiprazole, artenimol+piperaquine ,atazanavir, atomoxetine, asenapine, bedaquiline, bortezomib, buprenorphine, capecitabine, ceritinib, clomipramine, crizotinib,,clozapine, cyamemazine (cyamepromazine), dabrafenib, dasatinib, degarilix, delamanid, desipramine, dexmedetomidine, dolasetron, eribulin, ezogabine, famotidine, felbamate, fingolimod, foscarnet, gatifloxacin, gemifloxacin, granisetron, hydrocodone-ER, iloperidone, imipramine (melipramine), isradipine, , lapatinib, lenvatinib, leuprolide, loperamide, lithium, mifepristone, mirabegron, mirtazapine, moexipril, norfloxacin, nortriptyline, ofloxacin, olanzapine, osimirtinib, ondansetron (p.o. only at 4 mg or 8 mg), oxytocin, paliperidone, panabinostat, pasireotide, pazopanib, pipamperone, promethazine, quetiapine, ranolazine, rilpivirine, risperidone, roxithromycin, sertindole, sorafenib, sunitinib, telavancin, tetrabenazine, tizanidine, tolterodine, toremifene, tramadol, trimipramine, vardenafil, vemurafenib, venlafaxine, vorinostat, ziprasidone
Conditional[3]	Amantadine, amisulpride, amitriptyline, amoxapine, chloral hydrate, diphenhydramine, doxepin, fluoxetine, furosemide (frusemide), galantamine, hydrochlorothiazide, Hydroxychloroquine hydroxyzine, indapamide, itraconazole, ivabradine (on non US mkt), ketoconazole, metoclopramide, metronidazole, nelfinavir, pantoprazole, paroxetine, posaconazole, quinine sulfate, ritonavir, sertraline, solifenacin, telaprevir, torsemide (torasemide), trazodone, voriconazole

[1] Known risk: Substantial evidence supports the conclusion that these drugs prolong the QT interval AND are clearly associated with a risk of TdP, even when taken as directed in official labeling

[2] Possible risk: Substantial evidence supports the conclusion that these drugs can cause QT prolongation BUT there is insufficient evidence at this time that these drugs, when used as directed in official labeling, are associated with a risk of causing TdP.

[3] Conditional risk: Substantial evidence supports the conclusion that these drugs are associated with a risk of TdP BUT only under certain conditions (e.g. excessive dose, hypokalemia, congenital long QT or by causing a drug-drug interaction that results in excessive QT interval prolongation).

14.5 Appendix 5 – Statistical methodology LGX818 and MEK162 dual combination

14.5.1 Prior Distributions of 5 parameter dual combo (LGX818+MEK162) model

LGX818 (cps): The initial prior parameters for the capsule of the single agent are as specified in study [CLGX818X2101]. Detailed derivation of this prior distribution can be found in the protocol of CLGX818X2101, Section 10.4.2.

Using a meta-analytic predictive approach, an assumption about heterogeneity between trial [CLGX818X2101] and the current combination trial is captured in the prior distributions of the standard deviation of the model parameters ($\log(\alpha_1)$,$\log(\beta_1)$), denoted by τ_1 and τ_2. Both τ_1 and τ_2 were assumed to follow a log-normal distribution with mean log(0.25) and standard deviation 0.01, assuming moderate between-trial heterogeneity. This new distribution is then used as the prior distribution for the model parameters ($\log(\alpha_1)$,$\log(\beta_1)$).

MEK162: An informative bivariate normal prior for the model parameters ($\log(\alpha_2)$,$\log(\beta_2)$) is obtained as follows:

As a first step, a non-informative prior for ($\log(\alpha_2)$,$\log(\beta_2)$) was defined as follows:

- The median DLT rate at the reference dose (60mg) was assumed 1/3, i.e. $\text{mean}(\log(\alpha_{2,\text{fasted}})) = \log(1/2)$
- A doubling in dose was assumed to double the odds of DLT, i.e. $\text{mean}(\log(\beta_2)) = 0$
- The standard deviations of the two parameters were set to 2, such that the bivariate normal distribution covers approximately 95% of the probability space.
- The correlation between the two parameters was set to 0, assuming independence.

Data from the 15 patients eligible for the DDS of on-going study [ARRAY-162-111] was added into a 2-parameter BLRM for single agent.

The assumption about heterogeneity is captured in the prior distributions of the standard deviation of ($\log(\alpha_2)$,$\log(\beta_2)$), denoted by τ_1 and τ_2. Both τ_1 and τ_2 are assumed to follow a log-normal distribution with mean log(0.25) and standard deviation 0.01, assuming moderate between-trial heterogeneity.

The updated model parameters are estimated via simulation from the posterior distribution. This distribution is then used as the prior distribution for the parameters ($\log(\alpha_2)$,$\log(\beta_2)$).

Table 14-13 Data from ARRAY-162-111

Dose of MEK162 (mg, bid)	No of DLTs / No of evaluable patients
30	0/3
45	0/3
60	0/6
80	2/3

A weakly informative prior reflecting the current uncertainty about the toxicity of the combination treatment is used for η_{12}. In order to allow for the potentiality of both synergy and antagonism of the safety profiles, it was assumed that η_{12} is normally distributed with median

= 0 (no increase on odds of DLT, i.e. independence) and 97.5th percentile = log(20) (20-fold increase on odds of DLT).

The prior distributions of 5 parameter dual combo (LGX818+MEK162) model are provided in Table 14-14.

Table 14-14 Predictive distribution of model parameters

Parameter	Means	Standard deviations	Correlation
$\log(\alpha_1)$, $\log(\beta_1)$	-1.415, 0.463	1.231, 1.273	0.003
$\log(\alpha_2)$, $\log(\beta_2)$	-2.326, 1.564	1.107, 1.368	-0.535
η_{12}	0	1.528	N/A

For LGX818X2101, data up to dose escalation teleconference from 23/Nov/2011
Predictive: between-trial heterogeneity $\tau_1 \sim \text{lognormal}(\log(0.25), 0.01^2)$, $\tau_2 \sim \text{lognormal}(\log(0.25), 0.01^2)$ for $\log(\alpha_1)$, $\log(\beta_1)$, and $\tau_1 \sim \text{lognormal}(\log(0.25), 0.01^2)$, $\tau_2 \sim \text{lognormal}(\log(0.25), 0.01^2)$ for $\log(\alpha_2)$, $\log(\beta_2)$

A summary of the respective prior distribution of DLT rates for dual combo (LGX818+MEK162) is given in Table 14-15. Dose combinations not satisfying the overdose criteria, i.e. not eligible at the start of the study, are displayed in bold.

Note: the model was re-evaluated before the first dose escalation meeting with the available data from study [CLGX818X2101].

Table 14-15 Summary of prior probabilities of DLT rates

LGX818 (mg)	Prior probabilities that Pr(DLT) is in interval:			Mean	SD	Quantiles		
	[0.0, 0.16)	[0.16, 0.35)	[0.35,1.00]			2.50%	50.00%	97.50%
	MEK162 = 30mg							
50	0.674	0.206	0.12	0.147	0.166	0	0.086	0.616
100	**0.379**	**0.29**	**0.331**	**0.288**	**0.226**	**0.018**	**0.226**	**0.824**
150	**0.231**	**0.199**	**0.571**	**0.472**	**0.32**	**0.021**	**0.433**	**0.999**
200	**0.203**	**0.152**	**0.644**	**0.551**	**0.347**	**0.017**	**0.573**	**1**
250	**0.198**	**0.124**	**0.679**	**0.595**	**0.361**	**0.011**	**0.677**	**1**
300	**0.198**	**0.105**	**0.697**	**0.621**	**0.37**	**0.007**	**0.754**	**1**
	MEK162 = 45mg							
50	0.615	0.231	0.154	0.173	0.18	0.001	0.109	0.668
100	**0.365**	**0.254**	**0.381**	**0.319**	**0.256**	**0.014**	**0.249**	**0.891**
150	**0.255**	**0.165**	**0.58**	**0.489**	**0.342**	**0.011**	**0.466**	**0.999**
200	**0.238**	**0.123**	**0.639**	**0.559**	**0.37**	**0.006**	**0.616**	**1**
250	**0.238**	**0.098**	**0.664**	**0.596**	**0.385**	**0.003**	**0.722**	**1**
300	**0.242**	**0.083**	**0.675**	**0.616**	**0.395**	**0.001**	**0.798**	**1**
	MEK162 = 60mg							
50	**0.453**	**0.297**	**0.25**	**0.242**	**0.202**	**0.016**	**0.182**	**0.754**
100	**0.313**	**0.221**	**0.466**	**0.379**	**0.289**	**0.013**	**0.316**	**0.946**
150	**0.255**	**0.137**	**0.608**	**0.521**	**0.36**	**0.006**	**0.532**	**1**
200	**0.252**	**0.102**	**0.645**	**0.577**	**0.386**	**0.002**	**0.68**	**1**
250	**0.259**	**0.082**	**0.66**	**0.603**	**0.401**	**0.001**	**0.78**	**1**
300	**0.267**	**0.068**	**0.665**	**0.618**	**0.412**	**0**	**0.846**	**1**

Prior specifications of LGX818 New Regimen

If a different regimen (BID and/or every-other-day) for LGX818 is explored in this study, then two models will be fitted independently for the different dosing regimens. The dose escalation for the originally planned regimen will be guided by the model described previously. The dose escalation for the new regimen (NR) will be guided by a model using the same mathematical relationship as the one for the originally planned regimen but with different prior distributions based on a meta-analytic predictive approach. Details are given in Section 14.5.3.1.

Prior specifications for the MEK162 smaller tablet / new MEK162 tablet variant if to be evaluated for MTD/RP2D in MEK162X2110 patients

If it is decided that the MTD/RP2D of the LGX818 and MEK162 combination will need to be established with one or both of the two new MEK162 tablet variants, then all updated DLT data from the patients treated with the original tablet will be incorporated into a weakly informative prior distribution for MEK162 (smaller tablet /new tablet variant) using a meta-analytic predictive approach. Between variant variability will be assessed using the data from [CMEK162A2101] and [CMEK162X2108] and a down-weighting factor will be used to down-

weight the original tablet data. The assumption about the heterogeneity between the two tablet variants will be captured in the prior distributions of the standard deviations of (log(α),log(β)), denoted by $\tau(\tau_1, \tau_2)$. A mixture prior with high or low tox components may be used to add robustness to the model. The equivalent dose of the MEK162 smaller tablet and/or new MEK162 tablet variant with respect to the original MEK162 tablet will be calculated based on the bioavailability ratio from relative bioavailability study or relative PK from first dose cohort prior to first DETC. More details of this process will be provided at the dose-escalation teleconference and will be reported in the statistical appendix, Section 16.1.9 of the CSR.

14.5.2 Data from the ongoing study LGX818X2101

Table 14-16 Data from LGX818X2101- as of 23/Nov/2011

Dose of LGX818 (mg)	Nr. DLTs / Nr. evaluable patients
100 (micro-emulsion)	1/4

14.5.3 LGX818 change in regimen

If a different regimen (BID and/or every-other-day) for LGX818 is explored in this study, then two models will be fitted independently for the different dosing regimens. The dose escalation for the originally planned regimen will be guided by the model described on Section 10.4.2.1. The dose escalation for the new regimen (NR) will be guided by a model using the same mathematical relationship as the one for the originally planned regimen but with different prior distributions based on a meta-analytic predictive approach.

The parameters in the model for the new regimen (NR) will be denoted by γ_1, δ_1 for the LGX818 NR, by γ_2, β_2 for MEK162 BID, and by η_{NR} for the interaction parameter. The respective total daily doses will be denoted by b_1 and b_2, respectively. This model can thus be expressed as:

$\text{logit}(\mu_1(b_1)) = \log(\gamma_1) + \delta_1 \log(b_1/b_1^*)$

$\text{logit}(\mu_2(b_2)) = \log(\gamma_2) + \delta_2 \log(b_2/b_2^*)$

$\text{Odds}(\mu_{12}(b_1,b_2))) = \mu_{12}(b_1,b_2)/(1-\mu_{12}(b_1,b_2))$

$= \exp(\eta_{NR} b_1/b_1^* b_2/b_2^*)(\mu_1(b_1)+\mu_2(b_2) - \mu_1(b_1)\mu_2(b_2))/((1-\mu_1(b_1))(1-\mu_2(b_2))),$

where $b_1^* = 100$mg (NR) and $b_2^* = 60$mg (BID).

14.5.3.1 Prior specifications for LGX818 new regimen

At the time when a NR is introduced, the prior distribution for the parameters γ_1, δ_1, γ_2, δ_2 and η_{NR} will be derived in the following way:

γ_1, δ_1:

The posterior means, standard deviations and correlation of $\log(\alpha_1)$, $\log(\beta_1)$ incorporating all the data available at the time when a NR is introduced will be found via simulation.

The assumption about heterogeneity will be captured in the prior distributions of the standard deviation of $(\log(\gamma_1),\log(\delta_1))$, denoted by τ_1 and τ_2. Both τ_1 and τ_2 follow a log-normal distribution with mean log(0.2) and standard deviation 0.01, assuming small to moderate between-regimen heterogeneity.

The updated model parameter will be estimated via simulation from the predictive distribution. Means, standards deviations and correlation of this distribution will then be used as the prior distribution for the parameters ($\log(\gamma_1)$,$\log(\delta_1)$).

γ_2, δ_2:

since the parameters γ_2, δ_2 relate to the single-agent (the marginal) dose-toxicity relationship of MEK162, for which the same regimen will be used, no heterogeneity is expected. Therefore, the prior for γ_2, δ_2 will simply be the posterior means, standard deviations and correlation of $\log(\alpha_2)$, $\log(\beta_2)$ incorporating all the data available at the time when a BID regimen is introduced, found via simulation.

η_{NR}:

the posterior mean and standard deviation of η, denoted by mean(η|data), sd(η|data), incorporating all the data available at the time when a NR is introduced will be found via simulation. Based on the assumption of small to moderate between-regimen heterogeneity, the prior distribution of η_{NR} can be found analytically, as a normal distribution with mean = mean(η|data) and standard deviation = $(\text{sd}(\eta|\text{data})^{2.} + 2*0.2^2)^{0.5}$.

14.5.4 Operating characteristics of the Bayesian Logistic Regression Model and hypothetical dose escalation scenarios

14.5.4.1 The Bayesian logistic regression model

An adaptive Bayesian logistic regression model (BLRM) guided by the escalation with overdose control (EWOC) principle will guide the dose escalation of the combination treatment to its MTD(s)/RP2D(s). The use of Bayesian response adaptive models for Phase I studies has been advocated by the EMEA guideline on small populations (2006) and by (Rogatko 2007) and is one of the key elements of the FDA's Critical Path Initiative.

A 5-parameter BLRM (refer to the protocol Section 10.4.2 for detail) for combination treatment will be fitted on first 28 day dose limiting toxicity data (i.e. absence or presence of DLT) accumulated throughout the dose escalation to model the dose-toxicity relationship of LGX818 and MEK162 when given in combination. To check the performance of the model, the document summarizes the simulation results and some hypothetical dose escalation scenarios.

Details regarding dose recommendation are described in Section 10.4.2 of the protocol.

14.5.5 Simulated operating characteristics

14.5.5.1 Hypothetical scenarios

In order to show how the Bayesian combination model reacts, the following hypothetical scenarios were investigated:

- Scenario 1: no increases in odds of DLT, i.e., the simulation parameter values for the BLRM are set to the mean values of the prior.
- Scenario 2: is scenario 1 + 50% increase in odds of DLT, i.e., 50% increase in odds of DLT.

- Scenario 3: is scenario 1 + 100% increase in odds of DLT, i.e., 100% increase in odds of DLT.
- Scenario 4: is scenario 1 but with constant interaction across doses.
- Scenario 5: is scenario 2 but with constant interaction across doses.

Scenarios 4 and 5 represent stress tests since the underlying interaction is assumed constant across doses and not dose-dependent (as assumed in the model).

Table 14-17 True underlying probabilities of DLT for Scenario 1

LGX818 -QD (mg)	MEK162 - BID (mg)			
	15	30	45	60
30	0.035	0.039	0.06	0.126
50	0.076	0.081	0.103	**0.169**
100	**0.203**	**0.213**	**0.239**	**0.304**
150	**0.331**	**0.349**	0.38	0.443
200	0.445	0.469	0.504	0.564
250	0.539	0.568	0.606	0.662
300	0.615	0.648	0.686	0.737
350	0.676	0.711	0.749	0.795
400	0.725	0.761	0.797	0.839
450	0.765	0.8	0.835	0.872
Bold values indicate dose combinations in the targeted toxicity interval [16%, 35%)				

Table 14-18 True underlying probabilities of DLT for Scenario 2

LGX818 -QD (mg)	MEK162 - BID (mg)			
	15	30	45	60
30	0.036	0.041	0.066	0.141
50	0.08	0.089	0.118	**0.2**
100	**0.22**	**0.249**	**0.298**	0.396
150	0.366	0.421	0.491	0.594
200	0.495	0.57	0.651	0.744
250	0.601	0.686	0.767	0.844
300	0.684	0.772	0.845	0.904
350	0.748	0.833	0.896	0.941
400	0.798	0.877	0.93	0.963
450	0.837	0.909	0.952	0.977
Bold values indicate dose combinations in the targeted toxicity interval [16%, 35%)				

Table 14-19 True underlying probabilities of DLT for Scenario 3

LGX818 -QD (mg)	MEK162 - BID (mg)			
	15	30	45	60
30	0.037	0.043	0.07	0.151
50	0.083	0.095	0.13	**0.224**
100	**0.232**	**0.277**	**0.345**	0.466
150	0.391	0.474	0.572	0.692
200	0.531	0.639	0.742	0.838
250	0.643	0.758	0.849	0.917
300	0.729	0.839	0.912	0.957
350	0.793	0.892	0.948	0.978
400	0.841	0.927	0.969	0.988
450	0.876	0.95	0.981	0.994
Bold values indicate dose combinations in the targeted toxicity interval [16%, 35%)				

Table 14-20 True underlying probabilities of DLT for Scenario 4

LGX818- QD (mg)	MEK162 - BID (mg)			
	15	30	45	60
30	0.035	0.038	0.058	0.121
50	0.075	0.078	0.097	0.157
100	**0.196**	**0.198**	**0.215**	**0.267**
150	**0.316**	**0.319**	**0.333**	0.377
200	0.422	0.424	0.436	0.474
250	0.51	0.512	0.522	0.554
300	0.582	0.583	0.592	0.619
350	0.64	0.641	0.649	0.672
400	0.687	0.688	0.695	0.715
450	0.726	0.727	0.733	0.75
Bold values indicate dose combinations in the targeted toxicity interval [0.16, 0.35)				

Table 14-21 True underlying probabilities of DLT for Scenario 5

LGX818 -QD (mg)	MEK162 - BID (mg)			
	15	30	45	60
30	0.051	0.056	0.084	**0.171**
50	0.108	0.113	0.139	**0.218**
100	**0.267**	**0.271**	**0.291**	0.353
150	0.41	0.412	0.428	0.476
200	0.523	0.525	0.537	0.574
250	0.61	0.611	0.621	0.651
300	0.676	0.677	0.685	0.709
350	0.727	0.728	0.735	0.755
400	0.767	0.768	0.774	0.79
450	0.799	0.8	0.804	0.819
Bold values indicate dose combinations in the targeted toxicity interval [0.16, 0.35)				

14.5.5.2 Simulation parameters

500 trials were used to simulate each scenario and the total minimum number of DLT to control the declaration of MTD was fixed to one.

The maximal dose to jump to was orthogonal and follows the protocol specifications (Section 10.4.2.1 of the protocol):

Table 14- Preference matrix

LGX818 – QD (mg)	MEK162 - BID (mg)			
	15	30	45	60
50	1	2	3	4
100	2	3	4	5
150	3	4	5	6
200	4	5	6	7
250	5	6	7	8
300	6	7	8	9
350	7	8	9	10
400	8	9	10	10
450	9	10	10	10

The number of patients to enroll in each cohort and stopping rules used to declare MTD were defined as:

- Minimum cohort size: 3
- Minimum number of patients enrolled: 18
- Maximum number of patients enrolled: 60
- Minimum number of patients enrolled at a given dose combination in order to declare MTD: 6

14.5.5.3 Metrics

Operating characteristics were reviewed for the simulations to compare the relative performance under each true scenario. The metrics reviewed were:

I. Average proportion of patients receiving a target dose combination on study (I)
II. Average proportion of patients receiving a dose combination with true P(DLT) ≥ 35% on study (II)
III. Average proportion of patients receiving a dose combination with true P(DLT) < 16% on study (III)
IV. Probability of recommending a target dose combination as the MTD (correct final decision) (IV)
V. Probability of recommending a dose combinations with true P(DLT) ≥ 35% as the MTD (patient risk) (V)
VI. Probability of recommending dose combination with true P(DLT) < 16% as the MTD (VI)

14.5.5.4 Results

Table 14-23 presents the model for the 5 different scenarios studied, additionally showing how many of the trials were stopped before declaring MTD when all dose combinations were considered too toxic.

Table 14- Results

Scenario	Metric						
	I	II	III	IV	V	VI	Stopped
1	0.681	0.035	0.286	0.882	0.016	0.076	0.026
2	0.532	0.147	0.32	0.716	0.126	0.122	0.036
3	0.552	0.099	0.35	0.78	0.046	0.136	0.038
4	0.474	0.155	0.273	0.496	0.382	0.088	0.034
5	0.613	0.133	0.252	0.736	0.152	0.058	0.054

In summary, the simulated operating characteristics show:

- (Metric IV) that the identified MTD falls within the targeted interval in more than 72% of the cases, except for scenario 4.
- (Metric V) that on average, less than 15% of patients are treated at overly toxic doses, excluding scenario 4.
- (Metric I) The average proportion of patients receiving a target dose combination on study is 47% to 68%.
- Scenario 4 needs careful consideration, since the true underlying probability of DLT (15.7%) for the combination MEK162 60mg + LGX818 50mg is very close to the lower boundary of the targeted toxicity [16%, 35%). Unsurprisingly, this combination is therefore identified relatively often as an MTD. Had this combination been counted as a correct MTD as well, then metric IV improves to 56.8%.

14.5.6 Hypothetical dose escalation scenarios

In order to show how the Bayesian model reacts, different hypothetical dose escalation scenarios were investigated (Table 14-24). The design should make reasonable dose-recommendations during the clinical trial based on the observed DLTs. During the study, the decision to dose escalate after completion of a given cohort and the actual dose chosen for the subsequent cohort will depend on the recommendation of the BLRM per EWOC principle and medical review of available clinical and laboratory data.

It is assumed for most scenarios that each cohort has exactly 3 evaluable patients. Scenario 20 illustrates the ability for the model to handle cohorts of different size. Dose escalation follows the rule listed in Section 6.2.4.

Overall, in the early cohort scenarios, the model is showing appropriate behaviors, in agreement with clinical sense and decision-making process: progressive increase of the combination doses if no DLT is observed (e.g., scenarios 1, 4, 10), staying at the same dose level and opening of a new cohort at the same dose combination when 1 DLT is reported (e.g., scenario 2), and decrease when more than 1 DLT is reported in a cohort (e.g., scenarios 5,6).

Table 14-24 Hypothetical dose escalation scenarios

Scenario	Dose combination MEK162 / LGX818	Npat	Ntox	Next dose combination (NDC)	P(Target) NDC	P(over) NDC	Median DLT rate (NDC)
1	45/50	3	0	60/50	0.279	0.096	0.119
2	45/50	3	1	45/50	0.398	0.232	0.211
3	45/50	3	2	stop			
4	45/50 45/100	3 3	0 0	60/100	0.240	0.126	0.107
5	45/50 45/100	3 3	0 1	45/50	0.224	0.034	0.084
6	45/50 45/100	3 3	0 2	45/50	0.308	0.095	0.123
7	45/50 45/100 45/50	3 3 3	0 1 0	45/100	0.397	0.243	0.214
8	45/50 45/100 45/50	3 3 3	0 1 1	45/50	0.407	0.064	0.152
9	45/50 45/100 45/50	3 3 3	0 1 2	45/50	0.552	0.203	0.237
10	45/50 45/100 60/100	3 3 3	0 0 0	60/150	0.158	0.204	0.084
11	45/50 45/100 60/100	3 3 3	0 0 1	60/100	0.399	0.185	0.189
12	45/50 45/100 60/100	3 3 3	0 0 2	45/100	0.480	0.241	0.238
13	45/50 45/100 45/150	3 3 3	0 0 0	45/200	0.154	0.115	0.058
14	45/50 45/100 45/150	3 3 3	0 0 1	45/100	0.310	0.040	0.121
15	45/50 45/100 45/150	3 3 3	0 0 2	45/100	0.432	0.135	0.181
16	45/50 45/100 45/150 45/100	3 3 3 3	0 0 2 0	60/100	0.375	0.177	0.179
17	45/50 45/100 45/150 45/100	3 3 3 3	0 0 2 1	45/100	0.542	0.169	0.222
18	45/50 45/100 45/150 45/100	3 3 3 3	0 0 2 2	45/50	0.283	0.042	0.105

Scenario	Dose combination MEK162 / LGX818	Npat	Ntox	Next dose combination (NDC)	P(Target) NDC	P(over) NDC	Median DLT rate (NDC)
19	45/50 45/100 60/100 60/150	3 3 3 3	0 0 0 0	60/300	0.076	0.115	0.011
20	45/50 45/100 60/100 60/150	3 3 3 6	0 0 0 3	60/100	0.467	0.083	0.174

14.5.7 Power for analysis of key secondary variables

Not applicable.

14.5.8 References (available upon request)

Rogatko A, Schoeneck D, Jonas W, et al (2007) Translation of innovative designs into phase I trials. J Clin Oncol; 25(31): 4982-6.

14.6 Appendix 6 - Operating characteristics of the combination Bayesian logistic regression model and hypothetical dose escalation scenarios LGX818 and MEK162 and LEE011 triple combination

[This Section is <u>not</u> applicable to the USA and Singapore]

An adaptive Bayesian logistic regression model (BLRM) guided by the escalation with overdose control (EWOC) principle will guide the dose-escalation of the combination treatment to its MTD(s)/RP2D(s). The use of Bayesian response adaptive models for Phase I studies has been advocated by the EMEA guideline on small populations (2006) and by (Rogatko et al 2007) and is one of the key elements of the FDA's Critical Path Initiative.

A 10-parameter BLRM for combination treatment will be fitted on first 28 day dose limiting toxicity data (i.e. absence or presence of DLT) accumulated throughout the dose-escalation to model the dose-toxicity relationship of LGX818, MEK162 and LEE011 when given in combination. To check the performance of the model, the document summarizes some hypothetical dose escalation scenarios.

14.6.1 Statistical Model

Refer to Section 10.4.2 for the form of the model. Note that the 10 parameter model for the triple combination (LGX818+MEK162+LEE011) is an extension of 5 parameter model used for the dual combination (LGX818+MEK162). When the dose of LEE011 equals to 0, the 10 parameter model reduces to the existing 5 parameter model.

The Bayesian approach requires the specification of prior distributions for the model parameters.

$((\log(\alpha_1),\log(\beta_1)), (\log(\alpha_2),\log(\beta_2)), (\log(\alpha_4),\log(\beta_4))), \eta_{12}, \eta_{14}, \eta_{24}, \eta_{124}$

The prior information for parameters $(\log(\alpha_x),\log(\beta_x))$ (where x=1, 2, 4) come from prior available dose-DLT information of LGX818, MEK162 and LEE011.

14.6.2 Prior Specification

The prior derivation for the 5 parameter dual combo (LGX818+MEK162) model was described in the original protocol as shown in Appendix 5 (Section 14.5).

14.6.2.1 Prior distribution for $\log(\alpha_4),\log(\beta_4)$ (LEE011 single agent component)

For this trial, historical data from the ongoing study CLEE011X2101 (first-in-human LEE011 oncology study) were used to derive an informative prior for the $(\log(\alpha_4),\log(\beta_4))$ (see Table 14-25).

1. The informative bivariate normal prior for the model parameters $(\log(\alpha_4),\log(\beta_4))$ was obtained as follows:
   - The median DLT rate at the LEE011 reference dose (400 mg, 3 weeks on 1 week off) was assumed 1/10 i.e. $\text{mean}(\log(\alpha_4)) = \log(1/9)$.
   - A doubling in dose was assumed to double odds of DLT, i.e. $\text{mean}(\log(\beta_4)) = 0$.
   - The standard deviation of $\log(\alpha_4)$ was set to 2 and the standard deviation of $\log(\beta_4)$ to 1, which allows for considerably prior uncertainty for the dose-toxicity profile.

- The correlation between log(α_4) and log(β_4) was set to 0.

2. Data from 53 patients (treated with LEE011 3 week on 1 week off) eligible for the dose determining set of the study [CLEE011X2101] were used to update the dose-toxicity profile (See Table 14-25).

Three percentiles (2.5, 50, 97.5) of the posterior distribution are used to find the 5 parameters of the bivariate-normal distribution that is in best agreement with the percentiles for each dose level.

3. Heterogeneity between the historical and current study was incorporated by between-trial standard deviations and τ41 and τ42 for log(α4) and log(β4). Both τ41 and τ42 were set to follow a log-normal distribution. Mean log(0.25) and standard deviation 0.01 was chosen for τ41 and mean log(0.125) and standard deviation 0.01 was chosen for τ42 which correspond to moderate between-trial variability.

Table 14-25 Data from CLEE11X2101

Dose of LEE011 (mg, 3 weeks on, 1 week off)	No of DLTs / No of evaluable patients
50	1/4
70	0/2
140	0/3
260	0/4
280	1/4
350	0/5
400	1/4
600	0/4
750	1/7
900	1/13
1200	2/3

Table 14-26 Prior, posterior and predictive distribution of (log(alpha$_4$),log(beta$_4$))

Parameter	Means	Standard deviations	Correlation
Prior for (log(α_4),log(β_4))	(log(1/9), 0)	(2, 1)	0
Normalized Posterior for (log(α_4),log(β_4))	(-2.075, -0.744)	(0.396, 0.521)	-0.130
Predictive for (log(α_4),log(β_4))	(-2.066, -0.749)	(0.527, 0.563)	-0.116

Interaction

As shown above, the distribution of η_{12} is inherited from existing LGX818 and MEK162 dual-combo model. A non-informative prior reflecting the current uncertainty about the toxicity of the combination treatment is used for η_{14}, η_{24}, η_{124}. There is no interaction expected between MEK162 and LEE011, we set the median of η_{24} to be log (1.02) which assumes a 2% increase of odds. This is a conservative way to set the prior. The 97.5 percentile of η_{24} is set to be log (2.2) which assumes a 1.2 fold increase of odds. LGX818 and LEE011 have potential positive interaction. Hence we set the median of η_{14} to be log (1.1) which assumes a 10% increase in odds of toxicity. The 97.5 percentile of η_{14} is set to be log (3), which assumes a 2 fold increase

of odds. We also set a conservative prior for 3 way interaction. The median of η_{124} is set to be log (1.02). The 97.5 percentile is set to be log (2.2).

14.6.2.2 Summary

The prior distribution of the parameters is summarized in Table 14-27. The prior distribution of the DLT rates for provisional doses is summarized in Table 14-28. Note that the posterior probability of excessive toxicity of the proposed starting dose for triple combination (LGX818+MEK162+LEE011) is 10.2% which satisfies EWOC criteria.

Table 14-27 Prior distribution of model parameters

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
$(\log(\alpha_4),\log(\beta_4))$	(-2.066, -0.749)	(0.527, 0.563)	-0.116
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

Table 14-28 Summary of prior distribution of DLT rates for triple combo (LGX818+MEK162+LEE011) including current DLT data (up to Apr 16, 2013) from dual combo (LGX818+MEK162)

LEE011 (mg, 3 week on, 1 week)	Prior probabilities that Pr(DLT) is in interval			Mean	SD	Quantiles		
	[0.0, 0.16)	[0.16, 0.35)	[0.35,1.00]			2.50%	50.00%	97.50%
	MEK162 45mg BID, LGX818 450mg QD							
100	0.662	0.236	0.102	0.149	0.145	0.006	0.102	0.551
200	0.552	0.216	0.232	0.218	0.226	0.004	0.132	0.809
400	0.468	0.14	0.392	0.337	0.341	0.001	0.194	0.986
600	0.44	0.098	0.462	0.411	0.396	0	0.265	0.999
800	0.428	0.075	0.498	0.455	0.424	0	0.342	1
	MEK162 45mg BID, LGX818 600mg QD							
100	0.632	0.204	0.164	0.174	0.195	0.002	0.097	0.72
200	0.543	0.169	0.288	0.253	0.281	0.001	0.129	0.926
400	0.472	0.106	0.423	0.373	0.381	0	0.202	0.998
600	0.447	0.073	0.481	0.439	0.423	0	0.291	1
800	0.434	0.056	0.51	0.476	0.443	0	0.39	1

14.6.2.3 Hypothetical dose escalation scenarios for triple combo (LGX818+MEK162+LEE011)

The BLRM model should make reasonable decisions during a study based on the observed toxicities particularly in early cohorts. After completion of a given cohort, the decision to dose escalate and actual dose chosen for the subsequent cohort will depend on the recommendation of the BLRM EWOC principle and medical review of all relevant data available up to date.

Table 14-29 shows some scenarios of dose levels recommended by the 10-parameter BLRM for the specified DLT observations.

Note that the next dose level is selected in concordance with the provisional dose levels of LGX818 and LEE011 specified in the protocol, to mimic possible on-study escalation steps. MEK162 is maintained at 45 mg BID. Since the main goal of the dose escalation is to escalate LEE011, LGX818 is fixed at 450mg in the table.

Table 14-29 Dose decisions recommended by BLRM

Scenario	LEE011 (mg, 3 week on, 1 week off)	Npat	Ntox	Next dose level LEE011 (mg, 3 week on, 1 week off)	P(Target)	P(over)	Median DLT rate
1	100	3	0	200	0.193	0.109	0.079
2	100	3	1	100	0.399	0.155	0.178
3	100	3	2	50	0.505	0.227	0.233
4	100	6	1	200	0.308	0.221	0.172
5	100 200	3 3	0 0	400	0.131	0.130	0.042
6	100 200	3 3	0 1	200	0.367	0.181	0.178
7	100 200	3 3	0 2	100	0.527	0.126	0.200
8	100 200	3 6	0 1	300	0.281	0.188	0.147
10	100 200	3 8	0 1	400	0.221	0.225	0.131
11	100 200 400	3 3 3	0 0 0	800	0.072	0.104	0.007
12	100 200 400	3 3 3	0 0 1	400	0.326	0.242	0.191
13	100 200 400	3 3 3	0 0 2	200	0.505	0.105	0.188
14	100 200 400	3 3 6	0 0 1	600	0.233	0.229	0.139

The BLRM model is performing reasonably for the hypothetical dose escalation scenarios. Within Table 14-29, it can be seen that the model leads to decisions that are in agreement with clinical sense. When no DLTs are observed in a cohort, the decision is to escalate the dose. When 1 DLT is observed in one cohort, the decision is to stay in the current dose level, or dose escalation depending on the size of the cohort. When more than 1 DLT is observed in one cohort, the decision is to dose de-escalation.

14.6.3 References (available upon request)

EMEA (2006) Guideline on small populations (Internet) Available from: <emea.europa.eu.docs/en_GB/document_library/Scientific_guidiline/2009/09/WC500003615.pdf>.

Ho C, Sangha R, Beckett L, et al (2011) Escalating weekly doses of cetuximab and conelation with skin toxicity: a phase I study. Invest New Dmgs; 29: 680-7.

Rogatko A, Schoeneck D, Jonas W, et al (2007) Translation of innovative designs into phase I trials. J Clin Oncol; 25: 4982-6.

14.7 Appendix 7: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

14.7.1 Definition of AE

AE Definition
• An AE is any untoward medical occunence in a patient or clinical study patient, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnonnal laborato1y finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnonnal laborato1y test results (hematology, clinical cheinistiy, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator Any abnonnal laborato1y test results that meet any of the conditions below must be recorded as an AE: • Is associated with accompanying symptoms; • Requires additional diagnostic testing or medical/surgical intervention; • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant dmg ti·eatinent, or other therapy. • Exacerbation of a chronic or intennittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study ti·eatinent adininisti·ation even though it may have been present before the staii of the study. • Signs, symptoms, or the clinical sequelae of a suspected dmg-dmg interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concoinitant medication. Overdose per se will not be repo1ied as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-haiming intent. Such overdoses should be repo1ied regardless of sequelae. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reoo1ied as an AE or SAE if they fulfill the definition of an AE or SAE and meet the

requirements as per Section 8.1.8.1. Also, "lack of efficacy" or "failure of expected phannacological action" does not constitute an AE or SAE.

Events	Meeting the AE Definition
	• Any clinically significant abnonnal laborato1y findings or other abnonnal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occunence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the sta1t of the study that do not worsen. • Worsening of signs and symptoms of the malignancy under study should be recorded as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be repo1ted as AEs.

14.7.2 Definition of an SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The te1m "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occmTed or was necessaiy, the AE should be considered senous.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The te1m disability means a substantial dismption of a person's ability to conduct n01mal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diaiThea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial dismption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE repo1iing is appropriate in other situations such as impo1iant medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopai·dize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or

convulsions that do not result in hospitalization, or development of drng dependency or dmg abuse.

- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. Hospitalization due to signs and symptoms of disease progression should not be repo1ied as an SAE. If the malignancy has a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with CTCAE Grade 5 (see the Assessment of Intensity section).

14.7.3 Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for repo1iing serious adverse events on the CT SAE Repo1i Fo1m to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Repo1i Fo1m for repo1iing of SAE infonnation is not the same as the AE page of the CRF. When the same data are collected, the fo1ms must be completed in a consistent manner. AEs should be recorded using concise medical tenninology and the same AE te1m should be used on both the CRF and the CT SAE Repo1i Fo1m for repo1iing of SAE infonnation.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental fonn for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laborato1y repo1ts, and diagnostic repo1ts) related to the event.
- The investigator will then record all relevant AE/SAE infonnation in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the patient's medical records to Pfizer Safety in lieu of completion of the CT SAE Repo1t Fonn/AE/SAE CRFpage.
- There may be instances when copies of medical records for ce1tain cases are requested by Pfizer Safety. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical infonnation. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE repo1ted during the study and assign it to 1 of the following categories:

GRADE	Clinical Description of Severity
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occunence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be rnled out.
- The investigator will use clinical judgment to detennine the relationship.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.
- The investigator will also consult the IB and/or product infonnation, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator !!!!II! document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occuned, and the investigator has minimal infonnation to include in the initial repo1t to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up infonnation and send an SAE follow-up repo1t with the updated causality assessment.
- The causality assessment is one of the criteria used when detennining regulato1y repo1ting requirements.
- If the investigator does not know whether or not the study treatment caused the event, then the event will be handled as "related to study treatment" for repo1ting purposes, as defined by the sponsor. In addition, if the investigator detennines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and repo1t such an assessment in the dedicated section of the CT SAE Repo1t Fonn and in accordance with the SAE repo1ting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perfonn or anange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laborato1y tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- New or updated info1mation will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the infonnation.

14.7.4 Reporting of SAEs

SAE Reporting to Pfizer Safety via CT SAE Report Form
• Facsimile trnnsmission of the CT SAE Repo1i Fo1m is the prefened method to transmit this info1mation to Pfizer Safety. • In circllllstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Fonn sent by overnight mail or com .er serv ce. • Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Repo1i Fo1m pages within the designated repo1iing time frames.

14.8 Appendix 8: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drng who show no sign of liver injmy (as dete1mined by elevations in transaminases) are te1med "tolerators," while those who show transient liver injmy, but adapt are te1med "adaptors." In some patients, transaminase elevations are a harbinger of a more serious potential outcome. These patients fail to adapt and therefore are "susceptible" to progressive and serious liver injmy, commonly refened to as DILi. Patients who experience a transaminase elevation above 3 x ULN should be monitored more frequently to detennine if they are an "adaptor" or are "susceptible."

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 x ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 x ULN (ie, AST/ALT and TBili values will be elevated within the same laborato1y sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occmTence is still regarded as a potential DILi. Therefore, abnonnal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injmy have been excluded.

The threshold of laborato1y abnonnalities for a potential DILI case depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laborato1y abno1malities should be evaluated fmiher as potential DILI (Hy's law) cases to definitively detennine the etiology of the abnonnal laborato1y values:

- Patients with AST/ALT and TBili baseline values within the n01mal range who subsequently present with AST OR ALT values >3 x ULN AND a TBili value >2 x ULN with no evidence ofhemolysis and an alkaline phosphatase value <2 x ULN or not available.

- For patients with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:
    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).
    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The patient should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology.

A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (e.g., biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

14.9 Appendix 9: ECG Findings of Potential Clinical Concern

ECG Findings That May Qualify as AEs

- Marked sinus bradycardia (rate <40 bpm) lasting minutes.
- New PR interval prolongation >280 msec.
- New prolongation of QTcF to >480 msec (absolute) or by60 msec from baseline.
- New-onset atrial flutter or fibrillation, with contrnlled ventricular response rate: ie, rate <120 bpm.
- New-onset type I second-degree (Wenckebach) AV block of>30 seconds' duration.
- Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.

ECG Findings That May Qualify as Serious Adverse Events (SAEs)

- QTcF prolongation >500 msec.
- New ST-T changes suggestive of myocardial ischemia.
- New-onset left bundle branch block (QRS >120 msec).
- New-onset right bundle branch block (QRS >120 msec).
- Symptomatic bradycardia.
- Asystole:

  In awake, symptom-free patients in sinus rhythm, with documented periods of asystole3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;

  In awake, symptom-free patients with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer;

  Atrial flutter or fibrillation, with rapid ventricular response rate: rapid= rate >120 bpm.

- Sustained supraventricular tachycardia (rate>120 bpm) ("sustained"= sho1i duration with relevant symptoms or lasting>1 minute).

- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (hea1t rate <40 bpm), accelerated idioventricular rhythm (HR 40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR>100 bpm (such as torsades de pointes)).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heait block.

ECG Findings That Qualify as SAEs

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any aIThythmia classified as an adverse expenence.

The enumerated list of major events of potential clinical concem are recommended as "ale1ts" or notifications from the core ECG laborat01y to the investigator and Pfizer study team, and not to be considered as all inclusive of what to be reported as AEs/SAEs.

14.10 Appendix 10: Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 global pandemic and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

14.10.1 Eligibility

Emollment for this study was closed prior to the COVID-19 pandemic.

14.10.2 Telehealth Visits

In the event that in-clinic study visits cannot be conducted, eve1y effort should be made to follow up on the safety of study patients at scheduled visits per the Visit Schedules and

Assessments (Section 7, Table 7-2) or unscheduled visits. Telehealth visits may be used to continue to assess patient safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (e.g., audio, video, video-conferencing software) remotely, allowing the patient and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review and record study treatment(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.1.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the patient is adhering to the contraception method(s) required in the protocol. Refer to Section 7.2.2.5.5 and Section 14.10.3.1 of this appendix regarding pregnancy tests.

Study patients must be reminded to promptly notify site staff about any change in their health

14.10.3 Alternative Facilities for Safety Assessments

14.10.3.1 Laboratory Testing

If a study patient is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital. The following safety laboratory evaluations may be performed at a local laboratory:

- Refer to Section 7.2.2.5 for the list of safety laboratory evaluations, including pregnancy testing, required per protocol.

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/ accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the patient's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

If a patient requiring pregnancy testing cannot visit a local laboratory for pregnancy testing, a home urine pregnancy testing kit with a sensitivity of at least 25 IU/mL may be used by the patient to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the patient's source documents/medical records and relevant data recorded on the CRF. Confirm that the patient is adhering to the contraception method(s) required in the protocol.

14.10.3.2 Imaging

If the patient is unable to visit the study site for safety imaging assessments (e.g., ECHO or MUGA), the patient may visit an alternative facility to have the safety imaging assessments performed. Qualified study site personnel must order, receive, and review results.

14.10.3.3 Electrocardiograms

If the patient is unable to visit the study site for ECGs, the patient may visit an alternative facility to have the ECGs performed. Qualified study site personnel must order, receive, and review results.

14.10.3.4 Study Treatment

If the safety of a trial patient is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that patient from study treatment must be considered.

Study drugs may be shipped by courier to study patients if permitted by local regulations and in accordance with storage and transportation requirements for the study drugs. Pfizer does not permit the shipment of study drugs by mail. The tracking record of shipments and the chain of custody of study drugs must be kept in the patient's source documents/medical records.

The following is recommended for the administration of study drugs for patients who have active [confirmed (positive by regulatory authority-approved test) or presumed (test pending/clinical suspicion)] SARS-CoV2 infection:

- For symptomatic patients with active SARS-CoV2 infection, study drugs should be delayed for at least 14 days from the start of symptoms. This delay is intended to allow the resolution of symptoms of SARS-CoV2 infection.
- Prior to restarting treatment, the patient should be afebrile for 72 hours, and SARS-CoV2-related symptoms should have recovered to ≤ Grade 1 for a minimum of 72 hours. Notify the study team when treatment is restarted.
- Continue to consider potential drug-drug interactions as described in protocol Section 6.4 for any concomitant medication administered for treatment of SARS-CoV2 infection.

14.10.4 Home Health Visits

A home health care service may be utilized to facilitate scheduled visits per the Visit schedule and assessments. Home health visits include a healthcare provider conducting an in-person study visit at the patient's location, rather than an in-person study visit at the site. The following may be performed during a home health visit:

- Physical exam including dermatological lesions and vital signs
- Review and record study treatment(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.1.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.

- Review and record contraceptive method and results of pregnancy testing. Confirm that the patient is adhering to the contraception method(s) required in the protocol. Refer to Section 7.2.2.5.5 and Section 14.10.3.1 of this appendix regarding pregnancy tests.

14.10.5 Adverse Events and Serious Adverse Events

If a patient has COVID-19 during the study, this should be reported as an AE or SAE and appropriate medical treatment provided. Temporary discontinuation of the study treatment may be medically appropriate until the patient has recovered from COVID-19.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

14.10.6 Efficacy Assessments

If the patient is unable to visit the study site for imaging assessments (e.g., CT, MRI, X-ray, FDG-PET), the patient may visit an alternative facility to have the imaging assessments performed. Qualified study site personnel must order, receive, and review results.