Clinical Development

LEE011/MEK162

Clinical Trial Protocol CMEK162X2114

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

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List of abbreviations

λz	Smallest (slowest) disposition (hybrid) rate constant (time-1) may also be used for terminal elimination rate constant (time-1)
5 FU	Fluorouracil
ADME	Absorption, distribution, metabolism and excretion
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AP	Alkaline phosphatase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomic-Therapeutic-Chemical classification
AUC0-24h	Area under the curve from time zero to 24 hours
AUCinf	Area under the curve from time zero to infinity
AUClast	Area under the curve from time zero to the last measureable concentration time
BID	Twice daily
BLRM	Bayesian logistic regression model
BOR	Best overall response
BSEP	Bile salt export pump
BUN	Blood Urea Nitrogen
CBC	Complete blood count
CDK	Cyclin-Dependent Kinase
CFR	Code of federal regulations
CK	Creatinine Kinase
CL/F	Total body clearance of drug from the plasma
Cmax	Maximum plasma concentration after a single dose
CNS	Central nervous system
CPK	Creatine phosphokinase
CR	Complete response
CRF	Case Report/Record Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CSR	Central Serous Retinopathy
Css	Plasma concentration during steady state
CT	Computed tomography
CTCAE	NCI common terminology criteria for adverse events (version 4.0)
DDS	Dose-determining set
DLT	Dose-limiting toxicity
DNA	Deoxyribose nucleic acid
DOR	Duration of Response
DS&E	Drug Safety and Epidemiology
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form

EDC	Electronic data capture
EOT	End of Treatment
EWOC	Escalation with overdose control
FAS	Full analysis set
FDA	Food and Drug Administration
FFPE	Formalin fixed paraffin embedded
FMO	Flavin-containing monooxygenase
GCP	Good clinical practice
GGT	Gamma-glutamyltransferase
GI	Gastro intestinal
GLP	Good laboratory practice
GSH	Glutathione
HDPE	High density polyethylene
HIV	Human immunodeficiency virus
IC_{50}	Concentration resulting in 50% inhibition
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMS	Integrated medical safety
IN	Investigator notification
INR	International normalized ratio
IRB	Institutional Review Board
LC/MS/MS	Liquid chromatography-tandem mass spectrometry assay
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
LVEF	Left ventricular ejection fraction
MCL	Mantle Cell Lymphoma
MDRI	Multidrug-resistant protein 1
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multiple gated acquisition scan
MXR	Mitoxantrone resistant protein
NCI	National Cancer Institute
NIH	National Institutes of Health
NSCLC	Non-small cell lung cancer
OCRDC	Oracle clinical research data capture
OCT	Ocular coherence tomography
ORR	Objective response rate
OS	Overall survival
PD	Pharmacodynamic
PET	Positron emission tomography
PFS	Progression free survival
Pgp	P-glycoprotein
PIB	Powder in Bottle
PK	Pharmacokinetics
PK/PD	Pharmacokinetic/pharmacodynamics

CCI	[redacted]
PPS	Per-Protocol Set
PR	Partial response
pRb	Retinoblastoma protein
PT	Prothrombin time
PVC	Premature ventricular contraction
PXR	Pregnane X receptor
QD	Every day
QTcF	QT corrected with Fredericia's formula
Racc	Accumulation ratio
RAP	Report and Analysis Plan
Rb	Retinoblastoma protein
RBC	Red blood cell
REB	Research Ethics Board
RECIST	Response Evaluation Criteria for Solid Tumors
RNA	Ribonucleic acid
RPED	Retinal pigmented epithelial detachment
SAE	Serious adverse event
SD	Stable disease
SUSAR	Suspected, unexpected serious adverse reaction
SUV	Standardized uptake value
T1/2	Half life
T1/2,acc	Effective elimination half-life
TDI	Time-dependent inhibition
Tmax	Time to reach maximum (peak) plasma concentration
TSH	Thyroid-stimulating hormone
TTP	Time to progression
ULN	Upper limit of normal
US	United States
Vss/F	Apparent volume of distribution at steady state
Vz/F	The apparent volume of distribution during terminal phase after oral administration (associated with λz)
WBC	White blood cell
WCBP	Women of child bearing potential
WHO	World Health Organization

Amendment 3

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 and dose adjustment guidelines for hepatobiliary toxicities including ALT, AST, and total bilirubin have been added and separated from the dose modification guidance for other adverse events. Specific changes are as follows:
   a. Updates to dose modification language and the guidelines for the management of hepatic toxicity
   b. To specify that for patients meeting biochemical criteria for Hy's law (AST or ALT > 3.0 x ULN and total bilirubin > 2.0 x ULN in the absence of cholestasis or hemolysis), the study treatment must be permanently discontinued
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 and dose limiting toxicity definitions have been changed to more aggressively 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 ≥ 481 ms at any time before Cycle 7 Day 1
3. A change in study sponsorship was made from Novartis to Array BioPharma.

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.

- Changes in the header of this document and in multiple sections to reflect the study sponsorship changes from Novartis to Array BioPharma
- The Protocol Summary is updated to reflect the changes to the inclusion and exclusion criteria
- Section 5.2 Inclusion criteria has been updated with the following:

  - Clarification of inclusion criteria for serum total bilirubin for patients with Gilbert syndrome who are excluded if total bilirubin > 3.0 x ULN or direct bilirubin > 1.5 x ULN
  - Update of AST and ALT <2.5 x ULN, except in patients with tumor involvement of the liver who must have AST and ALT < 5 x ULN.
  - 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, Potassium, Magnesium, Inorganic phosphate, Calcium (corrected for serum albumin)
- Section 5.3 Exclusion criteria has been updated with the following:
  - Clarification of QTcF interval criteria on the ECG (ie: unreadable or not interpretable) or QTcF >450 ms (using Frederica's correction). All as determined by screening ECG (mean of triplicate ECGs).
  - Addition of symptomatic pericarditis within 12 months prior to starting study drug
  - Increase in exclusion window from 3 months to 12 months prior to starting study drug for angina pectoris
  - Increase in exclusion window from 3 months to 12 months prior to starting study drug for 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)
  - Addition of exclusion of agents that are known to induce Torsades de Pointes
  - 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 window, and cannot be discontinued 7 days prior to Cycle 1 Day 1, are excluded
  - Addition of criteria to exclude patients with history of retinal degenerative disease
  - Increase of time to 30 days after stopping treatment that a male should not father a child
- Section 6.1.1, added grapefruit hybrids, pummels and star-fruit to list of items to be avoided due to CYP3A4 mediated interaction
- Section 6.2.4, clarification of criteria to be followed for DLT
- Table 6-1 Criteria for defining dose-limiting toxicities, has been updated to:
  - Include grade 2 bilirubin >7 consecutive days
  - Clarification for CTCAE grade 3 ALT > 4 consecutive days
  - Addition of DLT for grade 4 ALT or both ALT and AST(isolated increases in AST without concomitant increases in ALT will not be considered dose-limiting, because of the non-specific nature of AST)
  - Addition of DLT for CTCAE grade 4 serum alkaline phosphatase > 7 consecutive days

- Section 6.3.1, clarification that during Cycle 1 the dose should not be reduced or interrupted unless the patient has experienced a DLT
- Section 6.3.1, clarification that if a patient discontinues either study drug, then the patient must discontinue the study.

- Table 6-3 Dose modification guidelines after Cycle 1, has been updated to:
  - Include new guidelines for the management of hepatic toxicity
  - 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 6.3.1.1 added to outline Additional follow-up for hepatic toxicities
- Section 6.4.1 updated to include medications that are known to induce Torsades de Pointes, as well as addition of grapefruit hybrids, pummelos and star-fruit
- Section 6.4.2 was updated with list of prohibited concomitant therapy
- CCI [redacted]
- Section 7.2.2.5.7 was updated to clarify follow-up guidelines in the event a QTcF value of ≥ 481 ms is observed prior to cycle 7
- Table 7-4 and 7-5, ECG collection plan, were updated to reflect the new ECG frequency and additional recommendations given with regards to ECG assessment in case of abnormalities and cardiologist consultation.
- CCI [redacted]
- Appendix 3 updated with prohibited concomitant therapies and therapies to be used with caution
- Appendix 4 was added to provide guidance on medications with a risk of Torsades de Pointes

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

IRB/IEC/REB Approval

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.

Summary of previous amendments

Amendment 2

Amendment rationale

Emerging safety data from this and other studies with LEE011 and MEK162 warrant the following changes to the protocol:

Preliminary evaluation of LEE011 and MEK162 indicates it is an active combination but associated with frequent adverse events necessitating dosing interruptions and reductions. In order to determine the most tolerable and efficacious dosing schedule for the combination, evaluation of alternate dosing schedules are incorporated.

Evaluation of the 28 day continuous dosing schedule was performed in the phase 1 single agent LEE011 study [CLEE011X2101]. Due to hematological toxicity, this schedule will not be pursued any longer. Therefore all references to continuous dosing schedule will be removed from this protocol. In addition, the eligibility criterion is modified to include only patients with ECOG performance score of 0 and 1.

PPD

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. Furthermore, coagulation assessments will be collected at screening and at C1D1 to exclude patients with abnormal coagulation evaluations.

Emerging safety data from the phase I single agent study [CLEE011X2101] suggest that LEE011 has an effect on cardiac repolarization. Therefore additional evaluations have been added to the ECG monitoring schedule to better assess the safety and tolerability of LEE011. An additional echocardiogram evaluation will be added to the C3D1 visit. The DLT definition and dose modification guidelines have been revised to monitor cardiac function more thoroughly as many patients have underlying hypertension and other cardiac conditions that could be affected by the study drugs.

Following consultation with a panel of ophthalmologists who have experience in treating MEK inhibitor associated visual toxicities, the exclusion criterion has been refined such that risk factors for central serous retinopathy (CSR) and current or history of CSR are no longer exclusionary. In order to better characterize the visual events related to MEK162 treatment, the amendment modifies the terminology used to identify the retinal abnormalities associated with MEK162. The term Central Serous Retinopathy-like (CSR-like) will no longer be applied generally to characterize the retinal events associated with MEK162. The term retinal pigmented epithelial detachment (RPED) will be applied, when appropriate imaging studies,

like ocular coherence tomography (OCT) support its diagnosis. The standard DLT criteria and dose modification guidelines have been updated to reflect the modified terminology.

The recommended dose modifications for CTCAE Grade 4 creatine phosphokinase (CPK) have been revised based on the growing safety data from this and other ongoing studies with MEK162. Blood CPK elevations are mostly asymptomatic and not clinically significant. Therefore, it is reasonable to recommend careful evaluation of the patients and consider dose modification for Grade 4 CPK elevation based on whether the patient is symptomatic or not.

The exclusion criteria related to hypertension, creatine phosphokinase (CPK) elevation, and prior malignancies have been modified in order to be in alignment with other MEK162 studies.

CCI [redacted]

MEK162 has been shown to have a potential teratogenic affect in preclinical studies. Therefore, additional serum pregnancy tests have been added to align with Novartis's standards.

To align with the MEK162 program standard language, the contraceptive washout following study drug discontinuation has been changed from 15 days to 30 days.

Results from the MEK162 food effect study and preliminary results from the LEE011 food effect study indicate that MEK162 and LEE011 can be administered with or without food. As of this amendment, MEK162 and LEE011 may be administered irrespective of food.

The objectives and endpoints and PK sections were updated to include CCI [redacted]

Finally, changes to correct typographical errors and harmonize protocol text where applicable have been made.

Changes to the protocol

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

- The Protocol summary section has been updated to include information regarding the alternate dosing schedule and to include the updated inclusion/exclusion criteria from Section 5.
- Section 1.2.1.4 Clinical experience, has been updated to include clinical information from the most recent LEE011 IB version 5 dated November 7, 2013.
- Section1.2.1.5 Clinical Pharmacokinetics of LEE011, has been updated to include clinical information from the most recent LEE011 IB version 5 dated November 7, 2013.
- Section 1.2.2.4 Clinical experience of MEK162, has been updated to include FDA mandated language regarding a hypertensive crisis that occurred in June 2013.

- Section 1.2.2.6 Clinical experience with the combination of LEE011 and MEK162 has been updated to include the most recent information available regarding the MEK162 and LEE011 combination study
- Section 2.2 Rationale for the study design has been updated to clarify the definition of MTD(s)/RP2D
- Section 2.3 Rationale for dose and regimen selection, has been updated with the following: The MTD/RP2D of LEE011
  1. Deleted information regarding the continuous dosing of LEE011 (28 days) Introduction of alternate schedule(s)
  2. Updated language regarding the starting dose of the alternate dosing schedules
- Table 3-1 Objectives and related endpoints has been updated to include the following:
  CCI [redacted]
- Section 4.1 Description of study design has been updated to include the following:
  1. The alternate dosing schedules
     a. 2 weeks on 1 week off of both LEE011 and MEK162
     b. 3 weeks on 1 week off of both LEE011 and MEK162
  2. To allow multiple cohorts to be open in parallel
  3. Updated the number of patient in phase Ib from "18" to "40" and replaced the word "will" with "expected" to enroll in phase Ib
  4. Updated the language around the MTD/RP2D declaration and schedule
  5. Added paired biopsy information for the 21 day schedule
  6. Replace the word "fresh" with "newly obtained" tumor biopsies in this section and throughout the protocol except for Section 7
  7. CCI [redacted]
  8. Updated total number of patients in phases Ib and II from "90" to "80"
  9. Updated the disease progression assessments (phase II only) from every "two" to every "three" months and removed follow up phone calls.
  10. Updated the survival follow up period (phase II only) from "24" to "12" months
- Figure 4-1 Study design has been updated to include the total of patients in phase Ib from "N≥15" to "N~40"
- Section 4.3 Definition of end of the study has been updated to include updated Novartis standard language
- Section 5.2 Inclusion criteria has been updated to include the following:
  1. Inclusion criteria #3 has been updated to change the ECOG status from "0-2" to "0-1"
  2. Inclusion criteria #5 has been updated to clarify that "patients with accessible tumors that are amenable for biopsy" must undergo a tumor biopsy in phase II
  3. Exclusion criteria #1 has been updated to exclude patients with brain metastases
  4. Exclusion criteria #2 has been updated to clarify GI disease as "active"

5. Exclusion criteria #3 has been added to exclude patients with uncontrolled hypertension
6. Exclusion criteria #4 has been updated to include updated standard cardiac assessments
7. Exclusion criteria #6 has been added to exclude patients with neuromuscular disorders associated with elevated CK
8. Exclusion criteria #7 has been updated to include a new coagulation assessment for organ function "PT/INR or aPTT ≤ 1.5 ULN"
9. Exclusion criteria #12 has been updated to include update MEK162 ophthalmologic information
10. Exclusion criteria #15 has been added to exclude patients with other malignancies within 3 years prior to enrollment
11. Exclusion criteria #17 has been updated to change the contraceptive washout following drug discontinuation from "15 days" to "30 days"
12. Certain exclusion criteria were shifted upwards based on priority

- Section 6.1.1 Dosing regimen and treatment administration has been updated with the new fasting guidance for MEK162 and LEE011. Fasting restrictions for both drugs have been lifted and drugs may be administered irrespective of food. In addition, this section was re-arrange to further clarify the different dosing requirements for LEE011 and MEK162
- Section 6.1.1.1 "Continuous dosing regimen of LEE011" has been deleted and replaced with the "Alternate dosing schedule of LEE011 and MEK162" to include the alternate schedules
- Section 6.2.2 Provisional dose levels has been updated and sentence "Only LEE011 can be escalated at the time of the dose escalation keeping MEK162 at the same starting dose level (e.g. for provisional dose level 2 only LEE011 is escalated from 200 mg to 400 mg when compared to dose level 1)" has been deleted.
- Table 6-1 Provisional dose levels has been updated with the following:
  1. New dosing reduction of MEK162 to "30mg QD" if approved by Novartis
  2. Deleted statement "In particular, LEE011 doses higher than 600mg may be evaluated depending on the observed safety, PK and PD data"
  3. Deleted "3weeks on 1 week off" and "continuous" language from the table to eliminate confusion
- Section 6.2.3.2 Dose Cohort Modification has been updated to include the following:
  1. Clarification around the initial dosing schedule
  2. Language around the dosing of the alternate dosing schedules
  3. Clarification that Bayesian models will be run for each alternate dosing schedule
- Table 6-2 Criteria for defining dose-limiting toxicities has been updated to include the most recent standard DLT criteria definition information from other MEK162 and LEE011 studies

- Section 6.2.4.1 Follow up evaluations for appearance of Retinal Events has been updated to include management guidelines of retinal events. The title has also been modified from "follow up evaluations for appearance of central serous retinopathy (CRS) to "Follow up evaluations for appearance of retinal events"
- Section 6.3.1 Dose modification and dose delays has been updated to include a second dose reduction of MEK162 to "30mg QD or 15 BID" when approved by Novartis
- Table 6-3 Dose Modification Guidelines has been updated to include updated MEK162 and LEE011 dose modification guidelines
- Sections 6.5.1 Subject numbering has been updated to include information regarding the use of IRT for drug management in phase II
- Section 6.5.2 Treatment assignment has been updated to include guidance on the treatment assignments using IRT in phase II
- Section 6.6.1 Study drug packaging and labeling has been update to include drug management with IRT
- CCI [redacted]
- Table 7-1 Visit Evaluation Schedule (28-day cycle) has been updated to include the following assessments:
  1. Additional ECG's and cardiac imaging assessments
  2. Hematology and chemistry sections were separated to minimize confusion
  3. A section for cardiac and muscle enzymes was added for additional clarification
  4. A section for coagulation assessments was added
  5. Additional follow up serum/urine pregnancy tests
  6. CCI [redacted]
  7. Additional guidance around tumor assessments
  8. Mandatory brain images was added
  9. Clarification of MEK162 and LEE011 dosing
  10. Removed disease progression monthly phone calls
  11. Merged disease progression and survival follow up rows and columns
  12. Additional footnotes were added for further clarification
- Table 7-2 Visit Evaluation Schedule (21-day cycle) has been inserted to include the schedule of assessments for the alternate dosing schedules of 21 days
- Section 7.1.4 End of treatment visit has been updated to include the current "end of treatment visit" language
- Section 7.1.5 Follow-up period has been updated to include current "follow-up period" language
- Section 7.1.5.1 30-day safety follow-up period has been updated to include current "30-day safety follow-up period"

- Section 7.1.5.2 Disease progression follow-up assessments (Phase II only) has been updated to change the disease progression follow up tumor assessments from “every two months” to “every three months”
- Section 7.1.5.3 Survival follow-up period (Phase II only) has been updated to change the survival follow-up period from “24 months” to “12 months”
- Section 7.2.1 Efficacy assessments has been updated to include the following:
  1. Mandatory baseline brain imaging to access CNS disease was added.
  2. Follow-up tumor assessments for the alternate dosing schedules
  3. Screening window has been extended from “14” to “28” days
  4. Clarification of evaluable sites (Chest, Abdomen and pelvis) for all follow up assessments
  5. Include central collection of radiological and photographic assessments in both “phases Ib and II” from “phase II” only
- Table 7-3 Clinical Laboratory Parameters Collection Plan has been updated to include additional cardiac, coagulation and serum/urine pregnancy assessments
- Section 7.2.2.5.5 Pregnancy Assessments has been updated to include new follow up serum pregnancy testing “every other month”
- Section7.2.2.5.6 Ophthalmic Examination has been updated to include additional guidance on ophthalmic examinations
- Table 7-4 ECG Collection Plan (28–day cycle) has been updated to include additional ECG assessments for the 28 day cycle
- Table 7-5 ECG Collection Plan (21–day cycle) has been added to include ECG assessments for the alternate dosing schedules (21 days)
- Section 7.2.2.5.7 Cardiac imaging - MUGA (multiple gated acquisition) scan or bilateral echocardiogram has been updated to include an additional assessment on “C3D1”
- Section 7.2.2.5.8 Cardiac Markers [Enzymes] has been updated to include additional cardiac marker assessments
- Section 7.2.3.1 PK blood sample collection and handling has been updated collection and handling instructions for blood PK
- Table 7-5 Pharmacokinetic blood collection log (Phase Ib) 28-day cycle has been updated to include “28-day cycle” on the header
- Table 7-6 Pharmacokinetic blood collection log (Phase Ib) 21-day cycle have been added to include collection and handling instructions for blood PK for the alternate dosing schedules
- Table 7-7 Pharmacokinetic blood collection log (Phase II) 28-day cycle has been updated to include “28-day cycle” on the header
- Table 7-8 Pharmacokinetic blood collection log (Phase II) 21-day cycle have been added to include collection and handling instructions for blood PK for the alternate dosing schedules
- Section 7.2.3.1.1 LEE011 has been updated to include updated LEE011 analytical methods

- Section 7.2.3.1.2 MEK162 has been updated to include updated LEE011 analytical methods
- CCI [redacted]
- Section 9.4 Database management and quality control has been updated to include information regarding the management of data by IRT
- Sections 10.1.4 Dose-determining analysis set has be updated to clarify the DLT evaluation period as cycle 1.
- Section 10.4.2 Statistical hypothesis, model and method of analysis, has been updated to include information around the use of historical data for the new dosing schedule
- Section 10.5.4 Pharmacokinetics, has been updated to include clarification regarding the LEE011 and MEK162 analysis
- CCI [redacted]
- Section 10.8 Sample size calculation has been updated to include information regarding the alternate dosing schedules
- Section 14.6 Appendix 6: Statistical details for the Phase Ib Part: Bayesian logistic regression model (BLRM), priors, design properties for hypothetical data scenarios and design operating characteristics has been updated with the following:
    1. Addition of "3 weeks on and 1 week off" in Table 14-15 through Table 14-26
    2. Section 14.6.1 Statistical model and prior distributions has been updated to include the sentence "of LEE011 administered on 3 weeks on/1 week off schedule " under LEE011 and "of MEK162 administered on BID continuous over 28 days schedule" in the MEK162 section
    3. Tables 14-14, 14-15, 14-16, 14-17, 14-21 through 14-26 have been updated to clarify the MEK162 dosing is BID and is continuous over 28 days
    4. Two sections were added "Alternative regimen: LEE011 QD and MEK162 BID, both 3 weeks on and 1 week off" and "Alternative regimen: LEE011 QD and MEK162 BID, both 2 weeks on and 1 week off" along with Table 14-20 to further clarify the alternate dosing schedules.

IRB/IEC/REB Approval

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

The purpose of this amendment is to implement health authority mandated changes. In addition, editorial changes have been made to sections where previous language was deemed inaccurate or ambiguous by site staff and study investigators, to ensure better protocol compliance.

- The statement, "there was no evidence of cardio vascular toxicity in the 4 week toxicology studies, and" "rare and isolated" have been removed from Section 1.2.1.3 to be consistent with language that will be included in an updated [LEE011 Investigator's Brochure].
- Section 1.2.2.4.1 has been updated to include information on cardiac toxicity that has been observed in patients who have received MEK162 post the release of the version 8 [Investigator's Brochure].
- Section 6.2.3.2 has been updated to include "If two or more patients experience CTCAE grade 2 or greater treatment-related toxicities at a dose level in any cohort, all future dose escalations of LEE011 will be ≤ 50%. Only toxicities that occur during the first cycle will necessarily be considered for decisions".
- Hepato-biliary related DLT criterion (Table 6-2) has been updated to "CTCAE grade 2 total bilirubin concurrent with grade 2 ALT is a DLT except for patients with known liver metastatic disease. The corresponding changes to the dose modification table have been made. Table 6-3 has been updated to "in the event of this DLT hold LEE011 and MEK162 until the toxicity resolves to ≤ Grade 1 and restart at one dose level below for both agents. If toxicity recurs at the lower dose, then discontinue from study".
- Investigations-related DLT criterion (Table 6-2) has been updated to "Serum CK/CPK CTCAE Grade 3 if symptomatic and Serum CK/CPK CTCAE Grade 4" will now be considered a DLT. The corresponding changes to the dose modification table have been made. Table 6-3 has been updated to "discontinue MEK162 if Serum CK/CPK CTCAE is Grade 4".
- Blood chemistry panel (Table 7-2) has been updated to include brain natriuretic peptide (BNP) and troponin measurements at each cycle of treatment for additional cardiac monitoring in patients.
- As patients are required to submit an FFPE sample from diagnosis or relapse at screening in this study, the statement "unless otherwise agreed upon by Novartis and the investigator" has been removed from Section 4.1 and Section 7.2.4 to comply with inclusion criteria.
- Patients with an LVEF less than 50% will be excluded from this study. There was a typographic error which has been corrected. Therefore exclusion criteria # 3 (first bullet) in Section 5.3 and corresponding criteria (#2a) in the protocol summary have been updated to:
    - Left ventricular ejection fraction (LVEF) < 50% as determined by multiple gated acquisition scan (MUGA) or echocardiogram (ECHO).

- Exclusion criteria # 12 has been updated to be consistent with new standard language for MEK162 in regards to male/female contraception during and post study.
- Section 7.2.4 has been updated to provide clarity around tumor sample collections. Per investigator's request, the option of providing an on-treatment biopsy during the dose escalation part (Ph1b) of the study has been added. This is to more thoroughly evaluate the pharmacodynamic effect of the LEE011 and MEK162 combination.
- Section 7.2.1 has been updated for clarification to reflect that "photographic assessments" in addition to radiologic assessments will be collected and held by an imaging CRO for those patients enrolled in the phase II.

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g. 21 or 28 days)
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Subject Number	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
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
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Supportive treatment	Refers to any treatment required by the exposure to a study treatment, e.g. premedication of vitamin supplementation and corticosteroid for pemetrexed disodium.
Treatment group	A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

Protocol summary:

Protocol number	CMEK162X2114
Title	A Phase Ib/II, multicenter, open label, study of LEE011 in combination with MEK162 in adult patients with NRAS mutant melanoma
Brief title	Study of safety and efficacy in adult melanoma patients with NRAS mutant tumors
Sponsor and Clinical Phase	Array BioPharma Phase 1b/II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	LEE011 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. MEK162 is an oral, ATP non-competitive, highly selective inhibitor of MEK1/2. The compound 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 IC50 values as low as 5 nM. Based on pathway biology and preclinical data, the combination of LEE011 and MEK162 has the potential to be effective in patients with NRAS mutant melanoma. In the phase Ib, the primary purpose is to establish the MTD(s)/RP2D of the LEE011 and MEK162 combination. Once the MTD(s)/RP2D have been determined, the phase II part will begin in order to assess antitumor activity of LEE011and MEK162 combination.
Primary Objective	**Phase Ib** Determine the Maximum Tolerated Dose(s) (MTD(s)) and/or Recommended Phase II Dose (RP2D) of LEE011 and MEK162 in combination **Phase II** Assess the anti-tumor activity of the LEE011 and MEK162 combination at the RP2D
Secondary Objectives	**Phase Ib** Characterize the safety and tolerability of the LEE011 and MEK162 combination. Characterize the pharmacokinetics of the LEE011 and MEK162 combination and any clinically significant metabolites that may be identified. To assess clinical efficacy of the LEE011 and MEK162 combinations. **Phase II** Characterize the safety and tolerability of the LEE011 and MEK162 combination. To assess the clinical efficacy of the LEE011 and MEK162 combination.
Study design	This is a multi-center, open label, two part study, with a dose escalation followed by a phase II part. Both parts of the study are limited to patients aged 18 or older with metastatic or locally advanced NRAS mutant melanoma. The phase II part will start after the MTD/RP2D has been determined in the phase Ib part. LEE011 will be administered orally, once daily for 21 days followed by a 1 week break in combination with MEK162 administered twice daily in a continuous dosing schedule (28 day cycle). In addition, the combination of LEE011 and MEK162 may be administered together for 14 days followed by a 1 week break in both drugs (21 day cycle) and/or together for 21 days followed by a 1 week break in both drugs (28 day cycle). For the purpose of establishing the MTD(s)/RP2D, the DLT evaluation period is 1 cycle.
Population	Patients, ≥ 18 years, with metastatic or locally advanced NRAS mutant melanoma

Inclusion criteria	1. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 – 1. 2. Patients enrolled into phase Ib may be enrolled with evaluable disease only. Patients enrolled into the phase II expansion must have at least one measurable lesion as defined by RECIST 1.1 criteria. 3. Patients must have adequate organ function, as defined by the following parameters: ● Bone marrow: a. Absolute Neutrophil Count (ANC) ≥ 1.5 x 10^9/L b. Hemoglobin (Hgb) ≥ 9 g/dL c. Platelets ≥ 75 x 10^9/L without transfusions within 21 days before 1st treatment d. PT/INR and aPTT ≤ 1.5 ULN. ● Serum creatinine ≤1.5 ULN ● Hepatic function: a. Serum total bilirubin ≤ 1.5 x upper limit of normal (ULN), except for patients with known Gilbert syndrome, who are excluded if total bilirubin > 3.0 x ULN or direct bilirubin > 1.5 x ULN b. Aspartate Aminotransferase (AST) (serum glutamic oxaloacetic transaminase (SGOT) and ALT (SGPT) ≤ 2.5 x ULN, except in patients with tumor involvement of the liver who must have AST and ALT < 5 x ULN ● Laboratory values within normal limits or corrected to within normal limits with supplements before the first dose of study medication: a. Sodium b. Potassium c. Magnesium d. Inorganic phosphate e. Calcium (corrected for serum albumin)
Exclusion criteria	1. Presence of any brain metastases detected by MRI or CT with i.v. contrast of the brain at screening. 2. Uncontrolled arterial hypertension despite medical treatment 3. Impaired cardiac function, clinically significant cardiac diseases, and/or recent cardiac events, including any of the following: a. Left ventricular ejection fraction (LVEF) < 50% as determined by multiple gated acquisition scan (MUGA) or echocardiogram (ECHO) b. Congenital long QT syndrome or family history of unexpected sudden cardiac death. c. On screening, inability to determine QTcF interval on the ECG (i.e.: unreadable or not interpretable) or QTcF >450 ms (using Frederica's correction). All as determined by screening ECG (mean of triplicate ECGs). d. Angina pectoris or symptomatic pericarditis within 12 months prior to starting study drug e. Acute myocardial infarction within 12 months prior to starting study drug f. Clinically significant resting bradycardia within 12 months prior to starting study drug g. History or presence of ventricular tachyarrhythmia within 12 months prior to starting study drug h. Unstable atrial fibrillation (ventricular response >100 bpm) i. Complete left bundle branch block within 12 months prior to starting study drug j. Right bundle branch block and left anterior hemi block (bifascicular block) within 12 months prior to starting study drug k. Obligate use of a cardiac pacemaker or implantable cardioverter defibrillator l. Any other clinically significant heart disease (e.g. documented congestive

	heart failure, documented cardiomyopathy) 4. Patients who are currently receiving treatment with agents that are known to cause QT prolongation or induce Torsades de Pointes in humans and cannot be discontinued 7 days prior to Cycle 1 Day 1 5. Patients who are currently receiving treatment with agents that are metabolized predominantly through CYP3A4 and that have a narrow therapeutic window and cannot be discontinued 7 days prior to Cycle 1 Day 1. Agents that are known strong inducers or inhibitors CYP3A4 are prohibited. 6. Patients with concurrent severe and/or uncontrolled concurrent medical conditions that could compromise participation in the study (e.g. uncontrolled diabetes mellitus, clinically significant pulmonary disease, clinically significant neurological disorder, active or uncontrolled infection) 7. History or current evidence of retinal vein occlusion (RVO) or current risk factors for RVO (e.g. uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes)
Investigational and reference therapy	LEE011 + MEK162
Efficacy assessments	**Phase Ib** Best Overall Response (BOR) and Overall response rate (ORR), Duration of response (DOR), Time to progression (TTP), Progression Free Survival (PFS), and Overall Survival (OS) as per RECIST 1.1. **Phase II** Best Overall Response (BOR) and Overall Response Rate (ORR), Duration of response (DOR), Time to progression (TTP), Progression Free Survival (PFS) and Overall Survival (OS) as per RECIST 1.1.
Safety assessments	Incidence rate of Dose Limiting Toxicities (DLT) during the first cycle of LEE011 and MEK162 combination treatment Adverse events and serious adverse events, changes in laboratory values, assessments of physical examinations, vital signs, electrocardiograms, and dose interruptions, dose reduction and dose intensity.
Other assessments	Plasma concentration-time profiles of LEE011 and MEK162, PK parameters, including but not limited to AUCtau, AUCtau,ss, Cmin,ss, Cmax, Cmax,ss, Tmax, Tmax,ss, accumulation ratio (R_{acc}), and T1/2,acc, CL/F(phase Ib). CCI [redacted]

Data analysis	The primary purpose of the study is to estimate the MTD(s) and/or identify the RP2D and schedule of LEE011 and MEK162 combination in adult patients with NRAS mutant melanoma. The corresponding primary endpoint is the incidence of DLTs in cycle 1. Estimation of the MTD of the treatment will be based upon the estimation of the probability of DLT in Cycle 1 for patients in the DDS (see definition below), using an adaptive BLRM guided by the EWOC principle. Unless otherwise specified, the Full Analysis Set (FAS) will be the default analysis set used for all analyses. It includes all patients who received at least one dose of LEE011 or MEK162. For all safety analyses, the safety set will be used. It includes all patients who received at least one dose of LEE011 or MEK162, and have at least one valid post-baseline safety assessment. The dose-determining set (DDS) will be used for the estimation of MTD. It consists of all patients from the safety set who meet a minimum exposure criterion as outlined in Section 10 and have sufficient safety evaluations, or discontinue earlier due to DLT. All the data will be summarized with respect to demographic, baseline characteristics and safety observations using descriptive statistics (quantitative data) and contingency tables (qualitative data). Pharmacokinetic parameters will be determined using either non-compartmental method(s) or fitting of the actual values to a population PK model. Anti-tumor activity will be summarized in terms of ORR, DOR, TTP, PFS and OS as per RECIST 1.1. CCI [redacted] The study data will be analyzed and reported based on all patients' data from the dose escalation and expansion parts. Details of the statistical analysis and data reporting will be provided in the Report and Analysis Plan (RAP) document finalized prior to database lock.
Key words	Phase Ib/II, adult, open-label, NRAS mutant melanoma

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Approximately 160,000 new cases of melanoma are diagnosed and 48,000 melanoma-related deaths occur worldwide each year (World cancer report 2008, International Agency for Research on Cancer 2008). Among cancers in patients under 40 years of age, the incidence of melanoma is second only to that of breast cancer for women and leukemia for men (Siegel 2012). 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 metastases 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 2010).

There is a high frequency of activating mutations in proteins of the RAS/RAF/MEK/ERK pathway in melanoma. The NRAS gene is mutated in 15-20% of melanomas. The most common mutations in NRAS occur at codons 12, 61 and less frequently at 13 (van Elsas 1995). The presence of NRAS mutations in melanoma causes a switch in MAPK signaling from BRAF to CRAF, initiating dysregulated cAMP signaling that allows CRAF to signal to MEK (Dumaz 2006). Mutations in NRAS are exclusive of alterations in PTEN, implying that mutations in NRAS alone may activate signaling through both the MAPK and PI3K pathways (Goel 2006, Davies 2009). Compared to other melanoma subtypes, melanomas with NRAS mutations are associated with a worse prognosis (Devitt 2011). Selective pharmacological inhibition of NRAS remains technically challenging because its GTPase activity has so far eluded the successful design of specific small-molecule antagonists. A number of clinical trials are underway to evaluate alternative strategies which combine inhibitors of molecules downstream of NRAS, such as BRAF and MEK inhibitor combinations and the combination of PI3K pathway inhibitors with drugs that inhibit the ERK pathway (Kelleher 2012). The efficacy of these various approaches is not yet established and there remains a need for effective therapy for NRAS mutated melanoma.

Deregulation of cell cycle check points have been well described in melanoma (Wang 1996). The loss of expression of the p16 (also known as INK4A) tumor suppressor, by mutation, deletion or transcriptional silencing of the CDKN2A locus, is a frequent event in melanoma (Yang 2005). Activating mutations in CDK4 have been described in familial melanoma, as well as in sporadic cases of melanoma, as has CDK4 amplification (Walker 1998). Intact p16 inhibits CDK4 activity, so genetic inactivation of p16 is thought to result in aberrant CDK4 activity. Amplification of cyclin D, which cooperates with CDK4 to drive cell cycle progression, is observed in a subset of melanoma and provides further genetic evidence that CDK4 activity is a fundamental element in melanoma transformation (Hodis 2012, Curtin 2005, Smalley 2008). Therefore, targeting the CCND1/CDK4 axis may provide therapeutic benefit to melanoma patients.

In addition to this genetic deregulation of the cell cycle, mutant NRAS itself plays a known central role in proliferation (Eskandarpour 2009). In an inducible mouse model of NRAS-

mutant melanoma, $NRAS^{Q61K}$ expression can be shut off genetically. This produces a near-complete cessation of mitotic activity after four days, accompanied by enhanced apoptosis (Kwong 2012). Importantly, this occurs despite the permanent deletion of $p16^{INK4A}$ by genetic engineering, indicating that this cell cycle arrest is independent of – and not rescued by – the loss of p16. When NRAS signaling is only partially inhibited, either by partial NRAS extinction at two days post-shutoff or by pharmacological MEK inhibitor treatment, apoptosis is induced but not cell cycle arrest. Therefore, while NRAS signaling cross-talks with the cell cycle machinery via the CDK4-Rb axis, NRAS signaling is not an all-or-nothing process: its outputs such as apoptosis can be decoupled from the cell cycle along a gradient of NRAS activity. Together, these data on the importance of the cell cycle in melanoma suggests that it may be a separate and therefore complementary target to MAPK pathway inhibition.

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

1.2.1 Overview of LEE011

LEE011 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 in adult cancer patients [CLEE011X2101].

1.2.1.1 Preclinical pharmacology

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 as a single agent. Tumor regression was achieved in two models, while tumor stasis was observed in five models. In addition, LEE011 has also demonstrated anti-tumor activity as a single agent in two NRAS-mutant melanoma models. In these models, LEE011 in combination with MEK162 resulted in tumor regression.

1.2.1.2 Non-clinical pharmacokinetics and metabolism

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 from 10% to 65% across animal species. Maximum serum drug concentration (Cmax) was between 2 and 4 hours. The 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 human 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 was dominated by CYP3A4 with a minor contribution by flavin-containing monooxygenase 3 (FMO3). LEE011 is a moderate substrate of P-glycoprotein (Pgp). LEE011 is a time-dependent CYP3A4 inhibitor and a reversible inhibitor of CYP1A2. LEE011 was found to inhibit the mitoxantrone-resistant protein (MXR), and human bile salt export pump (BSEP) but not the rat or dog BSEP. 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 h.

Overall, the elimination of LEE011 may potentially be affected by co-administered drugs that inhibit or induce CYP3A4. LEE011 may inhibit CYP3A4, CYP1A2 and BSEP depending on the dose administered.

1.2.1.3 Safety pharmacology and toxicology

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 premature ventricular contractions (PVCs) at higher exposure levels. 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 [LEE011 Investigators Brochure] for additional details.

1.2.1.4 Clinical experience

Safety and PK reported in this document are from the first-in-human (FIH) study, [CLEE011X2101] – "A phase I, multicenter, open label, dose escalation study of oral LEE011 in patients with advanced solid tumors and lymphomas".

As of 2 July 2013, 78 patients have been treated with increasing doses of LEE011 orally, once daily for 21 days followed by a 1 week rest (28-day cycle) in [CLEE011X2101]. Doses ranging from the starting dose of 50 mg to 1200 mg were evaluated on this schedule. In addition, continuous dosing of LEE011 at 600 mg was evaluated (once daily for 28 days of a 28-day cycle). A total of 10 events meeting DLT criteria were observed at the indicated doses and include grade 3 mucositis/stomatitis (n=1) at 50 mg, grade 3 pulmonary embolism (n=1) at 280 mg, grade 3 hyponatremia (n=1) and prolonged grade 3/4 neutropenia (n=1) at 400 mg, prolonged grade 2 elevated creatinine (n=1) at 600 mg, grade 4 thrombocytopenia (n=1) at 750 mg, grade 3 asymptomatic QTcF prolongation with grade 3 neutropenia in one patient at 900 mg and grade 4 febrile neutropenia (n=1) and grade 4 thrombocytopenia (n=1) at 1200 mg. There was also 1 DLT, grade 3 neutropenia at 600 mg on the continuous dosing schedule. Grade 1/2 neutropenia was observed at doses of 280 mg or higher (23%) and grade 3/4 neutropenia was seen at doses of 400 mg and higher (21%).

Asymptomatic grade 2 QTc prolongation was observed with increasing frequency starting at 600 mg with grade 3 prolongation in 2 patients. The most frequently reported AEs (>15%) regardless of study treatment relationship include neutropenia (44%), nausea (42%), anemia (41%), leukopenia (37%), fatigue (35%), diarrhea (31%), thrombocytopenia (28%), vomiting (28%), lymphopenia (27%), decreased appetite (24%), asthenia (23%), constipation (19%), hyperglycemia (17%), and hypoalbuminemia (17%). The majority of all reported adverse events were mild or moderate (grade 1-2) and reversible.

There have been no deaths related to LEE011 reported in the above referenced study.

CCI [redacted]

1.2.1.5 Clinical pharmacokinetics of LEE011

Following oral dosing, LEE011 is rapidly absorbed with median time to reach maximum plasma concentrations (Tmax) ranging from 1 to 4 hours (range of median Tmax values). LEE011 plasma exposure (maximum plasma concentration [Cmax] and AUC) exhibit slightly over-proportional increases in exposure across the dose range tested (50 to 1200 mg), with no

clear evidence of time-dependent auto-inhibition of its clearance mediated by CYP3A4. Steady-state is generally reached by Day 8 and the arithmetic mean effective T1/2 based on accumulation ratio (i.e., T1/2,acc) range from 15.9 to 43.1, hours across the 50 to 1200 mg dose cohorts. The accumulation ratio based on AUC obtained in a dosing interval (Racc) across the studied doses ranged from 1.55- to 3.13-fold.Following oral dosing, LEE011 is rapidly absorbed with median time to reach maximum plasma concentrations (Tmax) ranging from 1 to 4 hours. LEE011 plasma exposure (maximum plasma concentration [Cmax] and AUC) exhibit slightly over-proportional increases in exposure across the dose range tested (50 to 1200 mg). Steady-state is generally reached by Day 8 and the arithmetic mean effective T1/2 based on accumulation ratio ranges from 15.9 to 43.1, hours. The accumulation ratio based on AUC (Racc) ranged from 1.55- to 3.13-fold. The MTD of LEE011 is 900 mg QD with a 3 weeks on/1 week off schedule. The R2PD for future development is 600 mg QD with a 3 weeks on/1 week off schedule which has an acceptable safety profile, lower risk for QT prolongation, adequate exposures, and preliminary evidence of clinical activity.

For further information regarding clinical experience with LEE011, refer to the [Investigator's Brochure].

1.2.2 Overview of MEK162

MEK162, previously named ARRY-438162, is an oral, ATP non-competitive, highly selective inhibitor of MEK1/2. The compound 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 IC50 values as low as 5 nM. MEK162 is undergoing clinical evaluation for the treatment of a range of BRAFV600E and RAS-mutated solid-tumor indications including melanoma, colorectal and biliary cancers.

1.2.2.1 Preclinical pharmacology

MEK162 potentially inhibits the cell proliferation of mutant BRAF and RAS human cancer cell lines in vitro. NRAS mutation is a predictor of sensitivity to MEK inhibitors with a positive predictive value of 56% in a panel of 272 WT and mutant lines. MEK162 has demonstrated tumor regression in BRAF mutant melanoma xenograft models with clear evidence of pathway inhibition. MEK162 has demonstrated in vitro and in vivo antitumor activity in other cancer models driven by the MAPK pathway (colorectal, pancreatic, non-small cell lung) with tumor regressions in some. Tumor growth inhibition correlated with decreased phospho-ERK levels in all tumor xenografts. MEK162 has also shown significant anti-tumor activity in xenograft models in combination with targeted agents like LGX818, RAF265, and LEE011, and standard-of-care agents such as cisplatin, 5 FU, and taxanes.

1.2.2.2 Non-clinical pharmacokinetics and metabolism of MEK162

In animals, exposure (AUC) and Cmax generally increases in a dose proportional manner. The plasma clearance is low (range: ~2 to 8 mL/min/kg) and the mean plasma T1/2 ranges from 2 to 9 hours. MEK162 has moderate membrane permeability and is a substrate of P-gP and BCRP. MEK162 exhibits high plasma protein binding *in vitro* (> 96%, except dog 84%) and is predicted to have good stability with respect to hepatic metabolism. Nonclinical *in vitro* and *in vivo* data indicate that MEK162 is metabolized by multiple routes but primarily by

glucuronidation pathways (mainly via UGT1A1, 1A3 and 1A9) and to a lesser extent by oxidation pathways (mainly via CYP1A2 and 2C19). The formation of active metabolite AR00426032 is mediated primarily by CYP1A2 with minor contributions from other CYPs. MEK162 potently inhibits CYP2B6 and weakly inhibits CYP1A2 and 2C9. It is not considered a time-dependent inhibitor of CYP1A2, CYP2C9, CYP2D6 and CYP3A. *In vitro* evidence also suggests that MEK162 could induce CYP3A.

1.2.2.3 Safety pharmacology and toxicology

Nonclinical toxicological studies indicated that MEK162 was well tolerated. The most prominent in-life findings were dose-related, reversible hair loss and/or scabbing in rats and dose-related, reversible loose or watery stools in monkeys. Administration of MEK162 to rats was associated with microscopic findings of soft tissue mineralization, skin effects and minimal to mild clinical pathology changes. Gastric mucosal lesions were associated with MEK162 administration to rats at 100 mg/kg. In cynomolgus monkeys, administration of MEK162 was associated with soft stools, moderate clinical pathology changes in some animals and reversible histopathologic changes in the gastrointestinal tract.

There was no evidence of genotoxicity. Embryo-fetal development studies showed evidence of teratogenicity in rabbits (ventricular septal defects and outflow tract defects) and decreased ossification that is considered to be secondary to decreased fetal body weights at maternally toxic doses in rats.

For detailed information refer to the [MEK162 Investigator's Brochure].

1.2.2.4 Clinical experience

MEK162 has been tested in multiple clinical studies including healthy subjects, patients with rheumatoid arthritis, and patients with various advanced solid tumors. Some studies are complete and several are on-going. As of 29 Feb 2012, a total of 450 subjects/patients have received at least 1 dose of MEK162 and been evaluated for safety, including 70 healthy subjects, 164 patients with rheumatoid arthritis and 216 patients with advanced cancer. For detailed information regarding these clinical studies with MEK162, refer to the [Investigator's Brochure].

The 216 patients with advanced solid tumors have received or are currently receiving MEK162 (either as a single agent or in combination) at doses of 30 to 80 mg BID. MEK162 has target-related PD activity in skin at multiple-dose levels at and below the MTD of 60 mg BID.

As of the data-cutoff date of 29 February 2012, the most frequent treatment-related AEs in patients receiving MEK162 for advanced cancer were rash, dermatitis acneiform, nausea, diarrhea, peripheral edema, vomiting, fatigue and increase in blood creatine phosphokinase (CPK/CK).

130/171 patients treated with MEK162 as a single agent developed an AE of rash. Of those, 78% were assessed as related to MEK162. Most were Grade 1-2 in severity and improved or resolved with treatment (topical or oral antibiotics, topical or oral steroids). In most cases, MEK162 was continued throughout treatment of the rash, however a small number of patients required a dose hold and/or dose reduction. Grade 3/4 events of rash occurred in eight

patients, one of which was a DLT at the 80 mg BID dose level. In the combination studies of MEK162 with other PI3K or RAF inhibitors, rash was also one of the most commonly reported AEs.

Retinal events have occurred in 17 out of 90 patients tested in the [ARRAY-162-111] study at dose levels of 45 mg BID or higher and include 5 patients with Grade 1, 11 patients with Grade 2, and 1 patient with Grade 3 events. Approximately 71% of these patients reported visual symptoms associated with the retinal abnormalities. Symptoms have included "flashing lights/floaters, color variations, blurred vision, and seeing shapes upon opening the eye". Retinal events have been described as "leaky" type detachment with collections of sub-neurosensory fluid which is best visualized on optical coherence tomography. No "tear" type detachments have been reported. The retinal events have included central serous retinopathy (CSR), retinal deposits, retinopathy, chorioretinopathy and venous stasis retinopathy. To date, these retinal events have been reversible in all patients upon discontinuation or dose reduction of MEK162. In most patients, MEK162 was held until resolution of all signs and symptoms. In two patients in the 45 mg BID cohort, the dose was reduced without holding treatment and there was no reoccurrence of the event. Low grade (Grade 1/2) CSR-like events were also reported by 17/81 patients in the single agent [MEK162X2201] study and 3/3 patients in the Japanese single agent [MEK162X1101] study. Low grade (Grade 1/2) CSR-like events were also reported in all combination studies of MEK162 with PI3K or RAF inhibitors.

Diarrhea has been reported in 45/90 patients in the [ARRAY-162-111] study and in 36/81 patients in the [MEK162X2201] study. Of those, 41% and 30%, respectively, were assessed as related to MEK162. In addition, 2/3 Japanese patients in the [MEK162X1101] study reported treatment-related diarrhea. The majority of these events were Grade 1 or 2 and responded well to standard anti-diarrheal agents. Treatment-related diarrhea has also been reported in all trials where MEK162 has been used as a combination treatment.

Peripheral edema has been observed in 42/90 patients in the [ARRAY-162-111] study and in 34/81 patients in the [MEK162X2201] study. Of those, 34% and 27%, respectively, were assessed as related to MEK162. Events were reported in the 45, 60, and 80 mg BID cohorts, though none were reported in the 30 mg BID cohort. Most of the events were Grade 1 or 2 and responded well to diuretic agents. Two out of 81 patients reported Grade 3/4 peripheral edema in the [CMEK162X2201] study.

Adverse events of reversible elevations of CK were reported in 12/90 (13%) patients in the [ARRAY-162-111] study. Additionally, clinical laboratory results have shown that 64/90 (71%) patients had an elevated CK after starting study therapy. Most elevations were of Grade 1-2.

Eight patients had Grade 3 elevations and one patient had a Grade 4 elevation. Most of the CK elevations were asymptomatic and reversible. In the [CMEK162X2201] study, increase of the blood CK has been reported in 24/81 (30%) patients, including Grade 3/4 events reported by 16/81 patients. Of those, the event was reported as related to MEK162 treatment in 28% of patients. Adverse events of reversible elevations of CK have also been reported in the combination studies of MEK162 with PI3K or RAF inhibitors.

As of the data-cutoff date 32, (15%) out of 216 patients with advanced cancer treated with MEK162 (as a single agent or in combination with PI3K or RAF inhibitors) experienced liver-

related adverse events (19 patients Grade 1 or 2, 12 patients Grade 3, 1 patient Grade 4). Twenty three of 32 patients had liver metastases at baseline. The reported adverse events included elevations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), alkaline phosphatase (AP), bilirubin, hepatic pain, ascites, cytolytic hepatitis, bile duct obstruction, cholangitis, jaundice and cholestatic jaundice. One case of acute liver failure with fatal outcome at a dose of 60 mg BID, possibly related to MEK162 has been reported after the data-cutoff date. In this case, the investigator considered the liver failure was related to study drug; however, other diagnoses, such as muscular toxicity and/or thrombotic/vascular/hepatic events, may be considered. This is the only case of fatal liver failure reported in more than 450 subjects/patients that have received at least one dose of MEK162 to date.

One case of cardiac failure, possibly related to MEK162 has been reported after the data cutoff date. A second case of a non-serious decrease in cardiac ejection fraction was reported in a patient receiving MEK162 at a starting dose of 60 mg BID. This patient had, however, a number of confounding factors, including significant hypothyroidism and hypertension. Elevated CK was associated with the administration of MEK162, as described above. It cannot be excluded that in a small percentage of patients with advanced cancer MEK162 is associated with liver transaminase elevations. No other apparent trends in clinical laboratory parameters, vital signs or electrocardiograms (ECGs) were associated with the administration of MEK162.

Additionally, post the [MEK162 Investigator's Brochure] cut-off date of 29 February 2012 and 10 December 2012, Novartis received five serious adverse event (SAE) reports of cardiotoxicity that are considered possibly related to MEK162; patients received doses of 45 mg BID or 60 mg BID. In three cases MEK162 was used in combination with a RAF inhibitor.

The five cardiotoxicity cases were: reduced left ventricular ejection fraction (LVEF) (2 cases); cardiac failure with decreased LVEF (1 case); bradycardia with decreased LVEF (1 case) and atrial fibrillation with left and right ventricular dysfunction (1 case) The events were considered related to the study drug(s) by the investigators; however, four of the five patients had risk factors for cardiovascular disease, confounding a conclusive association with the study drug(s). Three of the five cardiac toxicities resolved to baseline levels following study drug discontinuation; one patient recovered with sequalae, and one patient's symptoms were ongoing (reduced LVEF and increased troponin) as of the 10 December 2012 cutoff.

There has been no evidence of phototoxicity or photosensitivity in humans treated with MEK162 for cancer or for rheumatoid arthritis. Given the embryo-lethal effects seen in rats and rabbits and the teratogenic effects seen in rabbits, MEK162 should not be used in pregnant women and women of child-bearing potential must be advised to use highly effective contraception methods.

In June 2013, one case of hypertensive crisis in a patient receiving MEK162 prompted a review of blood pressure data across all MEK162 studies. These data showed that hypertension could be an early onset adverse event isolated to a limited group of patients with a predisposition to hypertension.

For further information regarding clinical experience with MEK162 refer to the [MEK162 Investigator's Brochure].

1.2.2.5 Clinical pharmacokinetics of MEK162

In healthy subjects, MEK162 exposure (as quantified by Cmax and AUC) tended to increase in a dose-proportional manner following single and multiple doses over a dose range of 5 to 80 mg QD for single dose and 5 to 60 mg QD for multiple doses. One additional cohort received 20 mg BID for 14 consecutive days. The mean T1/2 was 7 to 8 hours, and the mean (Tmax) was 1.18 hrs. The AR00426032 metabolite represented < 13% of the parent drug in plasma and < 5% of the parent drug was excreted renally. Accumulation of MEK162 was < 40% following QD dosing and < 75% following BID dosing.

The initial evaluation of the PK of MEK162 in patients with advanced cancer ([ARRAY-162-111] and [CMEK162X2201]) at the doses evaluated to date (30 to 80 mg BID) indicated that both the plasma concentration-time profiles and PK parameters were similar to those in healthy subjects, as well as in patients with rheumatoid arthritis. The inter-subject variability for AUC and Cmax was ~40%. The mean active metabolite-to-parent ratio was less than 25% across all study days and dose levels tested. Steady-state is reached by Day 15 and accumulation of MEK162, as estimated using non-compartmental methods, is around 50% (or 1.5 fold).

To integrate all the available PK information, a preliminary population PK model describing the PK of MEK162 was built using data from 68 subjects from the Array and Novartis studies. The model suggests that the PK can be adequately described using linear kinetics (2 compartmental open model with first order absorption and a lag time). Clearance of MEK162 estimated as 17 L/h. For the typical individual, steady-state is reached by Day 15 and accumulation of MEK162 is around 70% (or 1.7 fold).

For further information regarding clinical experience with MEK162, refer to the [Investigator's Brochure].

1.2.2.6 Clinical experience with the combination of LEE011 and MEK162

As of 17 February 2014, 22 patients have been treated with the combination of LEE011 administered orally once daily for 21 consecutive days followed by a 1 week break (3 weeks on /1 week off) in combination with MEK162 administered orally twice daily in a continuous dosing schedule on a 28-day cycle [CMEK162X2114]. Four dose levels were explored; Cohort 1: LEE011 200mg QD + MEK162 45mg BID (9 patients), Cohort 2: LEE011 300mg + MEK162 45mg BID (6 patients), Cohort 3A: LEE011 300mg + MEK162 30mg BID (4 patients) and Cohort 3B: LEE011 250mg + MEK162 45mg BID (3 patients).

One DLT of grade 3 acute renal injury occurred in Cohort 1 (n=1) and two DLTs of grade 4 CPK elevation (n=1) and of grade 4 atrial fibrillation (AF) and grade 3 edema (n=1) occurred in Cohort 2. PPD

[redacted]

PPD . PPD

Interim safety summary from 17 patients (as of 17-Feb-2014) is listed below. Treatment-related AEs occurring in 2 or more patients (≥10%) included blood creatine phosphokinase increased (41%), acneiform dermatitis (41%), diarrhea (24%), fatigue (24%), nausea (24%), peripheral edema (24%), anemia (18%), aspartate aminotransferase (AST) elevation (12%), increased creatinine (12%), decreased appetite (12%), hyperphosphatemia (12%), hypoalbuminemia (12%), mucosal inflammation (12%), neutropenia (12%), acute renal failure (12%), retinopathy (12%), vomiting (12%), leukopenia (12%), and decreased white blood cell count (12%). Treatment-related CTCAE Grade 3-4 AE occurring in one or more patients included blood creatine phosphokinase increased (18%), acute renal failure (12%), atrial fibrillation (6%), hypertension (6%), hypokalemia (6%), hypophosphatemia (6%), neutropenia (6%), decreased neutrophil count (6%), and rash (6%).

PPD

Preliminary PK data are consistent with that of the respective single agents and there appears to be no evidence of drug-drug interaction. Of the 14 patients who have had at least one post-baseline scan, 1 confirmed partial response (PR), 5 unconfirmed PR, and 6 patients with stable disease (4 with >20% tumor shrinkage) have been reported. Of the 21 patients, 14 remain on treatment. A majority of patients have required multiple dose interruptions for management of toxicities, and 7 patients have required dose reductions for one or both drugs.

2 Rationale

2.1 Study rationale and purpose

There are no established therapies for patients with NRAS mutant melanoma and their prognosis is poor. Targeting the RAS/RAF/MEK/ERK pathway and the CCND1/CDK pathway downstream may be an effective strategy for treatment. MEK inhibitors act downstream of RAS and RAF and can potentially block signal transduction that results from either mutations or activation through cell surface receptors. In an inducible mouse model of NRAS-mutant melanoma, pharmacological MEK inhibition activated apoptosis but failed to trigger cell cycle arrest. This is in contrast to complete mutant NRAS extinction by genetic means, which induced both apoptosis and cell cycle arrest. Systems biology analyses of comparative microarray data demonstrated that the lack of cell cycle arrest with MEK inhibition centered on a CDK4-Rb axis. Accordingly, the combined pharmacological inhibition of MEK and CDK4 *in vivo* led to apoptosis, cell cycle arrest and tumor regression. This was validated in two independent NRAS-mutant human melanoma cell line xenograft models, one each of mucosal and cutaneous origin. The mechanism was also validated in an ex vivo model using a fresh patient biopsy. (Kwong 2012). Simultaneous inhibition of MEK and CDK4/6 could ensure complete inhibition of activated pathways and lead to enhanced anti-tumor activity.

In clinical studies, MEK162 has demonstrated single agent anti-tumor activity in patients with NRAS cutaneous melanoma [CMEK162X2201]. As of the data cutoff date May 31, 2012 thirty one patients with NRAS mutant status were evaluable for efficacy. 7 patients (23%) had a partial response (4 confirmed), 13 patients had stable disease (42%), and the disease control rate was 63%. The median PFS was 3.65 months (95 % CI: 2.53 - 5.36) [Ascierto PA. Abstract 8511. ASCO 2012]. LEE011 is a highly selective inhibitor of CDK4/6, which has shown in vitro and in vivo activity in models of NRAS melanoma both as single agent and in combination with MEK162. Based on pathway biology and preclinical data, the combination of LEE011 and MEK162 has the potential to be effective in patients with NRAS mutant melanoma. The purpose of this study is to evaluate the safety of the combination of these agents, evaluate ORR and PFS in comparison to the single agent activity of MEK162 in the ongoing studies in the same patient population. This study will be used to inform future development of the combination in NRAS mutant melanoma.

2.2 Rationale for the study design

The study will follow a phase Ib/II design. As outlined in Section 1.1, NRAS mutations are well known oncogenic drivers in melanoma and play a prognostic role in outcome. While deregulation of cell cycle check points occur frequently in melanoma, their role as oncogenic molecular drivers is less clear. Therefore, in this study patients will be pre-selected based on NRAS mutant status, but no pre-selection will be made based on aberrations in the CCND1/CDK4 axis. Only patients with a documented mutation in NRAS (e.g, substitutions at positions 60 and 61; Q61 R/K/L) will be included in both phases of the study. Intact Rb is present in >90% of NRAS melanoma tumors (Hodis 2012); therefore, no pre-screening for the presence of Rb will be required, but the analysis will be performed retrospectively.

The primary purpose of the phase Ib portion is to estimate the MTD(s) and/or the RP2D of the LEE011 and MEK162 combination. The dose escalation will be guided by an adaptive Bayesian logistic regression model (BLRM) with overdose control (EWOC) principle. The 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 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.

Once the MTD(s)/RP2D have been determined for each tested schedule, additional patients will be enrolled in the phase II portion of the study at the RP2D on the chosen schedule in order to assess the anti-tumor activity of the combination in addition to continued evaluation of safety. In the Phase II part of the study, a Bayesian design will be used in order to estimate the true overall response rate (ORR) in the phase II arm. No interim analysis will be performed due to the expectation that all patients will be recruited prior to any analysis time point.

2.3 Rationale for dose and regimen selection

The MTD for MEK162 single agent is 60 mg BID dosed continuously. The RP2D of 45 mg BID is the single agent dose used in ongoing studies in patients with melanoma. This dose has been shown to be very well tolerated and has demonstrated anti-tumor activity in patients with NRAS melanoma. Since the dose is safe and effective and the risk for drug-drug interaction is minimal, this study will use MEK162 at 45 mg BID from the first dose cohort without any planned escalation. If at the time of the dose escalation, the available safety, tolerability, PK, PD and efficacy data, as well as the recommendations from the BLRM do not support treatment of the next cohort of patients with any LEE011 doses in combination with MEK162 45 mg BID, then LEE011 doses in combination with MEK162 30 mg BID may be evaluated if they satisfy the EWOC criterion.

The MTD and RP2D for LEE011 are 900 mg QD and 600 mg QD, respectively, on a 3 weeks on/1 week off schedule. The starting dose of LEE011 in this study will be 200 mg QD based upon review of the safety, tolerability, and PK observed at different dose levels tested in [CLEE011X2101] study, as well as the BLRM recommendations based on EWOC criterion (see Section 10.4.2 and Appendix 5 for details). The dose of LEE011 will be escalated during the study to establish a MTD(s)/RP2D of the combination. At the 200 mg QD dose in adults, LEE011 was well tolerated with an acceptable safety profile. The phase Ib part of the study will begin with LEE011 administered orally once daily for 21 consecutive days followed by a 7-day planned break (3 weeks on /1 week off) in combination with MEK162 administered orally twice daily in a continuous dosing schedule on a 28-day cycle. In addition, should safety and PK data from the dose escalation part of this study and/or other MEK162/LEE011 study(s) indicate that alternate dosing schedules of MEK162 and LEE011 are more appropriate, alternate dosing schedules may be explored (see Section 4.1). All available safety and PK data collected from the initial dosing schedule will be considered and reviewed prior to exploring new alternate dosing schedule(s).

MTD(s) will be established for all tested dosing schedules. Based on their safety, tolerability, and efficacy, a single RP2D and schedule will be selected for the phase II part of the study in order to assess antitumor activity of the LEE011and MEK162 combination.

The starting dose decision for the initial dosing schedule (LEE011 QD on a 3 weeks on/1 week off and MEK BID on a continuous schedule) took into consideration all information currently available about the dose-DLT relationships of MEK162 and LEE011 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 EWOC criterion (less than 25% chance that true DLT rate > 35%). There is minimal overlap of toxicities between LEE011 and MEK162. Special attention will be paid to GI toxicities, edema, cardiac function, liver function, and ECGs in evaluating the combination. Based on CYP3A4 interaction, the risk for drug-drug interaction (DDI) is minimal. PK of both agents will be obtained to monitor for DDI.

The starting dose decision for any alternate dosing schedule will take into consideration all available safety and PK data collected from the initial dosing schedule and must satisfy the EWOC criterion at the time of the decision to switch to the new combination schedule (see Appendix 5 for details).

2.4 Rationale for choice of combination drugs

Please refer to Section 2.1 for the rationale for choice of combination drugs.

3 Objectives and endpoints

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

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4.
Phase Ib: To estimate the MTD(s)and/or to identify the RP2D and schedule of LEE011 and MEK162 in combination	Incidence of dose limiting toxicities in cycle 1	
Phase II: To describe the anti-tumor activity of the LEE011 and MEK162 in combination at the RP2D	ORR (CR and PR) according to RECIST 1.1	
Secondary		Refer to Section 10.5.
Phase Ib: To characterize the PK profiles of LEE011 and MEK162 as well as any other clinically significant metabolites that may be identified.	Plasma concentration-time profiles of LEE011 and MEK162, PK parameters, including but not limited to AUCtau, AUCtau,ss, Cmin,ss, Cmax, Cmax,ss,Tmax, Tmax,ss, accumulation ratio (R_{acc}), and T1/2,acc, CL/F	
Phases Ib and II: To characterize the safety and tolerability of LEE011 and MEK162.	Incidence and severity of adverse drug reactions and serious adverse drug reactions. Changes in hematology and chemistry values, vital signs, ECGs, and dose interruptions, dose reduction and dose intensity.	
Phases Ib and II: To assess clinical efficacy of the LEE011 and MEK162 combination	Duration of response (DOR), Time to progression (TTP), Progression Free Survival (PFS) and Overall Survival (OS) as per RECIST 1.1. Best Overall Response (BOR) according to RECIST 1.1	
CCI [redacted]		[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	

4 Study design

4.1 Description of study design

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

MEK162 will be administered orally at 45 mg twice daily (BID) on a continuous dosing schedule (28-day cycle). There is no planned escalation of MEK162, although a lower dose of 30 mg BID may be explored if the combination is not tolerated. Oral LEE011 will be administered once daily for 21 days followed by a 1 week break (28-day cycle) at a starting dose of 200 mg QD.

Should safety and PK data from the dose escalation part of this study and/or other MEK162/LEE011 study(s) indicate that alternate dosing schedules of MEK162 and LEE011may be more appropriate, the following schedules will be considered:

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

The phase Ib is the dose escalation part where successive cohorts of 3-6 newly enrolled patients receiving various dose pairs considering the recommendation from an adaptive BLRM incorporating the EWOC principle until MTD(s)/RP2D is defined. Patients with either measurable or evaluable disease will be eligible. If multiple alternate dosing schedules are explored in parallel, the allocation of patients will proceed in an alternating fashion (see Section 4.1). Approximately 40 patients are expected to be treated during the phase Ib part of the study.

Once the MTD(s)/RP2D have been determined for each tested schedule, the phase II part will begin at the RP2D on the chosen schedule in order to assess antitumor activity of the LEE011and MEK162 combination. Data from enrolled patients will also be used to better characterize the safety, tolerability and PK profile of the two agents. Patients enrolled in the phase II part of the study are required to have measurable disease. Approximately 40 patients will be treated in phase II.

All patients will be required to provide a representative tumor specimen upon study entry. This can either be an archival tumor biopsy with the corresponding pathology report or a newly obtained tumor biopsy. Tumor biopsies obtained at the time of diagnosis or any other time after that will be accepted. Most recent tumor biopsies are preferred. If a new tumor biopsy is collected at screening, patients in phase Ib have the option of providing an on-treatment biopsy.

In the phase II part of the study, all patients with accessible tumors that are amenable for biopsy must supply a newly obtained tumor sample at screening and at on-treatment to assess the pharmacodynamic effects of the combination.

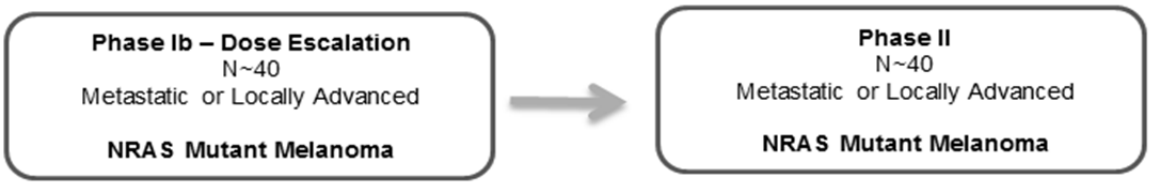
Patients may enroll on an optional companion protocol to study the mechanisms of resistance to therapy with LEE011 and MEK162. Patients who agree to participate in the companion study will provide samples for analysis of their cancer at study entry and again upon disease progression

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

Patients in phase Ib who discontinue study treatment for any reason will not be followed long term in this study. Patients in phase II who have not progressed at the time of discontinuation of study treatment will be followed via phone call by site study staff until progression, death or until a new cancer therapy is initiated (Section 7.1.5).

Approximately 80 patients will be treated in the entire study.

Figure 4-1 Study design



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 or Table 7-2 and Section 7.1.2).

Follow-up assessments

After study drug discontinuation, all patients must complete End of Treatment assessments within 14 days and the safety follow up assessments within 30 days after the last dose of the study treatment (see Section 7.1.4 and Section 7.1.5).

Disease progression assessments (Phase II only)

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 with CT/MRI scans every three months as detailed in Table 7-1 or Table 7-2 and Section 7.1.5.2, until disease progression, the initiation of subsequent anticancer therapies, death, or until patients have been followed for at least 12 months after their first dose of study treatment, have been lost to follow-up or withdrew consent, whichever occurs first. Newly started antineoplastic therapies during this follow up period must be recorded on the Antineoplastic therapy since discontinuation eCRF.

Survival follow-up period (Phase II only)

All patients enrolled in the Phase II part of the study will be followed for survival every three months via phone call until death, or until all patients have been followed for at least 12 months after their first dose of study treatment, or have been lost to follow up or withdrew consent, whichever occurs first. One additional phone call per quarter may be allowed. Possible newly started antineoplastic therapies during this follow up period must be recorded on the Antineoplastic therapy since discontinuation eCRF.

4.2 Timing of interim analyses and design adaptations

At the end of phase Ib the RP2D will be selected based on available safety, tolerability, PK, PD and efficacy data, as well as the recommendations from the BLRM using EWOC. The phase II will then begin with a new group of 40 patients recruited. Patients from the Phase Ib and Phase II parts will not be pooled for the primary ORR analysis.

4.3 Definition of end of the study

Phases Ib and II of the study will end when the treatment period, safety follow-up, disease follow-up and survival follow-up (only for phase II) have ended for all patients as described in, Section 7.1.5 or when the study is terminated early. A primary CSR will be written after all patients have completed at least six cycles of treatment or discontinued treatment, and a final CSR will be written at the end of the study.

4.4 Early study termination

The study can be terminated at any time for any reason by the Sponsor. Should this be necessary, the patients should be contacted within 24 hours, informed to stop taking the study drug and be seen as soon as possible. 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 ECs of the early termination of the trial.

5 Population

5.1 Patient population

This study is limited to patients with histologically or cytologically confirmed locally advanced or metastatic NRAS mutant melanoma.

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

5.2 Inclusion criteria

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

1. Written informed consent must be obtained prior to any screening procedures.
2. Patients aged ≥18 years with a histologically or cytologically confirmed diagnosis of locally advanced or metastatic NRAS mutant melanoma. Written documentation of NRAS mutation is required prior to enrollment in this study.
3. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 – 1.
4. Patients enrolled into phase Ib may be enrolled with evaluable disease only. Patients enrolled into the phase II expansion must have at least one measurable lesion as defined by RECIST 1.1 criteria for solid tumors.
5. All patients must agree to submit an archival or a newly obtained tumor biopsy specimen (performed at diagnosis or relapse) upon study entry in Phase Ib. If an archival specimen is submitted a corresponding pathology report must also be provided. In the phase II portion of the study, patients with accessible tumors that are amenable for biopsy must agree to undergo a tumor biopsy at the time of study entry and on-treatment.
6. A sufficient interval must have elapsed between the last dose of prior anti-cancer therapy (including cytotoxic and biological therapies) and enrollment in this study, to allow the effects of prior therapy to have been reduced:
   - Systemic antineoplastic therapy or any experimental therapy within 2 weeks before the first dose of study drugs (6 weeks for nitrosoureas and mitomycin-C).
   - Biologic therapy (e.g., antibodies): ≥ 4 weeks.
7. Patients must have adequate organ function, as defined by the following parameters:
   a. Absolute Neutrophil Count (ANC) ≥ 1.5 x 10^9/L.
   b. Hemoglobin (Hgb) ≥ 9 g/dL.
   c. Platelets ≥ 75 x 10^9/L without transfusions within 21 days before 1st treatment.
   d. PT/INR and aPTT ≤ 1.5 ULN.
   e. Serum creatinine ≤1.5 ULN.
   f. Serum total bilirubin ≤ 1.5 x upper limit of normal (ULN), except for patients with known Gilbert syndrome, who are excluded if total bilirubin > 3.0 x ULN or direct bilirubin > 1.5 x ULN
   g. AST and ALT <2.5 x ULN, except in patients with tumor involvement of the liver who must have AST and ALT < 5 x ULN.
   h. Patient must have the following laboratory values within normal limits or corrected to within normal limits with supplements before the first dose of study medication:
      - Sodium
      - Potassium
      - Magnesium
      - Inorganic phosphate
      - Calcium (corrected for serum albumin)

8. A negative serum βHCG test ≤ 72 hours before starting study treatment for pre-menopausal women and for women < 1 year after the onset of menopause.
9. Patients must give written informed consent to participate in this study prior to undergoing any study procedure.

5.3 Exclusion criteria

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

1. Presence of any brain metastases detected by MRI or CT with i.v. contrast of the brain at screening.
2. Impairment of gastro-intestinal (GI) function or active GI disease that may significantly alter the absorption of LEE011 or MEK162 such as ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection.
3. Uncontrolled arterial hypertension despite medical treatment
4. Impaired cardiac function, clinically significant cardiac diseases and/or recent cardiac events, including any of the following:
   a. Left ventricular ejection fraction (LVEF) < 50% as determined by multiple gated acquisition scan (MUGA) or echocardiogram (ECHO).
   b. Congenital long QT syndrome or family history of unexpected sudden cardiac death.
   c. On screening, inability to determine QTcF interval on the ECG (i.e.: unreadable or not interpretable) or QTcF >450 ms (using Frederica's correction). All as determined by screening ECG (mean of triplicate ECGs).
   d. Angina pectoris or symptomatic pericarditis within 12 months prior to starting study drug
   e. Acute myocardial infarction within 12 months prior to starting study drug
   f. Clinically significant resting bradycardia within 12 months prior to starting study drug
   g. History or presence of ventricular tachyarrhythmia within 12 months prior to starting study drug
   h. Unstable atrial fibrillation (ventricular response >100 bpm)
   i. Complete left bundle branch block within 12 months prior to starting study drug
   j. Right bundle branch block and left anterior hemi block (bifascicular block) within 12 months prior to starting study drug
   k. Obligate use of a cardiac pacemaker or implantable cardioverter defibrillator
   l. Any other clinically significant heart disease (e.g. documented congestive heart failure, documented cardiomyopathy)
5. Patients who are currently receiving treatment with agents that are known to cause QT prolongation or induce Torsades de Pointes in humans and cannot be discontinued 7 days prior to Cycle 1 Day 1.
6. Patients who have neuromuscular disorders that are associated with elevated CK (e.g., inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy) or elevated baseline CK levels (≥ Grade 2)
7. Patients who are currently receiving treatment with agents that are metabolized predominantly through CYP3A4 and that have a narrow therapeutic window and cannot

be discontinued 7 days prior to Cycle 1 Day 1. Agents that are known strong inducers or inhibitors CYP3A4 are prohibited. (Refer to Appendix 3). Patients are not permitted to receive enzyme inducing anti-epileptic drugs.

8. Patients with concurrent severe and/or uncontrolled concurrent medical conditions that could compromise participation in the study (i.e. uncontrolled diabetes mellitus, clinically significant pulmonary disease, clinically significant neurological disorder, active or uncontrolled infection).
9. Major surgery <2 weeks before starting study treatment.
10. Patients unwilling or unable to comply with the protocol.
11. Known diagnosis of human immunodeficiency virus (HIV) or hepatitis C (testing is not mandatory).
12. History or current evidence of retinal vein occlusion (RVO) or current risk factors for RVO (e.g. uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes).
13. In the phase II, prior exposure to CDK4/6 inhibitor (e.g., PD 0332991).
14. In the phase II, prior exposure to MEK inhibitor unless approved by the Sponsor.
15. Another malignancy within three years prior to enrollment, with the exception of adequately treated *in situ* carcinoma of the uterine cervix, basal or squamous cell carcinoma of the skin, or other indolent malignancies that have not required therapy within the past 3 years.
16. 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 βHCG laboratory test
17. 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 30 days after study drug discontinuation. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    - Male sterilization (at least 6 months prior to screening). For female subjects on the study the vasectomized male partner should be the sole partner for that subject.
    - 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 or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone 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

- In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.
- 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 have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. 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.

18. Sexually active males, unless they use a condom during intercourse while taking the drug and for 30 days after stopping treatment and should not father a child in this period. A condom is also required to be used by vasectomized men in order to prevent delivery of the drug via seminal fluid.

6 Treatment

6.1 Study treatment

The investigational drugs to be used in this trial are:

- LEE011, supplied as capsules for oral use.
- MEK162, supplied as film-coated tablets for oral use.

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

6.1.1 Dosing regimen and treatment administration

LEE011 will be taken orally, once a day for 21 consecutive days followed by a 7 day planned break. MEK162 will be taken orally twice daily on a continuous dosing schedule. Both drugs are given as part of a 28-day cycle of treatment.

Detailed instructions regarding administration of LEE011 capsules as well as MEK162 tablets will be supplied to Investigator sites in a separate document [CMEK162X2114 Pharmacy Manual] from this protocol.

LEE011 and MEK162 should be taken as follows:

- Patients should be instructed to take the study drug combination of one or more tablets of MEK162 and one or more capsules of 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, tablets of MEK162 and capsules of LEE011 should be administered with a glass of water, irrespective of food.

- The second dose of MEK162 should be administered with a glass of water 12 ± 2 hours after the first dose. On days when blood collection is scheduled at the clinic, patients will take LEE011 and MEK162 in the clinic under the supervision of the Investigator or designee. On all other days patients will take the LEE011 and MEK162 combination 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 a treatment cycle 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, star-fruit, or Seville (sour) oranges during the entire study and preferably 7 days before the first dose of study medications, due to potential CYP3A4 mediated interaction with the study medications. Orange juice is allowed.

The investigator or responsible site personnel should instruct the patient to take the study drugs as per protocol (promote compliance). All dosages prescribed 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 used/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.

6.1.1.1 Alternate dosing schedule of LEE011 and MEK162

Should safety and PK data from the dose escalation part of this study and/or other MEK162/LEE011 study(s) indicate that alternate dosing schedules of MEK162 and LEE011may be more appropriate, the following schedules will be considered:

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

Please refer to Section 4.1 for additional information.

6.1.2 Treatment duration

Patients may continue treatment with LEE011 and MEK162 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), as well as in the event of patients death. Patients who have documented progressive disease but continue to receive clinical benefit may be allowed to continue treatment with either or both drugs (depending on treatment status at time of consideration) after discussion between the Sponsor and the investigator.

6.2 Dose escalation guidelines

6.2.1 Starting dose rationale

Please refer to Section 2.3 for starting dose rationale.

6.2.2 Provisional dose levels

Provisional dose levels are listed in Table 6-1. With the exception of starting dose level 1 for the initial schedule (LEE011 3 weeks on/ 1 week off and MEK162 BID continuously), actual dose levels will be determined following a discussion with participating Investigators during dose escalation teleconferences and may differ from those presented within Table 6-1. Dose escalation will continue until MTD(s)/RP2D is/are reached.

Table 6-1 Provisional dose levels

Dose level	LEE011 mg QD	MEK162 mg BID
-1b	200 mg	30 mg
-1a	100 mg	45 mg
1	200 mg	45 mg
2	400 mg	45 mg
3	600 mg	45 mg

a. It is possible for additional and/or intermediate dose combinations to be investigated during the course of the study based on available data.

b. Doses -1a and -1b are applicable to those patients requiring a dose reduction from the starting dose of any dosing schedule. Dose reductions for MEK162 will be from 45 mg BID to 30 mg BID and from 30 mg BID to 15 mg BID or 30 mg QD. All dose reductions beyond 30 mg BID require prior approval by the Sponsor.

c. Cohorts may be added at any dose level below the estimated MTD(s)/RP2D in order to better understand safety, PK or PD.

At all decision timepoints, the adaptive BLRM permits alterations in the dose increments based on the observed DLTs. If the starting dose level does not satisfy the EWOC, MEK162 can be de-escalated below its single agent MTD.

6.2.3 Criteria for dose escalation and determination of MTD/RP2D

6.2.3.1 MTD definition

The MTD is defined as the highest combination drug dosage not causing medically unacceptable DLT in more than 35% of the treated patients in the first cycle of treatment.

Since the initial MEK162 45 mg BID tested with different LEE011 dose levels may be de-escalated to 30 mg BID and, additionally, different LEE011 and MEK162 dosing schedules may be investigated, several combinations may correspond to this definition and more than one MTD may be identified with different doses/schedules of the study drugs.

The applied adaptive Bayesian methodology provides an estimate of the combinations of MEK162 and LEE011 not exceeding the MTD. Typically the MTD is a tested dose with maximum probability of targeted toxicity (DLT rate between 16% to 35%). The use of EWOC principle limits the risk that a potential next dose will exceed the MTD (Section 10.4.2)

6.2.3.2 Dose cohort modification

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 dose at the initial schedule (LEE011 3 weeks on/1 week off and MEK162 BID continuously) as shown in Table 6-1. The starting dose for any alternate dosing schedule will be at a dose combination deemed to be safe in a previously tested schedule. Patients must complete a minimum of 1 cycle of treatment with the minimum safety evaluation and drug exposure 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. Dose escalation decisions will be made by Investigators and Sponsor study personnel.

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 dose for the next cohort of patients will be guided by the Bayesian logistic regression model (BLRM) with EWOC principle (please refer to Section 10.4.1 and Appendix 5). The adaptive Bayesian methodology provides an estimate of all combination dose levels of MEK162 and LEE011 within a dosing schedule that do not exceed the 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 to <35%) and will always satisfy the EWOC principle. (Note: If at any time on study, no dose pair satisfies the overdose criteria for a specific combination schedule, then the combination of MEK162 and LEE011 at that schedule will be terminated). In all cases, the combination dose for the next cohort will not exceed a 100% increase from the previous combination dose (e.g. up to 100% and 0% increase for LEE011 and MEK162 respectively). If two or more patients experience CTCAE grade 2 or greater treatment-related toxicities at a dose level in any cohort, all future dose escalations of LEE011 will be $\leq 50\%$. Only toxicities that occur during the first cycle will necessarily be considered for decisions. Smaller increases

in combination dose may be recommended by the Investigators and the Sponsor upon consideration of all of the available clinical data. 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 previously untested dose level experience a DLT, the next cohort will be opened at the next lower dose level or an intermediate dose level (see Table 14-15, Appendix 5). However, if the first 2 patients in a new cohort at a previously tested dose combination 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 dose cohort only if the combination still meets the overdose criteria and as agreed by Investigators and Sponsor personnel. Alternatively, if recruitment to the same cohort may not resume, a new cohort of patients may be recruited to a lower dose level as agreed by Investigators and Sponsor personnel and if the BLRM predicts that the risk for this dose to exceed the MTD remains below 25% (EWOC).

Dose escalation will continue until identification of the MTD(s) or a suitable lower combination dose for phase II. 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 15 patients have already been treated on the trial.
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.

To better understand the safety, tolerability and PK of MEK162 in combination with LEE011 additional cohorts of 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. Patients ongoing will continue treatment at their assigned dose levels.

6.2.3.3 Implementation of dose escalation decisions

At each decision time point, the adaptive BLRM provides the upper boundary for the combinations that meet the EWOC criterion. The available safety, tolerability, PK, PD and efficacy data, as well as the recommendations from the BLRM, will be 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.

When enrollment of the 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. Refer to Section 6.2.3 for the requirements to declare MTD(s)/RP2D.

To implement dose escalation decisions, the available toxicity information (including adverse events 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.

6.2.3.4 Intra-patient dose escalation

Intra-patient dose escalation prior to declaration of MTD(s)/RP2D is not permitted at any time during this study. However once the MTD(s)/RP2D is declared, individual patients may be considered for escalation/switching to treatment at the RP2D of the combination from the dose and schedule to which they were initially assigned. In order for a patient to be treated at the RP2D of the combination, he or she must have tolerated the lower dose pair for at least two cycles of therapy, i.e., 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.

Consultation with the Sponsor must occur prior to intra-patient dose escalation occurring. These changes must be recorded on the Dosage Administration Record eCRF.

6.2.4 Definitions of dose limiting toxicities (DLTs)

A dose-limiting toxicity (DLT) is defined as an adverse event or clinically significant abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurs within the first cycle of treatment with LEE011 and MEK162 and meets any of the criteria included in Table 6-3. National Cancer Institute Common Terminology Criteria for Adverse events (NCI CTCAE) version 4.03 will be used for all grading.

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 6.3.1. For the purpose of dose-escalation decisions, DLTs will be considered and included in the BLRM.

The investigator must notify the Sponsor immediately of any unexpected CTCAE grade ≥ 3 adverse events or laboratory abnormalities. Prior to enrolling patients into a higher dose level, CTCAE grade ≥ 2 adverse events will be reviewed for all patients at the current dose level.

Table 6-2 Criteria for defining dose-limiting toxicities

TOXICITY	DLT CRITERIA
Hematology	CTCAE grade 4 neutropenia lasting more than 7 consecutive days
	CTCAE grade 4 thrombocytopenia
	CTCAE Grade 3 or 4 neutropenia with fever (temperature ≥ 38.5°C)
Skin and subcutaneous tissue disorders	Rash or photosensitivity CTCAE Grade 3 > 7 consecutive days despite skin toxicity treatment (as per local practice)
	Rash or photosensitivity CTCAE Grade 4
Eye disorders: retinal events	Retinal events CTCAE grade 3 for > 14 consecutive days, confirmed by ophthalmologic examination
	Retinal events CTCAE grade 4, confirmed by ophthalmologic examination
Eye disorders: Retinal Vein Occlusion	CTCAE grade ≥ 1 confirmed by ophthalmologic evaluation
Eye disorders: Other	Any eye disorder CTCAE grade 3 >14 consecutive days
	Any eye disorder CTCAE Grade 4
Gastrointestinal	CTCAE grade ≥3 nausea or vomiting ≥ 48 hrs despite optimal anti-emetic therapy
	CTCAE grade ≥3 diarrhea ≥ 48 hrs despite optimal anti-diarrhea treatment
Hepatobiliary	CTCAE grade 2 bilirubin > 7 consecutive days
	CTCAE ≥ grade 3 total bilirubin
	CTCAE grade 2 total bilirubin concurrent with grade 2 ALT with the exception of known liver metastatic disease
	CTCAE grade 3 ALT > 4 consecutive days
	CTCAE grade 4 ALT or AST (isolated increases in AST without concomitant increases in ALT will not be considered dose-limiting, because of the non-specific nature of AST)
	CTCAE grade 4 serum alkaline phosphatase > 7 consecutive days
Cardiac disorders	Left ventricular systolic dysfunction ≥ Grade 3 Asymptomatic decrease of >10% in LVF from baseline (and is below the LLN)
	Other cardiac disorders CTCAE Grade ≥ 3
Investigations	Serum CK/CPK CTCAE Grade 3 if clinically significant (symptomatic)
	Serum CK/CPK CTCAE Grade 4
ECG QT Interval	QTc interval ≥ 501 ms on at least two separate ECGs
Renal	Serum creatinine CTCAE Grade ≥ 3
Non-hematologic events	≥ CTCAE grade 3, except for the exclusions noted below
Exceptions to DLT criteria	Grade 3 alopecia
	< 7 days of CTCAE grade 3 fatigue
	< 7 days of CTCAE grade 3 edema
	Grade 3 laboratory abnormalities that are responsive to oral supplementation or deemed by the investigator to be clinically insignificant
CTCAE version 4.03 will be used for all grading. Optimal therapy for vomiting, diarrhea, or skin disorders will be based on institutional guidelines, with consideration of the prohibited medications listed in this protocol.	

Follow-up for dose limiting 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 weeks intervals, until resolution or stabilization of the event, whichever comes first.

Appropriate clinical experts such as an ophthalmologist or dermatologist should be consulted as deemed necessary. Further guidelines and recommendations for the management of the specific study drug combination induced toxicities are provided in Table 6-3.

6.2.4.1 Follow up evaluations for appearance of retinal events

Patients on the study will be examined regularly to monitor for the possible development of retinal events, as the appearance of retinal events has been associated with MEK162 treatment. Ophthalmologic examinations will be performed periodically as outlined in Table 7-1 or Table 7-2. For patients developing retinal events of any grade it is recommended to follow up the retinal events with an ophthalmological exam every two weeks for 8 weeks, and subsequently at approximately a 4week's interval. Dose modification guidelines are outlined in Table 6-3.

6.3 Dose modification

6.3.1 Dose modification and dose delays

If a patient experiences a DLT, then treatment with both drugs must be interrupted. For all toxicity grades, if the toxicity resolves to grade 1 or baseline within 1 week of onset, treatment may be resumed at the same or a lower dose level at the investigator's discretion and following discussion with the Sponsor.

The dose during Cycle 1 should not be reduced or interrupted unless the patient has experienced a DLT.

For toxicities that result in treatment delays of more than 7 but not more than 21 days, treatment may be resumed at a lower dose level. 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. In this event, more frequent follow up as outlined in cycle 1 to monitor this toxicity may be appropriate. Changes to the dose or schedule must be recorded on the Dosage Administration Record eCRF. All patients will be followed for AEs and for SAEs for 30 days following the last dose of study drug.

Each patient is allowed a maximum of two dose reductions for LEE011 and two dose reductions for MEK162. After this, the patient will be discontinued from the study treatment. For each patient, once a dose level reduction has occurred, the dose level may not be re-escalated during subsequent treatment cycles.

Dose reductions for MEK162 will be from 45 mg BID to 30 mg BID and from 30 mg BID to 15 mg BID or 30 mg QD. All dose reductions beyond 30 mg BID require prior approval by the Sponsor. Dose reductions for LEE011 will be to the previously tested acceptable dose level. Specific dose modification guidelines are provided in Table 6-3.

If a patient discontinues either study drug, then the patient must discontinue the study.

Table 6-3 Dose modification guidelines after Cycle 1

Toxicity category	Severity	Action on study drug
Hematology	ANC <1.0 x 10^9/L and/or platelets < 75 x 10^9/L and/or Febrile neutropenia	Hold LEE011 and MEK162 until ANC is ≥1.0 x 10^9/L and the platelet count is ≥75 x 10^9/L. If treatment delay is ≤ 7 days, restart at same dose for both If treatment delay is >7 days but ≤ 21 days, restart one dose level down for both If treatment delay >21 days, discontinue treatment of both.
Nausea, emesis, and/or diarrhea with maximal prophylaxis	Grade 2	Hold MEK162 until it resolves to ≤ Grade 1 and restart at same dose.
	Grade 3	Hold LEE011 and MEK162 until it resolves to ≤ Grade 1 and restart one dose level down for both.
	Grade 4	Discontinue treatment of both.
Hepatobiliary	**Total Bilirubin without ALT/AST increase above baseline value**	
	Grade 1 total bilirubin (without ALT/AST increase) (confirmed 48-72h later)	Maintain dose level with LFTs monitored bi-weekly
	Grade 2 total bilirubin (without ALT/AST increase)	Dose interruption of LEE011 If resolved to ≤ grade 1 in ≤ 21 days, then maintain dose level If toxicity recurs and is resolved to ≤ grade 1 in ≤ 21 days, then reduce LEE011 1 dose level If toxicity recurs after two dose reductions, discontinue treatment of both
	Grade 3 total bilirubin (without ALT/AST increase)	Dose interruption of LEE011 and MEK162 If resolved to ≤ grade 1 in ≤ 21 days, lower 1 dose level of LEE011 and MEK162 If toxicity recurs, discontinue treatment of both
	Grade 4 total bilirubin (without ALT/AST increase)	Discontinue LEE011 and MEK162
	Confounding factors and/or alternative causes for increase of total bilirubin should be excluded before dose interruption/reduction. They include but are not limited to: evidence of obstruction, such as elevated ALP and GGT typical of gall bladder or bile duct disease, hyperbilirubinemia due to the indirect component only (i.e. direct bilirubin component ≤ 1 x ULN) due to hemolysis or Gilbert Syndrome, pharmacologic treatment, viral hepatitis, alcoholic or autoimmune hepatitis, other hepatotoxic drugs. For patients with Gilbert Syndrome, these dose modifications apply to changes in direct bilirubin only. Bilirubin will be fractionated if elevated.	
	AST or ALT without bilirubin elevation >2 xULN	
	AST or ALT same grade as baseline or increase from baseline grade 0 to grade 1 (confirmed 48-72h later)	No dose adjustment required with LFTs monitored per protocol if same grade as baseline or bi-weekly in case of increase from baseline grade 0 to 1

Toxicity category	Severity	Action on study drug
	AST or ALT Increase from baseline grade 0 or 1 to grade 2 (> 3.0 – 5.0 x ULN) or from baseline grade 2 to grade 3 (> 5.0 – 20.0 x ULN)	Dose interruption of LEE011 and MEK162 If resolved to ≤ baseline value in ≤ 21 days, then maintain dose level If toxicity recurs and is resolved to ≤ baseline in ≤ 21 days, then reduce LEE011 1 dose level If toxicity recurs after two dose reductions or recovery to ≤ baseline value is > 21 days, discontinue treatment of both
	AST or ALT Increase from baseline grade 0 or 1 to grade 3 (> 5.0 – 20.0 x ULN)	Dose interruption of LEE011 and MEK162 until resolved to ≤ baseline value ≤ 21 days, then lower 1 dose level of LEE011 and MEK162 If toxicity recurs, discontinue LEE011 and MEK162 If recovery to ≤ baseline value is > 21 days, discontinue treatment of both
	AST or ALT Grade 4 (> 20.0 x ULN)	Discontinue LEE011 and MEK162
	AST or ALT and concurrent Bilirubin	
	AST or ALT ≥ grade 2 (> 3 x ULN) in patients with normal values at baseline and total bilirubin > 2 x ULN or AST or ALT ≥ grade 3 (> 5 x ULN) in patients with grade 1 or 2 at baseline, and total bilirubin > 2 x ULN	Discontinue LEE011 and MEK162
	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.	

Toxicity category	Severity	Action on study drug
Eye Disorders	Grade 2 retinal events	Continue MEK162 and LEE011 but refer the patient to a retinal specialist for further evaluation and close follow-up. If resolved to Grade ≤ 1 in ≤ 21 days, then continue at same dose of MEK162. If resolved to Grade ≤ 1 in > 21 days, lower MEK162 dose by one level.
	Grade 3 retinal events and any other Grade 3 eye disorders	Hold MEK162 and refer the patient to a retinal specialist for further evaluation and close follow-up until resolved to grade ≤ 1. If resolved in ≤ 21 days, then restart at lower dose. If resolved in > 21 days, discontinue treatment of both.
	Grade ≥ 1 retinal vein occlusion, grade 4 retinal events, and grade 4 other eye disorders	Discontinue LEE011 and MEK162.
Rash/ HFSR/ photosensitivity despite maximal therapy	Grade 3 not responsive to treatment	Hold MEK162 until resolved to grade ≤ 1. If resolved in ≤ 7 days despite appropriate skin toxicity therapy (or ≤14 days for acneiform rash), then restart at lower dose. If resolved in > 7 days despite appropriate skin toxicity therapy (or >14 days for acneiform rash), discontinue treatment of both.
	Grade 4	Discontinue LEE011 and MEK162.
Cardiac	Asymptomatic decrease of >10% in LVEF compared to baseline **and** the LVEF is above the institution's lower limit of normal	Continue MEK162 and LEE011 and repeat evaluation of LVEF every 14 days until LVEF recovers. Subsequent follow ups as per protocol.
	Asymptomatic decrease of >10% in LVEF compared to baseline **and** the LVEF is below the institution's lower limit of normal	Hold MEK162 and LEE011 and repeat evaluation of LVEF within 14 days If the LVEF recovers (defined as ≥ LLN and decrease ≤ 10% compared to baseline) ≤ 14 days, then restart at lower dose of both. Monitor LVEF 14 days after restarting on MEK162, every 4 weeks for 12 weeks and subsequently as per protocol If LVEF recovers in > 14 days, discontinue MEK162 and LEE011
	Grade 3-4	Discontinue MEK162 and LEE011.

Toxicity category	Severity	Action on study drug
QTc prolongation	Grade 1 (QTc 450-480 ms)	No dose adjustment required
	Grade 2 (QTc 481-500 ms)	Hold LEE011 and MEK162 Perform a repeat ECG within one hour of the first QTcF of ≥ 481 ms. If QTcF < 481 ms, restart LEE011 and MEK162 at the same dose. No dose adjustment required for first occurrence. If QTcF remains ≥ 481 ms, repeat ECG as clinically indicated until the QTcF returns to < 481 ms. restart LEE011 and MEK162 at the same dose. No dose adjustment required for first occurrence. If QTcF ≥ 481 ms recurs, LEE011 should be reduced by 1 dose level. Refer to Table 6-1 for dose levels. 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 (QTc ≥ 501 ms on at least two separate ECGs)	Hold LEE011 and MEK162. 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, LEE011 will be reduced by 1 dose level. Refer to Table 6-1 for dose levels. 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 treatment of both
	Grade 4 (QT/QTc ≥ 501 or > 60 ms change from baseline and Torsades de pointes or polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia)	Discontinue LEE011 and MEK162. • 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. • Perform analysis of serum electrolytes (K+, Ca++, Phos, Mg++). If outside of the normal range, interrupt LEE011 and MEK162 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 LEE011 and MEK162.	
Serum creatinine	Grade 3	Hold LEE011 and MEK162 until it resolves to ≤ Grade 1 and restart one dose level down for both.

Toxicity category	Severity	Action on study drug
CK/CPK	Grade 3	If asymptomatic: Maintain dose of MEK162 and monitor closely. If symptomatic, hold MEK162 until resolved to grade ≤ 1. • If resolved in ≤ 14 days, then restart at lower dose. • If resolved in > 14 days, discontinue treatment of both.
	Grade 4	If asymptomatic: hold MEK162 until resolved to grade ≤ 1. • If resolved in ≤ 14 days, then restart at lower dose • If resolved in > 14 days, discontinue MEK162 If symptomatic, discontinue treatment of both
All other toxicities	≥Grade 3	Determine attribution of toxicity. Hold appropriate therapy until resolved to ≤ Grade 1 or baseline. If treatment delay is >7 days but ≤ 21 days, restart at lower dose. If treatment delay >21 days, discontinue treatment.

6.3.1.1 Additional follow-up for hepatic toxicities

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.
- 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.

6.4 Concomitant medications

6.4.1 Prohibited concomitant therapy

The following therapies are prohibited:

- Strong inducers or inhibitors of CYP3A4 (Refer to Appendix 3).
- Substrates of CYP3A4 with narrow therapeutic windows (Refer to Appendix 3).
- Medications with a known risk of prolonging the QT interval or inducing Torsades de Pointes.
- Grapefruit, grapefruit hybrids, pummelos, star-fruit and Seville oranges.
- Concurrent anti-neoplastic therapy, including radiotherapy for therapeutic purposes.

6.4.2 Permitted concomitant therapy requiring caution and/or action

The following medications are permitted in this study; however, they should be used with caution. Patients receiving such medication must be carefully monitored for potentiation of

toxicity due to any individual concomitant medication, and may require dose titration of the drug substance.

The solubility of MEK162 is pH dependent and a 10-fold decrease in solubility is observed between pH 1 and 2. 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 MEK162.

- Moderate inhibitors or inducers of CYP3A4/5.
- Known BSEP inhibitors.
- Sensitive substrates of CYP3A4/5 that do not have a narrow therapeutic index.
- Inhibitors of P-gp.
- Inhibitors of BCRP.
- Sensitive substrates of BCRP
- Sensitive substrates of the renal transporters, MATE1 and OCT2
- Substrates of CYP2B6.
- Medications that carry a possible risk for QT prolongation.
- Known inhibitors and inducers of UGT1A1.

Refer to Appendix 3 through Appendix 4.

6.4.3 Permitted concomitant therapy

Medications required to treat AEs, manage cancer symptoms, concurrent stable diseases and supportive care agents, such as PRBCs, pain medications, anti-emetics, short courses of steroids, and antidiarrheals are allowed. Oral contraceptive pills are permitted. The use of any other potential new concomitant medications may be discussed between the investigator and the sponsor on a case by case basis.

Transfusions or growth factor support for white cell counts or platelets are not permitted during Cycle 1, unless the patient has already experienced a DLT. Transfusions and growth factor support should not be used prophylactically during Cycle 1.

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

Patients taking concomitant medication chronically should be maintained on the same dose and dose schedule throughout the study period, as medically feasible.

The investigator should instruct the patient to notify the study site about any new medications including vitamins, supplements and herbal supplements he/she takes after the start of the study drug. All medications (other than study drug) including vitamins, supplements and herbal supplements and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be listed on the relevant pages of the eCRF.

Refer to the [LEE011 Investigator's Brochure] and [MEK162 Investigator's Brochure] for information on possible interactions with other drugs.

6.5 Subject numbering, treatment assignment or randomization

6.5.1 Subject numbering

Each patient is identified in the study by a Subject Number, that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject Number (Subject No.) consists of the Center Number (Center No.) as assigned by the Sponsor or designee to the investigative site with a sequential patient number suffixed to it, so that each patient is numbered uniquely across the OCRDC database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject Number available to the investigator in OCRDC.

In the Phase II part, the Investigator or designated staff will contact the Interactive Response Technology (IRT) and provide the requested identifying information for the patient to register them into the IRT. Once assigned, the Subject No. must not be reused for any other patient and the Subject No. for that individual must not be changed. If the patient fails to start treatment for any reason, the reason will be entered into the Screening Disposition eCRF.

IRT must be notified within 2 days that the patient was not enrolled on the study.

6.5.2 Treatment assignment

In phase Ib, the assignment of patients to a particular cohort will be coordinated by the Sponsor or designee.

In phase II, the assignment of patients will coordinated by IRT. Prior to dosing, all patients who fulfill all inclusion/exclusion criteria will be enrolled via IRT. The Investigator or his/her delegate will call or log on to the IRT and confirm that the patient fulfills all the inclusion/exclusion criteria. The IRT will then assign a Subject No. to each patient that fulfills all inclusion/exclusion criteria.

6.5.3 Treatment blinding

Treatment is not blinded for this study.

6.6 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the patient by authorized site personnel only.

The investigational drugs to be used in this trial are:

- LEE011, supplied as hard gelatin capsules for oral use of dosage strengths of 50 and 200 mg.
- MEK162, supplied as film-coated tablets for oral use of dosage strength 15 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 CRF.

6.6.1 Study drug packaging and labeling

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

For the phase II part where IRT is involved for medication management, the labels will have a unique medication number for tracking purposes.

Study drug two-part open 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.

6.6.2 Drug supply and storage

Study drugs will be centrally supplied by the Sponsor or 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 and in the [Investigator's Brochure].

6.6.3 Study drug compliance and accountability

6.6.3.1 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.

6.6.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. 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 log to the Sponsor or designee's monitor or to the Sponsor address provided in the investigator folder at each site.

6.6.4 Disposal and destruction

The study drug supply can be destroyed at the local Sponsor facility, Drug Supply group or third party, as appropriate. Drug supply is to be destroyed at the site only if permitted by local regulations and authorized by the Sponsor in a prior agreement.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 or Table 7-2 lists 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.

For all visits, there is a ± 3 days window on assessments to take into account scheduling over public or religious holidays except for assessments that are dose administration dependent such as ECG's and PK. All data obtained from these assessments must be supported in the patient's source documentation. Assessments that were completed within 72 hours of Cycle 1, Day 1 (C1D1) do not need to be repeated. For efficacy assessments refer to Section 7.2.1.

Table 7-1 Visit evaluation schedule (28-day cycle)

Day of cycle	Protocol Section	Screening	Cycle 1						Cycle 2			Cycle 3	Subsequent Cycles		End of Treatment (EOT)	30 day f/u	Disease Progression and Survival f/u
		-14 to -1	1	2	8	15	21	22	1	15	22	1	1	22	Within 14 days of last dose		Phase II only
Demography/Informed Consent	7.1.2.3.	X															
Inclusion / Exclusion Criteria	5.2 / 5.3.	X															
Medical History	7.1.2.3.	X															
Diagnosis and extent of cancer	7.1.2.3.	X															
Prior Antineoplastic Therapy	7.1.2.3.	X															
Physical Examination	7.2.2.1.	X	X			X			X	X		X	X		X		
Weight	7.2.2.3.	X	X						X			X	X		X		
Height	7.2.2.3.	X															
Vital Signs	7.2.2.2.	X	X		X	X	X		X	X		X	X		X		
Ophthalmic Examination	7.2.2.5.6.	X	X		X		X		X			X	X		X		
ECOG Performance Status	7.2.2.4.	X	X						X			X	X		X		
ECG	7.2.2.5.7.	X	X		X	X	X		X	X		X	X[1]		X		
Cardiac MUGA/ECHO	7.2.2.5.8.	X							X			X	X[2]		X		
Hematology	7.2.2.5.1.	X	X		X	X	X		X	X		X	X		X		
Biochemistry including BNP, Troponin I and/or Troponin T	7.2.2.5.9.	X	X		X	X	X		X	X		X	X		X		
Coagulation[12]	7.2.2.5.3.	X	X														
Total CPK/CK (If CK ≥3x ULN, follow isoenzymes and myoglobin in blood or urine weekly)	7.2.2.5.2.	X	X		X	X	X		X	X		X	X		X		

Day of cycle	Protocol Section	Screening	Cycle 1						Cycle 2			Cycle 3	Subsequent Cycles		End of Treatment (EOT)	30 day f/u	Disease Progression and Survival f/u
		-14 to -1	1	2	8	15	21	22	1	15	22	1	1	22	Within 14 days of last dose		Phase II only
Thyroid Function Tests (TSH only. If TSH abnormal, total T3 and free T4 should be performed)	7.2.2.5.4.	X							X				X[3]		X		
Pregnancy Test	7.2.2.5.5.	X	X									X[10]	X[10]		X		
PK Sampling (phase Ib)	7.2.3.		X	X	X	X	X	X	X			X	X[4]				
PK Sampling (phase II)	7.2.3.		X		X	X	X		X			X	X[4]				
Archival or Newly Obtained Tumor Biopsy (Phase Ib)	7.2.4.	X[5]				X[6]											
Paired Tumor Biopsy (Phase II)	7.2.4.	X[5]				X[11]											
	7.2.4.																
Standard MRI / CT Tumor Assessment	7.2.1.	X[7]									X			X[8]	X		X[9]
Brain MRI/CT	7.2.1.	X[7]															
MEK162 Dosing			Continuous or alternate (Days 1-21) in a 28-day cycle														
LEE011 Dosing			Days 1-21 in a 28-day cycle														
Antineoplastic therapies since discontinuation of study medication															X	X	X
Phone calls for survival and CT/MRI scans for disease progression f/u (every 3 months if applicable)																	X

Day of cycle	Protocol Section	Screening	Cycle 1						Cycle 2			Cycle 3	Subsequent Cycles		End of Treatment (EOT)	30 day f/u	Disease Progression and Survival f/u
		-14 to -1	1	2	8	15	21	22	1	15	22	1	1	22	Within 14 days of last dose		Phase II only
Prior/concomitant medications		X	CONTINUOUS													X	
Adverse Events		X	CONTINUOUS												X	X	

1. ECGs will be performed at screening and up to cycle 6 or as clinically indicated. If a QTcF value of ≥ 481 ms is observed at any time prior to cycle 7, the patient will continue to have a pre-dose ECG on day 1 of cycle 7 and all subsequent cycles. Additional ECGs at 2 hours post-dose, will be performed for these patients on day 1 of cycle 9 and every 3rd cycle.
2. Cardiac imaging will be performed at screening, C2D1, C3D1 and then every other cycle (e.g., Cycle 5, 7, 9 etc.) up to end of treatment or as clinically indicated.
3. Thyroid function test is required at screening, Day 1 of cycles 2, 4, 6 and every four cycles after cycle 6.
4. Blood PK will be collected at cycle 1 up to cycle 6. Additional samples may be collected if clinically indicated.
5. The screening window for the pre dose tumor biopsy 28 days.
6. **Phase Ib only:** optional on-treatment tumor biopsy to be submitted on C1D15 (± 7 days) only when a newly obtained tumor sample is submitted at screening.
7. Screening tumor assessments must be performed within 28 days of the start of treatment.
8. Subsequent tumor assessments will be performed on day 22 (± 7 days) of cycles 2 and 4 and 6 and then every four cycles.
9. **For phase II only:** disease progression and survival follow up will be performed every three months.
10. Pregnancy test will be performed at screening, C1D1, on Day 1 of every other cycle (3, 5, 7 and etc.) and at end of treatment. Serum beta-hCG test at screening/C1D1, serum or urine at subsequent cycles
11. Post dose tumor biopsy should be performed on C1D15 (±4 days).
12. Collection of PT, aPTT, and international normalized ratio (INR) will be performed at screening and C1D1.

Table 7-2 Visit evaluation schedule (21-day cycle)

Day of cycle	Protocol Section	Screening	Cycle 1					Cycle 2		Cycle 3	Subsequent Cycles		End of Treatment (EOT)	30 day f/u	Disease Progression and Survival f/u
		-14 to -1	1	2	8	14	15	1	14	1	1	14	Within 14 days of last dose		Phase II only
Demography/Informed Consent	7.1.2.3.	X													
Inclusion / Exclusion Criteria	5.2 / 5.3.	X													
Medical History	7.1.2.3.	X													
Diagnosis and extent of cancer	7.1.2.3.	X													
Prior Antineoplastic Therapy	7.1.2.3.	X													
Physical Examination	7.2.2.1.	X	X			X		X	X	X	X		X		
Weight	7.2.2.3.	X	X					X		X	X		X		
Height	7.2.2.3.	X													
Vital Signs	7.2.2.2.	X	X		X	X		X	X	X	X		X		
Ophthalmic Examination	7.2.2.5.6.	X	X		X	X		X		X	X		X		
ECOG Performance Status	7.2.2.4.	X	X					X		X	X		X		
ECGs	7.2.2.5.7.	X	X		X	X		X	X	X	X[1]		X		
Cardiac MUGA/ECHO	7.2.2.5.8.	X						X		X	X[2]		X		
Hematology	7.2.2.5.1.	X	X		X	X		X	X	X	X		X		
Biochemistry including BNP, Troponin I and/or Troponin T	7.2.2.5.9.	X	X		X	X		X	X	X	X		X		
Coagulation[12]	7.2.2.5.3.	X	X												
Total CPK/CK (If CK ≥3x ULN, follow isoenzymes and myoglobin in blood or urine weekly)	7.2.2.5.2.	X	X		X	X		X	X	X	X		X		

Day of cycle	Protocol Section	Screening	Cycle 1					Cycle 2		Cycle 3	Subsequent Cycles		End of Treatment (EOT)	30 day f/u	Disease Progression and Survival f/u
		-14 to -1	1	2	8	14	15	1	14	1	1	14	Within 14 days of last dose		Phase II only
Thyroid Function Tests (TSH only. If TSH abnormal, total T3 and free T4 should be performed)	7.2.2.5.4.	X						X			X[3]		X		
Pregnancy Test	7.2.2.5.5.	X	X							X[10]	X[10]		X		
PK Sampling (phase Ib)	7.2.3.		X	X	X	X	X	X		X	X[4]				
PK Sampling (phase II)	7.2.3.		X		X	X		X		X	X[4]				
Archival or Newly Obtained Tumor Biopsy (Phase Ib)	7.2.4.	X[5]				X[6]									
Tumor Biopsy (Phase II)	7.2.4.	X[5]				X[11]									
	7.2.4.														
Standard MRI / CT Tumor Assessment	7.2.1.	X[7]								X[8]	X[8]		X		X[9]
Brain MRI/CT	7.2.1.	X[7]													
MEK162 Dosing			Days 1-14 in a 21-day cycle												
LEE011 Dosing			Days 1-14 in a 21-day cycle												
Antineoplastic therapies since discontinuation of study medication													X	X	X
Phone calls for survival and CT/MRI scans for disease progression f/u (every 3 months if applicable)															X

Day of cycle	Protocol Section	Screening	Cycle 1					Cycle 2		Cycle 3	Subsequent Cycles		End of Treatment (EOT)	30 day f/u	Disease Progression and Survival f/u
		-14 to -1	1	2	8	14	15	1	14	1	1	14	Within 14 days of last dose		Phase II only
Prior/concomitant medications		X	Continuous											X	
Adverse Events		X	Continuous										X	X	

1. ECGs will be performed at screening and up to cycle 6 or as clinically indicated. If a QTcF value of ≥ 481 ms is observed at any time prior to cycle 7, the patient will continue to have a pre-dose ECG on day 1 of cycle 7 and all subsequent cycles. Additional ECGs at 2 hours post-dose, will be performed for these patients on day 1 of cycle 9 and every 3rd cycle.
2. Cardiac imaging will be performed at screening, C2D1, C3D1 and then every other cycle (e.g., Cycle 5, 7, 9 etc.) up to end of treatment or as clinically indicated.
3. Thyroid function test is required at screening, Day 1 of cycles 2, 4, 6 and at every four cycles after cycle 6.
4. Blood PK will be collected at cycle 1 up to cycle 6. Additional samples may be collected if clinically indicated.
5. The screening window for the pre dose optional tumor biopsy 28 days.
6. **Phase Ib only:** optional on-treatment tumor biopsy to be submitted on C1D14 (±1 day) only when a newly obtained tumor sample is submitted at screening.
7. Screening tumor assessments must be performed within 28 days of the start of treatment.
8. Subsequent tumor assessments will be performed every 6-8 weeks per standard of care.
9. **For phase II only:** disease progression and survival follow up will be performed every three months.
10. Pregnancy test will be performed at screening, C1D1, on Day 1 of every other cycle (3, 5, 7 and etc.) and at end of treatment. Serum beta-hCG test at screening/C1D1, serum or urine at subsequent cycles
11. Post dose tumor biopsy should be performed on C1D14 (±1 day).
12. Collection of PT, aPTT, and international normalized ratio (INR) will be performed at screening and C1D1.

7.1.1 Pre-screening assessments

Not applicable.

7.1.2 Screening

The informed consent form (ICF) must be dated and signed prior to any per protocol screening procedures. Once the ICF is signed, all AEs per the descriptions below will be captured in the Adverse Event CRF.

The screening period starts once a patient has provided written informed consent to participate in the study and ends on the day of first dose of LEE011 and MEK162. Screening assessments must be performed within 14 days prior to the first dose of LEE011 and MEK162 with the exception of the efficacy assessments and pre-treatment tumor biopsy which must be performed within 28 days.

7.1.2.1 Eligibility screening

The procedures for eligibility check, patient identification number assignments, and coordination among the sites involved will be provided in a separate document prior to study start.

7.1.2.2 Information to be collected on screening failures

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the Screening Disposition page eCRF. The only information on eCRFs which will be entered for screen failures will be:

- Demography
- Informed Consent
- Inclusion/Exclusion Criteria
- Screening Disposition page

No other data will be entered into the clinical database for screen failure patients, unless the patient experiences a SAE. SAE information will be entered onto the AE page for the purpose of reconciliation.

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

The treatment period commences on the first day of the first cycle (C1D1) of LEE011 and MEK162 and ends after the last dose of LEE011 and MEK162.

During the study treatment period, patients will be regularly monitored to assess the safety and early anti-tumor activity of the treatment. For the purpose of scheduling and evaluations, a treatment cycle will consist of 21/28 days.

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

7.1.4 End of treatment visit

At the time the patients discontinues study treatment; a visit should be scheduled as soon as possible and within 14 days after the decision to discontinue has been made, at which time all of the assessments listed for the End of Treatment (EOT) visit will be performed. An End of Treatment Phase Disposition CRF page should be completed, giving the date and 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 also should return for 30-day safety follow up (see Section 7.1.5), disease progression follow up (if applicable, see Section 7.1.5.2) and survival follow up (only for Phase II patients, see Section 7.1.5.3) assessments at visits according to Table 7-1 or 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 follow-up information.

If a patient discontinues study treatment, but continues study assessments, 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 Phase Completion Disposition CRF page.

If using IRT, the Investigator must contact the IRT to register the patient's discontinuation.

End of treatment/Premature withdrawal visit is not considered as the end of the study.

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

Escalation phase Ib:

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. Minimum and maximum numbers of evaluable patients per cohort are defined in Section 6.2.3.2.

Phase II:

Patients will not be replaced.

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 AE (including concomitant medication taken for ongoing AEs) and ongoing anti-neoplastic treatments will be collected for 30 days after the last dose of study treatment. 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 assessments (Phase II only)

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 with CT/MRI scans every three months as detailed in Table 7-1 or Table 7-2 and Section 7.2.1, until disease progression, the initiation of subsequent anticancer therapies, death, or until patients have been followed for at least 12 months after their first dose of study treatment, have been lost to follow-up or withdrew consent, whichever occurs first. Newly started antineoplastic therapies during this follow up period must be recorded on the Antineoplastic therapy since discontinuation eCRF.

7.1.5.3 Survival follow-up period (Phase II only)

All patients enrolled in the Phase II part of the study will be followed for survival approximately every three months per phone call until death, or until all patients have been followed for at least 12 months after their first dose of study treatment, or have been lost to follow-up or withdrew consent, whichever occurs first. One additional phone call per quarter may be allowed. Possible newly started antineoplastic therapies during this follow up 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 (Version 3.0) based on RECIST version 1.1 (see Appendix 2). The following assessments are required at screening/baseline (within 28 days of the start of treatment):

- Chest, abdomen and pelvis CT or MRI. The preferred radiologic technique is CT with intravenous (i.v.) contrast. If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the trial, a non-contrast CT of the chest (MRI is not recommended due to respiratory artifacts) plus a contrast-enhanced MRI (if possible) of the abdomen and pelvis should be performed.
- Brain MRI or CT with intravenous (i.v.) contrast scan to assess CNS disease. 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.
- Color photography of any skin lesions present. Color photography should include a metric ruler. Palpable subcutaneous tumors may be measured by physical examination using a ruler or calipers. Ultrasound should not be used to measure sites of disease.
- If bone metastases are suspected, a whole body bone scan per institutional standard of care (e.g. Tc-99 bone scan, whole body bone MRI, FDG-PET or sodium fluoride positron emission tomography (NaF PET). Localized CT, MRI or X-rays should be acquired for all skeletal lesions identified on the screening bone scan, which are not visible on the chest, abdomen and pelvis CT/MRI.
- If clinically indicated, CT or MRI of other areas of disease (e.g., neck) as appropriate.

Subsequent tumor evaluations will be performed on Day 22 (±7 days) of cycles 2, 4 and 6. After cycle 6 tumor evaluations will be performed on Day 22 (±7 days) of every 4th cycle (e.g., C10, C14, C18), or sooner if there is clinical evidence of disease progression.

For the 21-day dosing schedule, subsequent tumor evaluations will be performed every 6 to 8 weeks (Day 14 ±7 days) per standard of care, or sooner if there is clinical evidence of disease progression. After cycle 6 tumor evaluations will be performed on Day 14 (±7 days) of every 4th cycle or sooner if there is clinical evidence of disease progression.

Tumor evaluations will also be performed at EOT. If the last prior tumor evaluation was within 28 days of EOT or objective evidence of progressive disease has already been documented, then tumor evaluations do not need to be repeated at EOT.

Tumor evaluations after the screening assessment will include evaluation of all sites of disease identified at baseline, using the same technique that was used at screening. Chest, abdomen, pelvis scans need to be repeated at each tumor assessment visit (including if negative at baseline). 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.

All radiological and photographic assessments obtained for patients enrolled during phases Ib and II part of the study will be centrally collected and subjected to quality checks by an imaging CRO selected by the Sponsor. The site manual provided by the designated imaging CRO will provide further details regarding image collection.

7.2.2 Safety and tolerability assessments

Safety and tolerability assessments will include adverse event reporting and changes from baseline in laboratory measures and vital signs. Tolerability will be assessed by the incidence of AEs leading to study drug delay or discontinuation. For details on AE collection and reporting, refer to Section 8.

7.2.2.1 Physical examination

A full physical examination (PE) that evaluates all major organ systems will be performed at baseline. This should include a complete ophthalmologic and dermatologic exam. Subsequent PEs should be focused on sites of disease, clinical signs and symptoms, and include eye and skin exams.

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

PEs to be performed for each schedule are outlined in Table 7-1 or Table 7-2.

7.2.2.2 Vital signs

Vital signs (heart rate, blood pressure and temperature) will be obtained in the same position, either sitting or supine, as appropriate prior to any blood collection.

Vital signs to be obtained for each schedule are outlined in Table 7-1 or Table 7-2.

7.2.2.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured at screening. Subsequently, only weight measurements will be required. Assessments to be obtained for each schedule are outlined in Table 7-1 or Table 7-2.

7.2.2.4 Performance status

Performance status will be scored using the ECOG performance scale (see Appendix 1).

Performance status to be obtained for each dosing schedule as outlined in Table 7-1 or Table 7-2.

7.2.2.5 Laboratory evaluations

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

At any time during the study, abnormal laboratory parameters which are clinically relevant (e.g., require dose modification and/or interruption of study drug, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, must be recorded in the AE eCRF.

The Sponsor will be provided with a copy of the laboratory certification and tabulation of the normal ranges for each parameter required. 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.

For all visits, there is a ± 3 days window on assessments to take into account scheduling over public or religious holidays except for assessments that are dose administration dependent such as ECG's and PK. Laboratory assessments that were completed within 72 hours before Cycle 1, Day 1 (C1D1) do not need to be repeated.

7.2.2.5.1 Hematology

Please refer to Table 7-3 for a list of tests to be performed.

For timing of assessments for each schedule, refer to Table 7-1 or Table 7-2.

7.2.2.5.2 Clinical chemistry

Please refer to Table 7-3 for a list of tests to be performed.

For timing of assessments for each schedule, refer to Table 7-1 or Table 7-2.

7.2.2.5.3 Coagulation

Please refer to Table 7-3 for a list of tests to be performed.

For timing of assessments for each schedule, refer to Table 7-1 or Table 7-2.

7.2.2.5.4 Thyroid

Please refer to Table 7-3 for a list of tests to be performed. Only TSH is required at screening and subsequent visits. Only when TSH is abnormal, total T3 and free T4 should be performed.

For timing of assessments for each schedule, refer to Table 7-1 or Table 7-2.

Table 7-3 Clinical laboratory parameters collection plan

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

7.2.2.5.5 Pregnancy assessments

Serum beta-hCG pregnancy test will be performed at screening and C1D1. If screening assessments are performed within 72 hours of initial study treatment then C1D1 is not required. For follow up assessments, serum beta-hCG or urine tests will be performed on Day 1 of every other cycle (e.g. C3D1, C5D1, C7D1 and etc.) and at end of treatment.

For females to be considered "of non-childbearing potential", patient should meet one of the following:

- Surgically sterile for at least 6 weeks (hysterectomy with bilateral oophorectomy or tubal ligation). Documentation of sterilization method must be provided. The date of sterilization will be recorded.
- 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 have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to study entry. 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.

To ensure patient safety, each pregnancy in a patient on study drug must be reported to the Sponsor within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the Sponsor; follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Sponsor study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

7.2.2.5.6 Ophthalmic examination

Full ophthalmological examination performed by trained ophthalmologist including slit lamp examination, color vision test, visual acuity testing, visual field testing, tonometry (intraocular pressure [IOP]), optical coherence tomography (OCT), dilated indirect fundoscopy and color fundus photography with attention to retinal abnormalities, especially retinal pigmented epithelial detachment (RPED) and retinal vein occlusion (RVO) is required. Each time point is indicated in Table 7-1 or Table 7-2. If screening ophthalmic examination is collected within 72 hours of C1D1, it does not have to be repeated.

7.2.2.5.7 Electrocardiogram (ECG)

A standard 12-lead ECG will be performed after the patient has been resting for 5-10 min prior to each time point indicated in Table 7-4 or Table 7-5.

On cycle 1 day 1 (pre-dose), 3 ECG recordings must be taken at a minimum of 2-minute intervals. The combined QTcF values from these 3 ECGs will be averaged to provide a single baseline value for each patient.

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

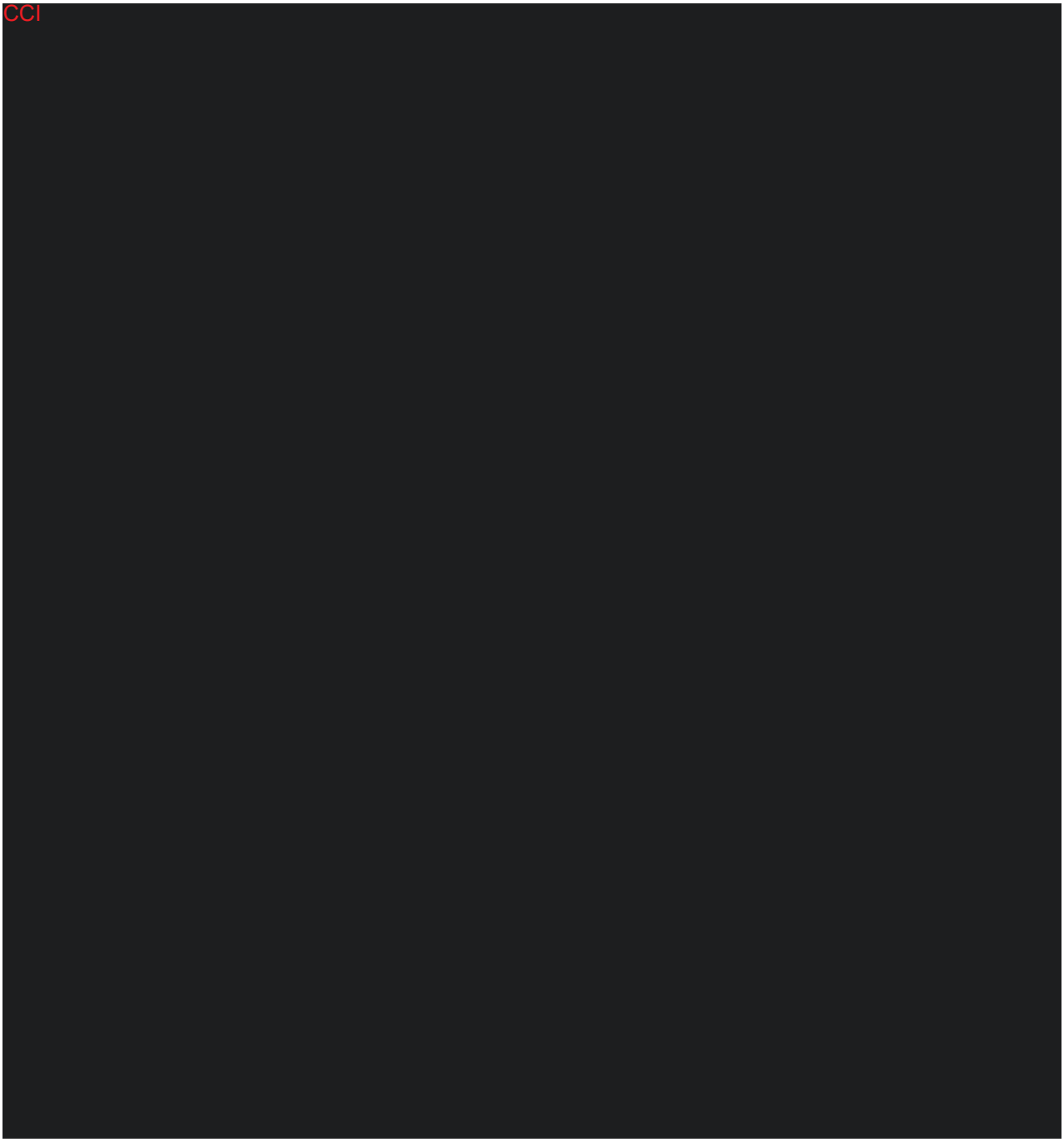
All ECGs will be transmitted to a central laboratory and will be centrally reviewed by an independent reviewer.

In the event that a QTcF value of ≥ 481 ms is observed at any time prior to cycle 7, the patient will continue to have a pre-dose ECG on day 1 of cycle 7 and all subsequent cycles. Additional ECGs at 2 hours post-dose, will be performed for these patients on day 1 of cycle 9 and every 3rd cycle.

CCI [redacted]

Each ECG tracing should be labeled with the study number, patient initials, subject number, date, and kept in the source documents at the study site. Clinically significant abnormalities at screening should be recorded on the relevant medical history/current medical conditions eCRF page.

CCI



CCI [redacted]

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

Cardiac imaging by MUGA/bilateral ECHO to be performed as outlined in Table 7-1 or Table 7-2 at screening, C2D1, C3D1, every other cycle, at end of treatment or as clinically indicated

CCI [redacted]

7.2.3 Pharmacokinetics

7.2.3.1 PK blood sample collection and handling

All blood samples will be taken either by direct venipuncture or through an indwelling cannula (e.g., inserted in a forearm vein, or central venous line) according to the Phase 1b schedule described in Table 7-6 and Table 7-7, and for the Phase II schedule described in Table 7-8 and Table 7-9. Residual plasma samples after the PK concentration analysis may be used for drug metabolism investigations or other bio-analytical purposes (e.g. cross check between different sites, stability assessment). Given the exploratory nature of the work, the analytical method used for those assessments will not be validated.

Refer to the [CMEK162X2114 Laboratory Manual] for detailed instructions for the collection, handling and shipping of samples.

Table 7-6 Pharmacokinetic blood collection log (Phase Ib) 28-day cycle

Cycle	Day	Scheduled time points* (hours)	Dose reference identifier for LEE011	Sample number for LEE011	Dose reference identifier for MEK162	Sample number for MEK162
1	1	pre-dose	1	101	1	201
1	1	0.5h post-dose (± 15 min)	1	102	1	202
1	1	1h post-dose (± 15 min)	1	103	1	203
1	1	2h post-dose (± 15 min)	1	104	1	204
1	1	4h post-dose (± 30 min)	1	105	1	205
1	1	8h post-dose (± 30 min)	1	106	1	206
1	2	24h post dose (± 1 h, pre-dose for the next dose)	1	107	2	207
1	8	pre-dose	2	108	3	208
1	15	pre-dose	3	109	4	209
1	21	pre-dose	4	110	5	210
1	21	0.5h post-dose (± 15 min)	4	111	5	211
1	21	1h post-dose (± 15 min)	4	112	5	212
1	21	2h post-dose (± 15 min)	4	113	5	213
1	21	4h post-dose (± 30 min)	4	114	5	214
1	21	8h post-dose (± 30 min)	4	115	5	215
1	22	24h post dose (± 1 h, pre-dose for the next dose)	4	116	6	216
2	1	pre-dose	5	117	7	217
3	1	pre-dose	6	118	8	218
4	1	pre-dose	7	119	9	219
5	1	pre-dose	8	120	10	220
6	1	pre-dose	9	121	11	221
CCI [redacted]						
Unscheduled	Anytime			2001+		3001+
*All measurement times are relative to dose of LEE011+MEK162 unless otherwise specified.						

Table 7-7 Pharmacokinetic blood collection log (Phase Ib) 21-day cycle

Cycle	Day	Scheduled time points* (hours)	Dose reference identifier for LEE011	Sample number for LEE011	Dose reference identifier for MEK162	Sample number for MEK162
1	1	pre-dose	1	1501	1	1601
1	1	0.5h post-dose (± 15 min)	1	1502	1	1602
1	1	1h post-dose (± 15 min)	1	1503	1	1603
1	1	2h post-dose (± 15 min)	1	1504	1	1604
1	1	4h post-dose (± 30 min)	1	1505	1	1605
1	1	8h post-dose (± 30 min)	1	1506	1	1606
1	2	24h post dose (± 1 h, pre-dose for the next dose)	1	1507	2	1607
1	8	pre-dose	2	1508	3	1608
1	14	pre-dose	3	1509	4	1609
1	14	0.5h post-dose (± 15 min)	3	1510	4	1610
1	14	1h post-dose (± 15 min)	3	1511	4	1611
1	14	2h post-dose (± 15 min)	3	1512	4	1612
1	14	4h post-dose (± 30 min)	3	1513	4	1613
1	14	8h post-dose (± 30 min)	3	1514	4	1614
1	15	24h post dose (± 1 h, pre-dose for the next dose)	3	1515	5	1615
2	1	pre-dose	4	1516	6	1616
3	1	pre-dose	5	1517	7	1617
4	1	pre-dose	6	1518	8	1618
5	1	pre-dose	7	1519	9	1619
6	1	pre-dose	8	1520	10	1620
CCI [redacted]						
Unscheduled		Anytime		8001+		9001+

*All measurement times are relative to dose of LEE011+MEK162 unless otherwise specified.

Table 7-8 Pharmacokinetic blood collection log (Phase II) 28-day cycle

Cycle	Day	Scheduled time points* (hours)	Dose reference identifier of LEE011	Sample number of LEE011	Dose reference identifier of MEK162	Sample number of MEK162
1	1	Pre-dose	1	301	1	401
1	1	0.5h post-dose (± 15 min)	1	302	1	402
1	1	2h post-dose (± 15 min)	1	303	1	403
1	1	4h post-dose (± 30 min)	1	304	1	404
1	8	Pre-dose	2	305	2	405
1	15	Pre-dose	3	306	3	406
1	21	Pre-dose	4	307	4	407
1	21	0.5h post-dose (± 15 min)	4	308	4	408
1	21	2h post-dose (± 15 min)	4	309	4	409
1	21	4h post-dose (± 30 min)	4	310	4	410
2	1	Pre-dose	5	311	5	411

Cycle	Day	Scheduled time points* (hours)	Dose reference identifier of LEE011	Sample number of LEE011	Dose reference identifier of MEK162	Sample number of MEK162
3	1	Pre-dose	6	312	6	412
4	1	Pre-dose	7	313	7	413
5	1	Pre-dose	8	314	8	414
6	1	Pre-dose	9	315	9	415
CCI [redacted]						
Unscheduled		Anytime		4001+		5001+
*All measurement times are relative to dose of LEE011+MEK162 unless otherwise specified.						

Table 7-9 Pharmacokinetic blood collection log (Phase II) 21-day cycle

Cycle	Day	Scheduled time points* (hours)	Dose reference identifier of LEE011	Sample number of LEE011	Dose reference identifier of MEK162	Sample number of MEK162
1	1	Pre-dose	1	1701	1	1801
1	1	0.5h post-dose (± 15 min)	1	1702	1	1802
1	1	2h post-dose (± 15 min)	1	1703	1	1803
1	1	4h post-dose (± 30 min)	1	1704	1	1804
1	8	Pre-dose	2	1705	2	1805
1	14	Pre-dose	3	1706	3	1806
1	14	0.5h post-dose (± 15 min)	3	1707	3	1807
1	14	2h post-dose (± 15 min)	3	1708	3	1808
1	14	4h post-dose (± 30 min)	3	1709	3	1809
2	1	Pre-dose	4	1710	4	1810
3	1	Pre-dose	5	1711	5	1811
4	1	Pre-dose	6	1712	6	1812
5	1	Pre-dose	7	1713	7	1813
6	1	Pre-dose	8	1714	8	1814
CCI [redacted]						
Unscheduled		Anytime		1301+		1401+
*All measurement times are relative to dose of LEE011+MEK162 unless otherwise specified.						

Analytical method

7.2.3.1.1 LEE011

The plasma samples from all patients will be assayed for concentrations of LEE011 and LEQ803 at a designated CRO using a validated liquid chromatography-tandem mass spectrometry assay (LC/MS/MS). Values below the lower limit of quantification (LLOQ) of 1.00 ng/mL will be reported as 0 ng/mL. Missing values will be labeled accordingly.

7.2.3.1.2 MEK162

Plasma concentrations of MEK162 and its metabolite, AR00426032, will be measured at a designated CRO using a validated LC/MS/MS assay with an LLOQ of 1.00 ng/mL. Values

below the lower limit of quantification (LLOQ) of 1.00 ng/mL will be reported as 0 ng/mL. Missing values will be labeled accordingly.

Refer to the [CMEK162X2114 Laboratory Manual] for detailed instructions for the collection, handling, and shipping of samples.

CCI

[redacted]

CCI

[redacted]

CCI [redacted]

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An AE is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical condition(s).

AEs occurring after the signing of the informed consent should be recorded in the Adverse Events eCRF under the signs, symptoms or diagnosis associated with them.

AEs 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, or grades 1 - 4, will be used. CTCAE grade 5 (death) will not be used in this study; rather, this information will be collected in the End of Treatment eCRF page. AE monitoring should be continued for at least 30 days following the last dose of study treatment.

Abnormal laboratory values or test results occurring after signing the informed consent form constitute AEs only if they induce clinical signs or symptoms, or require therapy, (e.g., any hematologic abnormality that requires transfusion or hematological stem cell support) or changes in study medication(s), or are of CTCAE Grade ≥3 Such abnormal laboratory values or test results should be recorded on the AE eCRF under the signs, symptoms or diagnosis associated with them. In addition, isolated abnormal laboratory values that are considered clinically significant (e.g., cause study discontinuation or constitutes in and of itself a SAE) should be recorded on the AE eCRF. The occurrence of AEs should be sought by non-directive questioning of the patient during the screening process after signing informed consent and at each visit during the study. AEs also may be detected when they are volunteered by the patient during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each AE should be evaluated to determine:

1. The CTCAE grade 1-4.
2. Causality (reasonable possibility that AE is related to the study treatment; no, or yes).
3. Its duration (start and end dates or if continuing at final exam).
4. Action taken with respect to study treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable).
5. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown).
6. Whether it is serious, where a SAE is defined as in Section 8.2.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements (Section 8.2).

All AEs should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e., further observation only); study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this AE; concomitant medication given; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged. The action taken to treat the adverse event should be recorded on the AE eCRF.

Once an AE 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 drug, the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (i.e., RECIST 1.1 criteria) should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

Whenever possible, a diagnosis should be reported instead of underlying signs and symptoms.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Abnormal laboratory values or test results that constitute adverse events or underlying conditions should not be reported separately in addition to the respective adverse events or underlying diagnosis.

Additionally, laboratory abnormalities that are considered clinically significant due to induction of clinical signs or symptoms, or requiring concomitant therapy (e.g. any hematologic abnormality that requires transfusion or cytokine treatment) or changes in study medication(s), should be recorded on the Adverse Events eCRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for adverse events should be followed until they have returned to normal or an adequate explanation of the abnormality is found.

Laboratory abnormalities, that do not meet the criteria of clinical significance, as judged by the investigator, should not be reported as adverse events except CTCAE grade ≥ 3. A grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol and should not contribute to designation of a lab parameter abnormality as a SAE.

8.1.3 Adverse events of special interest

Not Applicable.

8.1.3.1 Definitions and reporting

Not Applicable.

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening.
- Results in persistent or significant disability/incapacity.
- Constitutes a congenital anomaly/birth defect.
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  a. Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes).
  b. Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent.
  c. Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission.
  d. Social reasons and respite care in the absence of any deterioration in the patient's general condition.
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event.
- Any SAEs that are expected due to the condition being treated, including if the SAE is a primary outcome measure, and whether there has been a clear agreement with regulators not to consider these as SAEs, provided the information is collected elsewhere.

8.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring;

- after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment/participation.
- after the patient is enrolled and until at least 30 days after the patient has stopped study treatment.
- after the patient begins taking study drug and until at least 30 days after the patient has stopped study treatment.
- after protocol-specified procedures begin (e.g., placebo run-in, washout period, double-blind treatment, etc.) and until at least 30 days after the patient has stopped study treatment.

- after the start of any period in which the study protocol interferes with the standard medical treatment given to a patient (e.g., treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication) and until at least 30 days after the patient has stopped study treatment.

They must be reported to the Sponsor within 24 hours of learning of its occurrence. (Any SAEs experienced after this 30 days period should only be reported to the Sponsor if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs (either initial or follow up information) is collected and recorded on the Serious Adverse Event Report Form within the OCRDC system (where available) or on the paper SAE Form. The Investigator must assess the relationship to each specific study drug (if there is more than one study drug) and complete the electronic or paper SAE Report Form in English.

When SAEs are recorded electronically in the OCRDC system, these should be entered, saved and e-signed within 24 hours of awareness of the SAE. These data will automatically be submitted to the Sponsor immediately after investigator signature or 24 hours after entry, whichever occurs first.

When SAEs are recorded on the paper SAE form, these should be faxed within 24 hours of awareness of the SAE to the Sponsor. The telephone and fax number of the contact persons in the local department of Drug Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Note that any follow up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not and whether the patient continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. If the SAE is not previously documented in the [Investigator's Brochure] or Package Insert (new occurrence) and is thought to be related to the Sponsor study drug, the Sponsor may urgently require further information from the investigator for Health Authority reporting. The Sponsor may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Pregnancies

To ensure patient safety, each pregnancy in a patient on study drug must be reported to the Sponsor within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth,

and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the investigator to the Sponsor. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Sponsor study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

8.4 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 [Investigators Brochure] 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.

8.5 Data Safety Monitoring Board

A Drug Safety Monitoring Board (DSMB) will not be in place for this trial. Instead, the Sponsor and the investigators of the dose-escalation part will meet at the end of each treatment cohort to discuss and evaluate all of the gathered safety data. At the dose escalation teleconference the clinical course (safety information including both DLTs and all = CTCAE Grade 2 toxicity data during the first cycle of treatment, and PK data) 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 Bayesian logistic regression model's (with EWOC) recommendation, and a medical review of relevant clinical, PK and laboratory data. The parties 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.

At these meetings, the Sponsor and the investigators must reach a consensus on whether to escalate the dose any further, or whether to de-escalate and/or expand recruitment into particular cohorts. The Sponsor or designee will prepare minutes from these meetings and circulate them to the investigators.

8.6 Steering Committee

Not applicable.

9 Data collection and management

9.1 Data confidentiality

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

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

In the event that a patient revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the patient experienced any new or worsened AEs) 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.

Prior to entering key sensitive personally identifiable information (Patient Initials and exact Date of Birth), the system will prompt site to verify that this data is allowed to be collected. If the site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit Patient Initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the patient satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

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 CRFs 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 CRFs, 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 CRFs 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 CRF entries. Sponsor 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 CRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

For studies using Electronic Data Capture (EDC), 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, allows 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.

9.4 Database management and quality control

For studies using eCRFs, 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 OCRDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications 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.

Samples and/or data will be processed centrally and the results will be sent electronically to the Sponsor (or a designated CRO).

Data about all study treatments dispensed to patients and all IRT assigned dosage changes will be tracked using an Interactive Response Technology. The system will be supplied by a vendor(s), who will also manage the database. The data will be sent electronically to Sponsor personnel (or designated CRO). For EDC studies, 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

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.

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:** All summaries, listings, figures and analyses will be performed by study arm.

The analysis of study data will be based on all patients' data of the dose escalation and phase II parts up to the time when all patients have potentially completed at least six cycles of treatment or discontinued the study. Any additional data for patients continuing to receive study treatment past the cut-off date for the primary CSR, as allowed by the protocol, will be reported once all patients have discontinued the study.

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.

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, 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 LEE011 or MEK162. Patients will be classified according to the planned treatment combination. The FAS will be used for all listings of raw data. Unless otherwise specified the FAS will be the default analysis set used for all analyses.

10.1.2 Safety set

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

The Per-Protocol Set (PPS) consists of a subset of the patients in the FAS who are compliant with the following requirements of the CSP.

- Diagnosis corresponds to that defined in inclusion criteria (Section 5.2) prior treatment corresponds to that defined in inclusion criteria (Section 5.2).
- The patient received at least 50% of the planned dose of each compound within the first 8 weeks of study.
- Treatment the patient was evaluated for primary efficacy variable at or beyond week 10, or discontinued due to adverse event, disease progression, or died prior to the first evaluation of the primary efficacy variable.

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

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

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

10.1.4 Dose-determining analysis 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 criterion if having received at least 75% of the planned daily combination doses of MEK162 (BID), 75% of the planned daily combination doses of LEE011 and at least 50% of the planned combination doses of the two compounds administered together (in the same day) within the first 21/28 days of treatment. The length of the DLT evaluation period is cycle 1.

Patients who do not experience DLT during the first cycle will be considered to have sufficient safety evaluations if they have been observed for at least 1 cycle (21 or 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.

10.1.5 Pharmacokinetic analysis set

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

Note: patients will be removed from the estimation of certain PK parameters on an individual basis depending on the number of available blood samples. These patients will be identified at the time of the analyses.

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 LEE011 and MEK162 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 total daily doses of LEE011 and MEK162 for each patient will be summarized using descriptive statistics (e.g. mean, median, and modal doses). The FAS will be used.

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 and dose group 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 by treatment group. Compliance to the study drug will be assessed by the number of dose reductions and dose interruptions, see Section 10.5.

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 of the LEE011 and MEK162 combination in patients with locally advanced or metastatic NRAS mutant melanoma.

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 anti-tumor activity of the RP2D of the LEE011 and MEK162 combination in patients with locally advanced or metastatic NRAS mutant melanoma.

10.4.1 Variable

Phase Ib

The primary variable is the incidence of dose limiting toxicities (DLTs) in Cycle 1. Estimation of the MTD(s) 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.

Phase II

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

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 investigator's assessment of overall lesion responses.

10.4.2 Statistical hypothesis, model and method of analysis

Phase Ib

An adaptive BLRM guided by the EWOC principle will guide the dose escalation of the combination treatment to its MTD(s)/RP2D. A 5-parameter BLRM for combination treatment will be fitted on the Cycle 1 dose-limiting toxicity data (i.e. absence or presence of DLT) accumulated throughout the dose escalation to model the dose-toxicity relationship of MEK162 and LEE011 when given in combination. All information currently available about the dose-DLT relationships of single agents MEK162 and LEE011 will be summarized in prior distributions. For this study, available clinical data from studies [ARRAY-162-111] (first-in-human MEK162 oncology study) and [LEE011X2101] will be used to derive informative priors for the BLRM parameters describing the dose-DLT relationships of the 2 agents when given as monotherapy.

Any additional information on the dose-DLT relationship generated by these studies will be incorporated into the prior distribution before the first dose escalation decision is made within this study in order to reflect all relevant information at that time. No pre-clinical data informing on the toxicity of the combination treatment is available. Therefore, a weakly informative prior will be used for the interaction parameter. This prior allows for the cases of synergistic or antagonistic safety profiles, i.e. increases or decreases in the odds of DLT over independence.

The 5-parameter BLRM is formulated in the following way: Let $\pi_1(d_1)$be the probability of a DLT if LEE011 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:

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

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

$\text{Odds}(\pi_{12}(d_1,d_2))) = \pi_{12}(d_1,d_2)/(1- \pi_{12}(d_1,d_2))$

$= \exp(\eta(d_1/d_1^*)(d_2/d_2^*))(\pi_1(d_1)+ \pi_2(d_2) - \pi_1(d_1)\, \pi_2(d_2))/((1- \pi_1(d_1))(1- \pi_2(d_2))),$

where $\text{logit}(\pi.(d.)) = \log[\pi.(d.)/\{1- \pi.(d.)\}]$, $d_1^* = 350$ mg and $d_2^* = 30$ mg (BID) are the reference doses of LEE011 and MEK162 respectively, $\alpha_1, \alpha_2, \beta_1, \beta_1 > 0$ and $-\infty < \eta < \infty$ is a scalar.

Details for prior specification of the model parameters and performance of the BLRM under different hypothetical data scenarios are presented in Appendix 5.

If a different dosing schedule will be considered, historical data collected for the initially planned regimen will be taken into account in order to derive an informative prior estimation of the dose-DLT relationship for the new dosing schedule. This informative prior will be combined with DLT data for the new dosing schedule using a 2-parameter BLRM (full details in Appendix 5).

Dose recommendation

Dose recommendations will be based on summaries of the posterior distribution of model parameters and the posterior distribution of DLT rates, including the mean, median, standard deviation, 95%-credibility 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 recommended dose combination 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.

Decisions on dose escalation will follow the procedure as outlined in Section 6.2.3.

Listings of DLTs

DLTs will be listed and their incidence summarized by primary system organ class, worst Grade based on the CTCAE version 4.03 and type of AE.

Phase II

A Bayesian design will be used in order to estimate the distribution of the ORR (see Section 10.4.1) and to provide inferential summaries (e.g., mean, median, interval probabilities) in relation to the Phase II population (NRAS mutant melanoma).

The primary analysis will be performed when all patients have completed at least 6 cycles of treatment or discontinued prior to that time for any reason.

Patients who discontinue early due to progressive disease (PD), who are of Unknown (UNK) response, were not assessed (NA) at or beyond week 10 or who are lost to follow up prior to week 10 will be considered as failures in the analyses of ORR. Definitions of CR, PR, SD, PD, UNK and NA are per RECIST v1.1 (See Appendix 2).

For a Bayesian design we are required to specify a prior distribution for the parameter of interest ORR. For the current study, the prior clinical assumption for the combination of MEK162 and LEE011 in the selected patient populations is used in order to derive a minimally informative unimodal Beta prior distribution that reflects the level of uncertainty around ORR before starting the current trial (See Appendix 5).

At completion of the study, this prior distribution will be updated with all the data available from the patients in the FAS by arm. All responses and progressions will be determined as per RECIST 1.1.

Once updated, the distribution summarizes the probability that the true ORR at the RP2D used in the study arm lies in the following categories:

- [0, 25%) unacceptable efficacy.
- [25%, 35%) moderate efficacy.
- [35%, 100%] substantial efficacy.

If the observed ORR is equal or greater than or equal to 35%, then this will be considered as preliminary evidence of clinically relevant activity of the combination in NRAS-mutant population. Note that for a sample size of n = 40 (See Section 10.8), if the observed ORR is greater than or equal to 35% (i.e. $\geq$ 14 CR or PR), then the true ORR has posterior risk of being in the unacceptable efficacy category of less than 10%. If the observed ORR is between 25% and 35% then this will be considered as evidence of moderate activity and the inferential summaries for the 3 categories above will be assessed. If the observed ORR is less than 25% (i.e. $\leq$ 9 CR or PR) then inactivity will be declared.

10.4.3 Handling of missing values/censoring/discontinuations

Phase Ib: Patients who are ineligible for the DDS will be removed from the primary analysis and additional patients may be recruited. Their data will be used for all remaining analyses.

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

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 paragraph.

The reason for discontinuation from study will be summarized and listed, along with dates of first and last study drug treatment, duration of exposure to study drug treatment 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

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

Moreover, the primary analysis of the phase II will be repeated using the PPS.

CCI [redacted]

10.5 Secondary objectives

10.5.1 Key secondary objectives

Not applicable.

10.5.2 Other secondary efficacy objectives

Phase Ib

Individual lesion measurements will be listed along with the overall lesion response. Best overall response (BOR), duration of response (DOR) for patients who experience a CR or PR at any time on study, PFS and TTP will be listed by patient and treatment group. Kaplan-Meier analyses of PFS will be provided only if there are at least 10 patients within the same treatment group.

Phase II

Individual lesion measurements BOR, PFS, DOR, TTP and OS data will be listed by patient.

PFS and TTP will be presented graphically using Kaplan Meier plots. In addition, the PFS/TTP distributions will be summarized by presenting the median time with accompanying 95% confidence interval along with the Kaplan-Meier estimates for PFS and TTP at 10 weeks and 4, 8 and 12 months. DOR will be presented graphically using Kaplan Meier plots for all patients who achieved a CR or PR on study. Similarly, the median DOR and corresponding 95% confidence interval will be presented. Moreover, Kaplan Meier plots will also be shown for OS, along with the median time accompanying 95% confidence interval and estimates for OS at 4 and 12 months.

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for analyses

For all safety analyses, the safety set will be used.

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

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

10.5.3.2 Adverse events (AEs)

Summary tables for adverse events (AEs) have to include only AEs that started or worsened during the on-treatment period, the **treatment-emergent** AEs. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment by treatment group.

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event and treatment group.

10.5.3.3 Laboratory abnormalities

For laboratory tests covered by CTCAE version 4.03, the study's biostatistical and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests where Grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

If the lower limits of normal ranges used in CTCAE definitions are missing, then they have to be replaced by a clinical meaningful limit.

The following summaries will be generated separately for hematology, biochemistry and urinary laboratory tests:

- Frequency table for newly occurring on-treatment Grades 3 or 4.
- Shift tables using CTCAE Grades to compare baseline to the worst on-treatment value.
- For laboratory tests where CTCAE Grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.
- Listing of all laboratory data with values flagged to show the corresponding CTCAE Grades and the classifications relative to the laboratory normal ranges.

CCI [redacted]

10.5.3.4 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 assessments for all patients with at least one abnormality.
- Table with frequency of ocular events by cycle will be produced by treatment group.

10.5.3.5 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 and LEE011 will be listed by patient and summarized. Categories for relative dose intensity for MEK162 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.

10.5.4 Pharmacokinetics

PK parameters will be determined for all PK-evaluable patients using non-compartmental method(s) using Phoenix (Pharsight, Mountain View, CA). PK parameters listed in Table 10-1 will be estimated and reported, when feasible. The parameters that require terminal phase determination may not be adequately calculated by non-compartmental methods.

CCI [redacted]

For plasma LEE011, LEQ803, and MEK162, the LLOQ is 1.0ng/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 PK parameters displayed on Table 10-1 will be estimated and reported.

Table 10-1 Non-compartmental pharmacokinetic parameters

Variable	Definition
Cmax	Maximum observed plasma concentration after drug administration (mass x volume^{-1})
Cmax,ss	Maximum observed plasma concentration during a dosing interval at steady state (mass x volume^{-1})
Cmin,ss	Measured concentration at the end of a dosing interval at steady state (taken directly before next administration) (mass x volume^{-1})
Tmax	Time to reach Cmax (time)
Tmax,ss	Time to reach Cmax at steady state (time)
AUCtau	Area under the concentration-time curve during a dosing interval (mass x time x volume^{-1})
AUCtau,ss	Area under the concentration-time curve during a dosing interval at steady state (mass x time x volume^{-1})
CL/F	Apparent total plasma clearance of drug after oral administration (volume x time^{-1})
Racc	Accumulation ratio calculated as AUCtau,ss/AUCtau,dose1
t1/2, acc	Effective elimination half-life

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) and specified in the RAP.

10.5.4.1 Data handling principles

10.5.4.1.1 Analysis sets

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

10.5.4.1.2 Basic tables, figures and listings

Descriptive statistics (mean, standard deviation, CV% or median (range)) will be presented for all parameters by treatment group and study day. When a geometric mean is presented, it will be stated as such. CL/F will be assessed for MEK162, LEE011 and LEQ803, and only median values and ranges will be given for Tmax.

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

10.5.4.1.3 Advanced data analysis methods

CCI [redacted]

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

PK of MEK162, LEE011 and LEQ803 in this combination trial may be compared to historical data from the respective monotherapy studies, if feasible, to assess drug-drug interaction potential.

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

10.7 Interim analysis

Phase Ib

No formal interim analyses are planned. However, the dose escalation design foresees that decisions based on the current data are taken before the end of the study. More precisely, after each cohort in the dose escalation phase, the next dose combination MEK162 and LEE011 has to be chosen depending on the observed data.

Phase II

No interim analysis will be performed for the phase II due to the expectation that all patients will be recruited prior to any analysis timepoint.

10.8 Sample size calculation

Phase Ib

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

Phase II

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

10.9 Power for analysis of key secondary variables

Not Applicable.

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 or designee's monitors, auditors, 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 patient's Informed Consent was actually obtained will be captured in their CRFs. The Sponsor or designee will provide to investigators, in a separate document, a proposed 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 or designee'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.

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 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 patients. 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, patients' 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 patient 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 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

11.7 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.

11.8 Audits and inspections

Source data/documents must be available to inspections by the Sponsor or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start and upon changes to site staff as applicable.

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 at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

13 References (available upon request)

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14 Appendices

14.1 Appendix 1: ECOG Performance Status

Table 14-1 ECOG performance scale

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
* As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.	

14.2 Appendix 2: Response Evaluation Criteria in Solid Tumors (RECIST 1.1)

14.2.1 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 et al 2000).

The efficacy assessments described in Section 14.2.2 and the definition of best response (Section 14.2.9) are based on the RECIST criteria but also give more detailed instructions and rules for determination of best response. Section 14.2.10 is summarizing the "time to event" variables and rules which are mainly derived from internal discussions, as the RECIST criteria do not define these variables in detail. Section 14.2.18 of this guideline describes data handling and programming rules. This section may be used in the analysis plan(s) to provide further details needed for programming.

14.2.2 Efficacy assessments

Tumor evaluations are made based on RECIST criteria (Therasse et al 2000), New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16 and revised RECIST guidelines (version 1.1) (Eisenhauer et al 2009) European Journal of Cancer; 45:228-247.

14.2.3 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 14.2.21.

- **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, if the soft tissue component meets the definition of measurability.
- 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 ≥10 mm and <15 mm 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.

- **Cystic lesions:**
  - Lesions that meet the criteria for radiographically defined simple cysts (i.e., spherical structure with a thin, non-irregular, non-nodular and non-enhancing wall, no septations, and low CT density (water-like) content) should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
  - 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.
- **Non-measurable lesions** - all other lesions are considered non-measurable, including small lesions (e.g. longest diameter <10 mm with CT/MRI or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions e.g., blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

14.2.4 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 Overall Response Rate (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 14.2.21.

14.2.5 Methods of tumor measurement-general guidelines

In this document, the term "contrast" refers to intravenous (i.v) contrast.

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.
- 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 5 mm 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 have a medical contraindication to CT contrast or develops a contraindication 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.
- **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 corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT are needed to determine if there is truly progression occurring at that Site (if so, the date of PD will be the date of the initial abnormal CT scan).
- If the positive FDG-PET at follow-up corresponds 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 surrounded by aerated lung. However, CT is preferable.
- **Ultrasound:** When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm 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 expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- CCI [redacted]

- **Cytology and histology:** Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).
- **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.

14.2.6 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, photography) should be at least 10 mm in longest diameter. See Section 14.2.3.
- **Nodal target:** See Section 14.2.3.

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 metastases). Each non-target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

14.2.7 Follow-up evaluation of target and non-target lesions

To assess tumor response, the sum of the longest 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 14-2) and nontarget lesions (Table 14-3) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and nontarget lesions together (Table 14-4) as well as the presence or absence of new lesions.

The response for nontarget lesions is CR only if all nontarget lesions which were evaluated at baseline are now all absent. If any of the nontarget lesions is still present, 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 nontarget lesions (in which case response is PD).

If tumor markers are used as nontarget 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.

14.2.8 Follow-up and 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.

14.2.8.1 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.

Measurements of non-nodal target lesions that become 5 mm or less in longest diameter are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). Actual measurement should be given for all lesions larger than 5 mm in longest diameter irrespective of slice thickness/reconstruction interval.

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.

14.2.8.2 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.

Measurements of nodal target lesions that become 5 mm or less in short axis are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).Actual measurement should be given for all lesions larger than 5 mm in short axis irrespective of slice thickness/reconstruction interval.

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.

14.2.9 Determination of target lesion response

Table 14-2 Response criteria for target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter of all target lesions, taking as reference the baseline sum of the longest diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of the longest diameter of all measured target lesions, taking as reference the smallest sum of longest diameter of all target lesions recorded at or after baseline.
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.
SOD for CR may not be zero when nodal lesions are part of target lesions Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR Methodology change See Section 14.2.5.	

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 14-2 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 with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to patients who have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.
- 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 100 mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit is 140 mm (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 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.
- Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm 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 any single nodal lesion is at least 10 mm and there is at least 20% increase in sum of the diameters of all nodal target lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.

Table 14-3 Response criteria for non-target lesions

Response Criteria	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions
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 nontarget 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. < 10 mm). 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 '**Non-CR/Non-PD**' 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. 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 even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 14.2.9 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

14.2.10 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 lesion
- 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 14.2.11).
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ≥ 10 mm for the first time in the study plus 5 mm absolute increase.
  FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 14.2.5.

14.2.11 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 14-4.

Table 14-4 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

[1]. This overall lesion response also applies when there are no non-target lesions identified at baseline
[2]. Once confirmed PR was achieved, all these assessments are considered PR.
[3]. As defined in Section 14.2.6.

If there are no baseline scans available at all, 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.

14.2.12 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 14.2.21 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

14.2.13 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 30 days after the last dose of study treatment 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 confirmation of 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).
- PD = progression ≤ 12 weeks after randomization/ start of treatment (and not qualifying for CR, PR or SD).
- 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 200 mm at baseline and then 140 mm - 150 mm - 140 mm - 160 mm - 160 mm 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 140 mm confirms the PR for this patient. All subsequent assessments are considered PR even if tumor measurements decrease only by 20% compared to baseline (200 mm to 160 mm) at the following assessments.

If the patient progressed but continues study treatment, further assessments are not considered for the determination of best overall response.

Note: these cases may be described as a separate finding in the CSR but not included in the overall response or disease control rates.

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.

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).

14.2.14 Time to event variables

The protocol should state which of the following variables is used in that study.

14.2.15 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.

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.

14.2.16 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 known date patient alive, 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 known date patient alive.

14.2.17 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.

14.2.18 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.

14.2.19 Duration of response

The analysis of the following variables should be performed with much caution when restricted to responders since treatment bias could have been introduced. 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 achieve 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 et al (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 SD the start and end date as well as censoring is defined the same as that for time to progression.

14.2.20 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 14.2.18. 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 event is the worst possible outcome as it means 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.

14.2.21 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

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.
  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 14.2.17).
  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 end of treatment visit.

- Date of last contact is defined as the last date the patient was known to be alive. This corresponds to the latest date for either the visit date, lab sample date or tumor assessment date. If available, the last contact date from that survival follow-up page is used. If no survival follow-up is available, the date of discontinuation is used as last contact date.
- Date of secondary anti-cancer therapy is defined as the start date of any additional (secondary) antineoplastic therapy or surgery.

14.2.22 Handling of patients with non-measurable disease only at baseline

It is possible that patients with only non-measurable disease present at baseline are entered into the study, either because of a protocol violation or by design (e.g. in Phase III studies with PFS as the primary endpoint). In such cases the handling of the response data requires special consideration with respect to inclusion in any analysis of endpoints based on the overall response evaluations.

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.

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 14-5.

Table 14-5 Overall lesion response at each assessment: patients with non-target disease only

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

[1] As defined in Section 14.2.7.

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 only 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".

For PFS, it is again recommended that the main ITT analyses on these endpoints include all patients with only 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 with only non-measurable disease.

14.2.23 Sensitivity analyses

This section outlines the possible event and censoring dates for progression, as well as addresses 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 RAP 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 14.2.20, 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 14-6 Options for event dates used in PFS, TTP, duration of response

Situation		Options for end-date (progression)[1] (1) = default unless specified differently in the protocol or analysis plan	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment	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
F	New anticancer therapy given	(1) Date of last adequate assessment (2) Date of secondary anti-cancer therapy	Censored Censored
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP)

[1] =Definitions can be found in Section 14.2.20.
[2] =After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 14.2.16.
[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 14-6 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.

14.2.24 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).

14.2.25 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).

14.2.26 End of treatment phase completion

Patients **may** voluntarily withdraw from the study treatment or may be taken off the study treatment at the discretion of the investigator at any time. For patients who are lost to follow-up, the investigator or designee 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.

The end of treatment visit and its associated assessments should occur within 14 days of the last study treatment.

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

- Adverse event(s)
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor
- Non-compliant with study treatment
- No longer requires treatment
- Treatment duration completed as per protocol (optional, to be used if only a fixed number of cycles is given)

14.2.27 End of post treatment follow-up (study phase completion)

End of post-treatment follow-up visit will be completed after discontinuation of study treatment and post-treatment evaluations but prior to collecting survival follow-up.

Patients may provide study phase completion information for one of the following reasons:

- Adverse event
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision

- Death
- New therapy for study indication
- Progressive disease
- Study terminated by the sponsor

14.2.28 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 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 elects 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.

14.2.29 Programming rules

The following should be used for programming of efficacy results:

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.

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 14.2.16. 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.

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.

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)'.

Study/project specific programming

The standard analysis programs need to be adapted for each study/project.

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 (treatment / study evaluation / survival)
- Lost to follow-up (during treatment* / study evaluation* / survival)

For PFS and TTP (and therefore duration of responses) the following censoring reasons are possible:

- Ongoing without event (treatment / study evaluation)
- Lost to follow-up (during treatment / study evaluation)
- Withdrew consent (during treatment* / study evaluation)
- Study evaluation stopped (when follow-up for progression is stopped after certain number of events or at certain time, i.e. reason='Administrative problems' on study evaluation completion page, or when patients are not followed for progression after treatment completion)
- Death due to reason other than underlying cancer *(only used for TTP)*
- New cancer therapy added

***Note** = this category is to be used if no further information is available (as information on death may be available in patients who were originally lost to follow-up, and information on progression may be received in patients who withdrew consent to continue study drug).

Medication and herbals to be excluded or to be used with caution

Any patient who requires a prohibited medication should not be enrolled on a trial for LEE011 and MEK162 until further information becomes available.

Note: This is not a comprehensive list of cytochrome P450 isoenzymes and transporter substrates or their inducers or inhibitors, and QT prolongation medications. This is only meant to be used as a guide. Please contact the medical monitor with any questions.

14.2.30 References (available upon request)

Dent S, Zee (2001) application of a new multinomial phase II stopping rule using response and early progression, J Clin Oncol; 19: 785-791.

Eisenhauer E, et al (2009) New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). European Journal of Cancer; 45: 228-247.

Ellis S, et al (2008) Analysis of duration of response in oncology trials. Contemp Clin Trials 2008; 29: 456-465.

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. Cont Clin Trials; 9: 11-18.

Therasse P, Arbuck S, Eisenhauer E, et al (2000) New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute; 92: 205-216.

14.3 Appendix 3: List of prohibited concomitant therapies and therapies to be used with caution

Table 14-7 List of prohibited medications during LEE011 and MEK162 treatment

Category	Drug Name
Strong CYP3A Inhibitors – AUC substrate increased by ≥ 5 fold	clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, sequinavir/ritonavir, telaprevir, telithromycin, voriconazole, indinavir/ritonavir, tipranoavir/ritonavir, cobicistat, troleandomycin, danoprevir/ritonavir, eltegravir/ritonavir grapefruit juice
Strong CYP3A Inducers – AUC decreased by ≥ 80%	mitotane, enzalutamide ,carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin[2], Avasimibe, St. John's wort[1,2]
CYP3A substrates with narrow therapeutic index (NTI)	Quinidine, astemizole, terfanadine, cyclosporine, sirolimus, tacrolimus, diergotamine, cisapride, ergotamine, pimozide, alfentanil, fentanyl, thioridazine, diergotamine, dihydroergotamine, ergotamine
Medications with knows risk of QT prolongation	Amiodarone, anagrelide, arsenic trioxide, astemizole (Off US mkt), azithromycin, bepridil (Off US mkt), chloroquine, chlorpromazine, cisapride (Off US mkt), citalopram, clarithromycin, cocaine, disopyramide, dofetilide, domperidone (Not on US mkt), dronedarone, droperidol, erythromycin, escitalopram, flecainide, grepafloxacin (Off market worldwide), halofantrine, haloperidol, ibutilide, levofloxacin, levomethadyl (Off US mkt), mesoridazine (Off US mkt), methadone, moxifloxacin, ondansetron, pentamidine, pimozide, probucol (Off US mkt), procainamide (Oral off US mkt), quinidine, sevoflurane, sotalol, sparfloxacin (Off US mkt), sulpiride (Not on US Mkt), terfenadine (Off US mkt), thioridazine, vandetanib

[1] Herbal product
[2] PgP Inducer

This list of CYP substrates was compiled from Clinical Pharmacology internal memo: drug-drug Interactions (DDI) database, 2015, which is compiled primarily from the FDA's "Guidance for Industry, Drug Interaction Studies", the Indiana University School of Medicine's Drug Interactions Database, the University of Washington's Drug Interaction Database, and crediblemeds.org

Table 14-8 List [1] of medications to be used with caution during LEE011 and MEK162 treatment

Category	Drug Name

Category	Drug Name
Sensitive CYP3A substrates[2]	Alpha-dihydroergocryptine, alfentanil, almorexant, aplaviroc, aprepitant, atazanavir, atorvastatin, avanafil, bosutinib, brecanavir, brotizolam, budesonide, buspirone, capravirine, casopitant, conivaptan, danoprevir, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, elvitegravir, eplerenone, everolimus, felodipine, fluticasone, ibrutinib, indinavir, ivacaftor, levomethadyl, lomitapide, lopinavir, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, midostaurin, neratinib, nisoldipine, perospirone, quetiapine, ridaforolimus, saquinavir, sildenafil, simeprevir, simvastatin, ticagrelor, terfenadine, ticagrelor, tilidine,tipranavir, tolvaptan, triazolam, vardenafil, vicriviroc, voclosporin.
Moderate CYP3A inhibitors	amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, nilotinib imatinib, tofisopam, cyclosporin, ciprofloxacin, verapamil, dronedarone, crizotinib, casopitant, amprenavir, atazanavir/ritonavir, duranavir, netupitant, schisandra sphenanthera[3], cimetidine, lomitapide
Moderate CYP3A Inducers	bosentan, efavirenz, etravirine, modafinil, nafcillin, genistein, ritonavir, thioridazine, tipranavir, semagacestat, talviraline, lopinavir, lersivirine
Known inhibitors of BSEP	Atorvastatin, cerivastatin, cyclosporine, glyburide, reserpine, rifampicin, troglitazone, valinomycin,
BCRP Substrates	Atorvastatin daunorubicin, doxorubicin, hematoporphyrin, imatinib, methotrexate, mitoxantrone, pitavastatin, rosuvastatin, SN-38 (irinotecan), ethinyl estradiol, simvastatin, sulfasalazine, sofosbuvir, topotecan, sulfasalazine
MATE 1/2 substrates	Acyclovir, cimetidine, ganciclovir, fexofenadine[4], metformin[4], procainamide, topotecan, glycopyrronium[4], topotecan
Substrates of CYP2B6	Bupropion, efavirenz, methadone, nevirapine, sibutramine,
BCRP Inhibitors	abacavir, amprenavir, atazanavir[4], atorvastatin, cerivastatin, cyclosporine[4], daunomycin, delavirdine, efavirenz, elacridar, eltrombopag[4] erlotinib, fluvastatin, fumitremorgin, gefitinib, lopinavir, nelfinavir, nilotinib, pitavastatin, rosuvastatin, saquinavir, simvastatin, sulfasalazine, SN-38 (irinotecan), pantoprazole
P-gp inhibitors	alogliptin, amiodarone[5], azithromycin[5], canaglifozin, captopril[5], carvedilol[5], clarithromycin[5], conivaptan[5], cremophor RH40, curcumin, diltiazem[5], dronedarone[5], elacridar[5], erythromycin[5], felodipine[5], fluvoxamine[5], ginko[3,5], indinavir[5], indinavir/ritonavir[5], itraconazole[5], ketoconazole, lapatinib, lopinavir/ritonavir, mibefradil[5], milk thisle[3,5], mirabegron, nelfinavir[5], nifedipine[5], nitredipine[5], paroxetine[5], propafenone, quercetin[5] , quinidine[5], ranolazine[5], rifampin[5], ritonavir[5], sequinavir/ritonavir[5], schisandra chinesis extract[3,5], simepravir, St. John's wort extract[3,5], talinolol[5], telaprevir[5], telmisartan[5], ticagrelor[5], tipranavir/ritonavir[5], tolvaptan[5], valspodar, vandetanib, verapamil[5], voclosporin.

Category	Drug Name
UGT1A1 inhibitors	atazanavir, erlotinib, flunitrazepam, gemfibrozil, indinavir, ketoconazole, nilotinib, pazopanib, propofol, regorafenib, sorafenib, *silybum marianum*[3] (also known as milk thistle), *valeriana officinalis*[3],

Category	Drug Name
UGT1A1 inducers	carbamazepine, rifampicin, testosterone propiate, cigarette smoke

[1] Any drug mentioned in the above list should be contraindicated if they are excluded based on any other exclusion criteria as specified in Section 5.3 of the Study Protocol or listed in Table 14-7.
[2] Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor.
[3] Herbal product
[4] Have been shown to have DDI in vivo. Others reports as substrates in vitro
[5] Dual P-gp and CYP3A4 inhibitor

This list of CYP substrates was compiled from Clinical Pharmacology internal memo: drug-drug Interactions (DDI) database, 2015, which is compiled primarily from the FDA's "Guidance for Industry, Drug Interaction Studies", the Indiana University School of Medicine's Drug Interactions Database, the University of Washington's Drug Interaction Database, and crediblemeds.org

14.4 Appendix 4: Guidance on medications with a risk of Torsades de Pointes

Table 14-9 Drugs with a conditional risk of Torsades de Pointes

Generic Name	Brand Name	Class/Clinical Use
Amisulpride	Solian® and others	Antipsychotic, atypical /
Amitriptyline	Elavil®	Tricyclic Antidepressant / depression
Ciprofloxacin	Cipro®	Antibiotic / bacterial infection
Clomipramine	Anafranil®	Tricyclic Antidepressant / depression
Desipramine	Pertofrane®	Tricyclic Antidepressant / depression
Diphenhydramine	Benadryl®, Nytol®	Antihistamine / Allergic rhinitis, insomnia
Doxepin	Sinequan®	Tricyclic Antidepressant / depression
Fluconazole	Diflucan®	Anti-fungal / fungal infection
Fluoxetine	Sarafem®, Prozac®	Anti-depressant / depression
Galantamine	Reminyl®	Cholinesterase inhibitor / Dementia, Alzheimer's
Imipramine	Norfranil®	Tricyclic Antidepressant / depression
Itraconazole	Sporanox®	Anti-fungal / fungal infection
Ketoconazole	Nizoral®	Anti-fungal / fungal infection
Nortriptyline	Pamelor®	Tricyclic Antidepressant / depression
Paroxetine	Paxil®	Anti-depressant / depression
Protriptyline	Vivactil®	Tricyclic Antidepressant / depression
Ritonavir	Norvir®	Protease inhibitor / HIV
Sertraline	Zoloft®	Anti-depressant / depression
Solifenacin	VESIcare®	muscarinic receptor anatagonist / treatment of overactive bladder
Trazodone	Desyrel®	Anti-depressant / Depression, insomnia
Trimethoprim-Sulfa	Septra® or Bactrim®	Antibiotic / bacterial infection
Trimipramine	Surmontil®	Tricyclic Antidepressant / depression

Substantial evidence supports the conclusion that these drugs prolong the QT interval and have a risk of TdP but only under certain known conditions (e.g. excessive dose, drug interaction, etc.).

Table 14-10 Drugs with a possible risk of Torsades de Pointes

Generic Name	Brand Name	Class/Clinical Use
Alfuzosin	Uroxatral®	Alpha1-blocker / Benign prostatic hyperplasia
Amantadine	Symmetrel®	Dopaminergic/Anti-viral / Anti-infective/ Parkinson's Disease
Artenimol+piperaquine	Eurartesim®	Anti-malarial /
Atazanavir	Reyataz®	Protease inhibitor / HIV
Chloral hydrate	Noctec®	Sedative / sedation/ insomnia
Clozapine	Clozaril®	Anti-psychotic / schizophrenia
Dolasetron	Anzemet®	Anti-nausea / nausea, vomiting
Dronedarone	Multaq®	Anti-arrhythmic / Atrial Fibrillation
Eribulin	Halaven®	Anti-cancer / metastatic breast neoplasias
Escitalopram	Cipralex®, Lexapro®	Anti-depressant / Major depression/ Anxiety disorders

Generic Name	Brand Name	Class/Clinical Use
Famotidine	Pepcid®	H2-receptor antagonist / Peptic ulcer/ GERD
Felbamate	Felbatrol®	Anti-convulsant / seizure
Fingolimod	Gilenya®	Immunosuppressant / Multiple Sclerosis
Foscarnet	Foscavir®	Anti-viral / HIV infection
Fosphenytoin	Cerebyx®	Anti-convulsant / seizure
Gatifloxacin	Tequin®	Antibiotic / bacterial infection
Gemifloxacin	Factive®	Antibiotic / bacterial infection
Granisetron	Kytril®	Anti-nausea / nausea and vomiting
Iloperidone	Fanapt®	Antipsychotic, atypical / Schizophrenia
Indapamide	Lozol®	Diuretic / stimulate urine & salt loss
Isradipine	Dynacirc®	Anti-hypertensive / high blood pressure
Lapatinib	Tykerb®, Tyverb®	Anti-cancer / breast cancer, metastatic
Levofloxacin	Levaquin®	Antibiotic / bacterial infection
Lithium	Lithobid®, Eskalith®	Anti-mania / bipolar disorder
Moexipril/HCTZ	Uniretic®	Anti-hypertensive / high blood pressure
Nicardipine	Cardene®	Anti-hypertensive / high blood pressure
Nilotinib	Tasigna®	Anti-cancer / Leukemia
Octreotide	Sandostatin®	Endocrine / acromegaly, carcinoid diarrhea
Ofloxacin	Floxin®	Antibiotic / bacterial infection
Ondansetron	Zofran®	Anti-emetic / nausea and vomiting
Oxytocin	Pitocin®	Oxytocic / Labor stimulation
Paliperidone	Invega®	Antipsychotic, atypical / Schizophrenia
Perflutren lipid microspheres	Definity®	Imaging contrast agent / Echocardiography
Quetiapine	Seroquel®	Anti-psychotic / schizophrenia
Ranolazine	Ranexa®	Anti-anginal / chronic angina
Risperidone	Risperdal®	Anti-psychotic / schizophrenia
Roxithromycin*	Rulide®	Antibiotic / bacterial infection
Sertindole	Serdolect®, Serlect®	Antipsychotic, atypical / Anxiety, Schizophrenia
Sunitinib	Sutent®	Anti-cancer / RCC, GIST
Tacrolimus	Prograf®	Immunosuppressant / Immune suppression
Tamoxifen	Nolvadex®	Anti-cancer / breast cancer
Telithromycin	Ketek®	Antibiotic / bacterial infection
Tizanidine	Zanaflex®	Muscle relaxant /
Vardenafil	Levitra®	phosphodiesterase inhibitor / vasodilator
Venlafaxine	Effexor®	Anti-depressant / depression
Voriconazole	VFend®	Anti-fungal / anti-fungal
Ziprasidone	Geodon®	Anti-psychotic / schizophrenia

Substantial evidence supports the conclusion that these drugs cause QT prolongation but there is insufficient evidence that they, when used as directed in labeling, have a risk of causing TdP.

14.5 Appendix 5: Statistical details for the Phase Ib part: Bayesian logistic regression model (BLRM), priors, design properties for hypothetical data scenarios and design operating characteristics

An adaptive Bayesian design using escalations with overdose control EWOC will guide the dose-escalation of the combination treatment to its MTD(s)/RP2D. The use of Bayesian response adaptive designs 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.

This section provides details of the statistical model, the derivation of prior distributions for the model parameters, and the properties of the adaptive design (dosing recommendations for hypothetical data scenarios and frequentist operating characteristics).

14.5.1 Statistical model and prior distributions

This section is organized in the following way:

- A short motivation is provided.
- The single-agent prior distribution for LEE011 is derived.
- The single-agent prior distribution for MEK162 is derived.
- The prior distribution for the interaction parameter (eta) is derived.
- Numerical values and summary statistics at different dose levels are shown.

Motivation

A 5-parameter BLRM (refer to the protocol Section 10.4.2 for detail) will be used to model the dose limiting toxicity rate of the first cycle to assess the dose-toxicity relationship of LEE011 in combination with MEK162.

Details regarding dose recommendation are described in Section 10.4.2 of the protocol.

The Bayesian approach requires the specification of prior distributions for all model parameters, which comprise the single-agent parameters for LEE011 and MEK162, and for the interaction parameter (see model definition in Section 10.4.2). Derivation of these is provided in the following subsections.

LEE011

Currently available historical data of LEE011 administered on 3 weeks on/1 week off schedule from study [CLEE011X2101] up to October 31st 2012 have been used in order to derive the prior for the BLRM parameters ($\log(\alpha_1)$,$\log(\beta_1)$).The bivariate normal prior for the model parameters ($\log(\alpha_1)$,$\log(\beta_1)$) is obtained as follows:

1. The following non-informative prior for ($\log(\alpha_1)$,$\log(\beta_1)$) was used:
    - The median DLT rate at the LEE011 combination reference dose (350 mg QD) was assumed 1/10, i.e. mean ($\log(\alpha_1)$) = $\log(1/9)$.
    - A doubling in dose was assumed to double odds of DLT, i.e. mean($\log(\beta_1)$) = 0.

- The standard deviation of $\log(\alpha_1)$ was set to 2, and the standard deviation of $\log(\beta_1)$ to 1, which allows for considerably prior uncertainty for the dose-toxicity profile.
- The correlation between $\log(\alpha_1)$ and $\log(\beta_1)$ was set to 0.

2. Data from 37 patients eligible for the dose-determining set of the on-going study [CLEE011X2101] were used to update the dose-toxicity profile (see Table 14-11).
3. Heterogeneity between the historical and current study was incorporated by between-trial standard deviations $\tau 1$ and $\tau 2$ for $\log(\alpha 1)$ and $\log(\beta 1)$. Both $\tau 1$ and $\tau 2$ were set to follow a log-normal distribution. Mean $\log(0.5)$ and standard deviation 0.01 was chosen for $\tau 1$, and mean $\log(0.25)$ and standard deviation 0.01 for $\tau 2$, which correspond to substantial between-trial variability.

Table 14-11 Data from study [LEE011X2101]

Dose of LEE011 (QD - 3 weeks on/1 week off)	No of DLTs/No of evaluable patients
50 mg	1/4
70 mg	0/2
140 mg	0/3
280 mg	1/4
400 mg	2/4
260 mg	0/4
350 mg	0/5
600 mg	0/4
900 mg	1/7

MEK162

Currently available historical data of MEK162 administered on BID continuous over 28 days schedule from study [ARRAY-162-111] has been used in order to derive the prior for the BLRM parameters $(\log(\alpha_2),\log(\beta_2))$.The bivariate normal prior for the model parameters $(\log(\alpha_2),\log(\beta_2))$ is obtained as follows:

1. The following non-informative prior for $(\log(\alpha_2),\log(\beta_2))$ was used:
   - The median DLT rate at the MEK162 combination reference dose (30 mg BID) was assumed 1/5, i.e. mean $(\log(\alpha_2)) = \log(1/4)$.
   - A doubling in dose was assumed to double odds of DLT, i.e. $\text{mean}(\log(\beta_2)) = 0$.
   - The standard deviation of $\log(\alpha_2)$ was set to 2, and the standard deviation of $\log(\beta_2)$ to 1, which allows for considerably prior uncertainty for the dose-toxicity profile.
   - The correlation between $\log(\alpha_2)$ and $\log(\beta_2)$ was set to 0.
2. Data from 15 patients eligible for the dose-determining set of the on-going study [ARRAY-162-111] were used to update the dose-toxicity profile (see Table 14-12).
3. Heterogeneity between the historical and current study was incorporated by between-trial standard deviations $\tau 3$ and $\tau 4$ for $\log(\alpha 2)$ and $\log(\beta 2)$. Both $\tau 3$ and $\tau 4$ were set to follow a log-normal distribution. Mean $\log(0.25)$ and standard deviation 0.01 was chosen for $\tau 3$, and mean $\log(0.125)$ and standard deviation 0.01 for $\tau 4$, which correspond to moderate between-trial variability.

Table 14-12 Data from study [ARRAY-162-111]

Dose of MEK162 (BID continuous 28 days)	No of DLTs/No of evaluable patients
30 mg	0/3
45 mg	0/3
60 mg	0/6
80 mg	2/3

Interaction parameter

The prior reflecting the current uncertainty about the toxicity of the combination treatment is used for the parameter modeling the interaction (η). Because a potential interaction between the small molecules MEK162 and LEE011 cannot be excluded a priori, the parameter η is given a prior normal distribution with median = 0.095 (~1.1 fold increase in odds of DLT compared to independence at the combination reference dose) and 97.5th percentile = 0.698 (~2 fold increase on odds of DLT at the combination reference dose). This assumes, a priori, that there will be a small interaction, but also allows for the potential of both synergism and antagonism between the safety profiles of the 2 drugs.

Since the interaction is dose-dependent (see model definition in Section 10.4.2), the prior for the interaction parameter has a simple interpretation only at the combination reference dose of MEK162 = 30mg **and** LEE011 = 350mg. Table 14-13 shows the prior median and 95% interval for the interaction at all provisional dose levels and the combination reference dose.

Table 14-13 A priori interaction at provisional dose levels

LEE011 mg (QD - 3 weeks on/1 week off)	MEK162 mg (BID continuous 28 days)	
	30	**45**
100	1.03 (0.87, 1.22)	1.04 (0.81, 1.35)
200	1.06 (0.75, 1.49)	1.09 (0.65, 1.81)
350	**1.10 (0.61, 2.00)**	1.15 (0.47, 2.83)
400	1.12 (0.56, 2.21)	1.18 (0.42, 3.28)
600	1.18 (0.42, 3.28)	1.28 (0.28, 5.94)
Presented are median (95% probability interval). The a priori interaction at the combination reference dose is highlighted in bold.		

Numerical values and summary statistics

Table 14-14 summarizes the information for all model parameters: distributions for the single-agent parameters (weakly-informative prior, posterior from historical data, and discounted prior due to between-trial heterogeneity), and the prior for the interaction parameter. Table 14-15 summarizes the prior distribution of DLT rates corresponding to the prior.

Table 14-14 Prior, posterior and predictive distribution of model parameters

Parameters	Means	Standard deviations	Correlation
1. Weakly-informative priors for LEE011 and MEK162			
$\log(\alpha_1),\log(\beta_1)$	-2.197, 0.000	2.000, 1.000	0.000
$\log(\alpha_2),\log(\beta_2)$	-1.386, -0.000	2.000, 1.000	0.000
2. Posterior from available data			
$\log(\alpha_1),\log(\beta_1)$	-1.956, -0.929	0.493, 0.673	-0.050
$\log(\alpha_2),\log(\beta_2)$	-2.887, 0.195	1.056, 0.859	-0.629
3. Prior used for CMEK162X2114 (incorporates between-trial heterogeneity)			
$\log(\alpha_1),\log(\beta_1)$	-1.958, -0.939	0.862, 0.751	-0.034
$\log(\alpha_2),\log(\beta_2)$	-2.930, 0.207	1.117, 0.882	-0.586
eta	0.095	0.305	N/A

Table 14-15 Prior summaries (derived from priors in Table 14-14)

LEE011 doses (mg, QD - 3 weeks on/1 week off)	Prior probabilities that Pr(DLT) is in interval:			Mean	SD	Quantiles		
	(0, 0.16)	**(0.16, 0.35)**	**(0.35, 1)**			**2.5%**	**50%**	**97.5%**
	MEK162 = 30mg (BID)							
100	0.556	0.362	0.081	0.173	0.113	0.034	0.145	0.460
200	0.449	0.429	0.122	0.202	0.122	0.046	0.174	0.511
400	0.319	0.461	0.220	0.249	0.144	0.055	0.219	0.602
600	0.261	0.421	0.318	0.290	0.172	0.055	0.255	0.695
	MEK162 = 45mg (BID)							
100	0.374	0.469	0.157	0.225	0.134	0.053	0.195	0.556
200	0.289	0.486	0.225	0.256	0.144	0.063	0.226	0.608
400	0.211	0.432	0.357	0.310	0.174	0.067	0.278	0.714
600	0.193	0.353	0.454	0.358	0.209	0.058	0.322	0.817
Note: bold values indicate dose combinations not meeting the overdose criterion.								

In any case, the prior parameters ($\log(\alpha_1),\log(\beta_1)$) will be updated at the time of the first DETC in order to include all the historical DLT rate data collected from [CLEE011X2101] after October 31st 2012 and before the first dose escalation meeting.

Note that if a different dosing schedule will be considered for LEE011 in combination with MEK162 BID, a Bayesian Meta-analytic approach will be used to take into account historical data collected for the LEE011 initially planned schedule in combination with MEK162 in the actual study, in order to derive an informative prior estimation of the dose-toxicity relationship for the new LEE011 dosing regimen administered with MEK162 BID. This informative prior will be updated with DLT data for combination administered with the new LEE011 dosing schedule using a 5-parameter BLRM.

Alternative regimen: LEE011 QD and MEK162 BID, both "3 weeks on and 1 week off"

Due to expected differences in levels of exposure between the MEK162 continuous and intermittent dosing schedules, the contribution of the data from the combination of LEE011 QD "3 weeks on 1/week off" and MEK BID continuous dosing regimen will be applied appropriately, as follows:

- Patients treated at the initial regimen, having the minimum treatment exposure as defined in DDS for the new schedule (Section 10.1) or DLT in the first 21 days of treatment and not experiencing DLT within the last 7 days of cycle 1 will be included in the historical dose determining set.
- Only patients with DLT occurred within the first 21 days of treatment will be incorporated as historical DLT data.

Table 14-16 shows the actual DLT data from initial combination dosing regimen, calculated according to the two criteria mentioned above.

Table 14-16 Current data from initial combination dosing regimen included as historical data for the new regimen

LEE011 QD "3 week on/ 1 week off"	MEK162 dose (BID continuously)	No. of DLTs/No. of evaluable patients
200 mg	45 mg	1/6
300 mg	45 mg	0/3

Selection of the starting dose level is according to the EWOC principle, which recommends doses only for which the risk of excessive toxicity (true DLT rate exceeding 0.35) is less than 25%. In addition, it must not exceed the combination of doses which is found to be safe in the previously tested schedule.

Alternative regimen: LEE011 QD and MEK162 BID, both "2 weeks on and 1 week off"

Due to expected differences in levels of exposure between the MEK162 continuous and intermittent dosing schedules, as well as between LEE011 QD given with initial regimen (3 weeks on/1 week off) and alternative regimen (2 weeks on/1 week off), the contribution of the data from the combination at the initial dosing regimen will be appropriately applied, according to the approach presented in the previous section. In particular:

- Patients treated at the initial regimen, having the minimum treatment exposure as defined in DDS for the new schedule (Section 10.1) or DLT in the first 14 days of treatment, and not experiencing DLT within the third week of cycle 1 will be included in the historical dose determining set.
- Only patients with DLT occurred within the first 14 days of treatment will be incorporated as historical DLT data.

In the case that also data from 3 weeks on/1 week off combination schedule (see section above) will be available at the time of the decision to explore this new regimen, then same logic will be adopted for inclusion of this set of data.

Selection of the starting dose level is according to the EWOC principle, which recommends doses only for which the risk of excessive toxicity (true DLT rate exceeding 0.35) is less than 25%. In addition, it must not exceed the combination of doses which is found to be safe in the previously tested schedule.

14.5.2 Hypothetical dose escalation scenarios

Table 14-17 shows on-study dosing recommendations for some hypothetical data scenarios, considering the initial dosing regimen.

Note that the next dose combination is selected in concordance with the provisional dose levels specified in Section 6.2.3 of the protocol, to mimic possible on-study escalation steps.

For example, in scenario 5, the next dose combination (600/45) is below the maximal increase allowed by the model and below the 100% increase limit. However, since this is one of the provisional dose levels suggested for the next cohort, it has been selected accordingly.

In addition, if in one of the next dose combinations recommended by the model the suggested dose of MEK162 is below 45 mg, these combinations are not presented. The only exception is when there is no combination with a dose of MEK162 of at least 45 mg which satisfies the overdose criterion. Similarly, if in one of the next dose combinations recommended, at least one of the doses is above 600 mg for LEE011 with fixed MEK162 at 45 mg, these scenarios are not presented.

Table 14-17 On-study decisions for dosing

Scenario	Dose combination LEE011 /MEK162	Npat	Ntox	Next dose combination (NDC)	P(target) NDC	P(over) NDC	Median DLT rate
1	200/45	3	0	400/45	0.48	0.18	0.207
2	200/45	3	1	200/45	0.56	0.23	0.247
3	200/45	3	2	100/30	0.51	0.20	0.226
4		3	3	STOP			
5	200/45 400/45	3 3	0 0	600/45	0.41	0.15	0.177
6	200/45 400/45	3 3	0 1	400/45	0.55	0.21	0.236
7	200/45 400/45	3 3	0 2	200/45	0.62	0.20	0.245
8	200/45 200/45	3 3	1 0	400/45	0.53	0.22	0.237
9	200/45 200/45	3 3	1 1	200/45	0.60	0.24	0.264
10	200/45 200/45	3 3	1 2	100/30	0.56	0.16	0.221
11	200/45 400/45 600/45	3 3 3	0 0 0	1200*/45	0.24	0.17	0.126

Scenario	Dose combination LEE011 /MEK162	Npat	Ntox	Next dose combination (NDC)	P(target) NDC	P(over) NDC	Median DLT rate
12	200/45 400/45 600/45	3 3 3	0 0 1	600/45	0.50	0.17	0.215
13	200/45 400/45 600/45	3 3 3	0 0 2	400/45	0.63	0.22	0.260
Note that the overdose criterion is defined as P(over) < 0.25. *Additional dose levels may be added if allowed by the BLRM.							

Within Table 14-17, it can be seen that the model leads to decisions that are in agreement with clinical sense: progressive increase of the combination doses if no DLT is observed, enrolling of a new cohort at the same dose combination when 1 DLT is reported, and decrease when more than 1 DLT is reported in a cohort.

14.5.3 Operating characteristics for Phase Ib

14.5.3.1 Scenarios

In order to show how the design performs, 5 hypothetical scenarios were investigated considering the initial dosing regimen and using the following scenarios:

1. For scenario 1, the odds of DLT in are in line with the prior information, i.e. the simulation parameter values for the BLRM are set similar to the median values of the prior.
2. For scenario 2 it was assumed that MEK162 would be the primary driver of toxicity.
3. For scenario 3 it was assumed that LEE011 would be the primary driver of toxicity.
4. Scenario 4 represents a scenario assuming low toxicity, i.e. the true underlying toxicity is lower than what would be predicted from the prior.
5. Finally, Scenario 5 represents a scenario assuming high toxicity, i.e. the true underlying toxicity is higher than what would be predicted from the prior.

Table 14-18 True underlying probabilities of DLT for Scenario 1

LEE011 doses (mg, QD - 3 weeks on/1 week off)	MEK162 (mg, BID continuous over 28 days)	
	30	**45**
200	**0.16**	**0.19**
400	**0.21**	**0.25**
600	**0.25**	**0.30**
Bold values indicate dose combinations in the targeted toxicity interval (16%, 35%).		

Table 14-19 True underlying probabilities of DLT for Scenario 2

LEE011 doses (mg, QD - 3 weeks on/1 week off)	MEK162 (mg, BID continuous over 28 days)	
	30	**45**
200	**0.16**	**0.32**
400	**0.21**	0.42
600	**0.25**	0.50
Bold values indicate dose combinations in the targeted toxicity interval (16%, 35%).		

Table 14-20 True underlying probabilities of DLT for Scenario 3

LEE011 doses (mg, QD - 3 weeks on/1 week off)	MEK162 (mg, BID continuous over 28 days)	
	30	**45**
200	**0.16**	**0.19**
400	**0.32**	0.38
600	0.48	0.47
Bold values indicate dose combinations in the targeted toxicity interval (16%, 35%).		

Table 14-21 True underlying probabilities of DLT for Scenario 4

LEE011 doses (mg, QD - 3 weeks on/1 week off)	MEK162 (mg, BID continuous over 28 days)	
	30	**45**
200	0.10	0.13
400	**0.16**	**0.18**
600	**0.22**	**0.23**
Bold values indicate dose combinations in the targeted toxicity interval (16%, 35%).		

Table 14-22 True underlying probabilities of DLT for Scenario 5

LEE011 doses (mg, QD - 3 weeks on/1 week off)	MEK162 (mg, BID continuous over 28 days)	
	30	**45**
200	**0.28**	**0.32**
400	0.40	0.44
600	0.52	0.56
Bold values indicate dose combinations in the targeted toxicity interval (16%, 35%).		

14.5.3.1.1 Simulation detalis

Data for 1000 trials were simulated for each scenario and the total minimum number of DLT to control the declaration of MTD was fixed to one. The starting dose combination was chosen as 200 mg LEE011 45 mg MEK162, and the maximal dose to jump to was orthogonal, and follows the protocol specifications (Section 10.4.2 of the protocol). If there is no combination of LEE011 which satisfies EWOC with MEK162 at 45 mg, MEK162 can be de-escalated to 30 mg.

Among the different dose combinations considered, the one maximizing the probability of the true DLT rate being in the targeted toxicity interval (16%, 35%) is selected.

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: 15.
- Maximum number of patients enrolled: 60.
- Minimum number of patients enrolled at a given dose combination in order to declare MTD: 6.

14.5.3.1.2 Metrics to assess operating characteristics

Operating characteristics were reviewed for the simulations to compare the relative performance under each true scenario. The metrics reviewed were:

1. Average proportion of patients receiving a target dose combination on study (I).
2. Average proportion of patients receiving a dose combination with true P(DLT) ≥ 35% on study (II).
3. Average proportion of patients receiving a dose combination with true P(DLT) < 16% on study (III).
4. Probability of recommending a target dose combination as the MTD (correct final decision) (IV).
5. Probability of recommending a dose combinations with true P(DLT) ≥ 35% as the MTD (patient risk) (V).
6. Probability of recommending dose combination with true P(DLT) < 16% as the MTD (VI).

14.5.3.1.3 Operating characteristics

Table 14-23 below summarizes the operating characteristics of the design for the 5 different scenarios studied using the metrics shown above. Additionally, the percentage of trials stopped before declaring MTD when all dose combinations were considered too toxic are presented.

Table 14-23 Results

Scenario	Metrics						
	I	II	III	IV	V	VI	Stopped
1	1	0	0	0.921	0	0	0.079
2	0.911	0.089	0	0.644	0.087	0	0.269
3	0.776	0.224	0	0.676	0.243	0	0.081
4	0.410	0	0.590	0.601	0	0.373	0.026
5	0.910	0.090	0	0.576	0.091	0	0.333

The simulated operating characteristics presented show that the combination model performs reasonably well under the hypothetical scenarios investigated.

The proportion of patients treated at overly toxic dose combinations (metric II) is below 10% for all scenarios, excepted scenario 3, in which the combinations have either a true probability of DLT lying in the overdosing interval or have a true risk DLT a bit higher than the upper bound of the under-dosing interval. Furthermore, the identified MTD falls within the targeted interval (metric IV) in more than 55% for all scenarios, showing a good targeting of the MTD (even higher than 90% in Scenario 1).

Of note for scenario 4, as there were no combinations which had true P(DLT) > 0.35, this explains why any of the recommended combinations not falling in the target interval is a combination with true P(DLT) < 0.16 (exception for the 2% of stopped trial). Therefore, 37% of all simulated trials declared a combination with P(DLT) < 0.16 as MTD.

The relatively high number of trials (around 30%) that were stopped in Scenario 2 and 5 because all combinations were considered too toxic reflects the fact that even the lowest dose combination of 200 mg LEE011 and 30mg MEK162 has a considerable chance of DLT (16% and 28% in Scenario 2 and Scenario 5, respectively). Please note that in this context also Scenario 1 and 3 have the lowest dose combination with a considerable chance of DLT (16%) but they behave differently from scenario 2 because of two different reasons. In scenario 1 a lot of combinations have true risk of DLT lying in the middle of the target interval, so that the identified MTD falls very often within it. In scenario 3 the combinations have either a true probability of DLT lying in the overdosing interval or have a true risk DLT a bit higher than the upper bound of the under-dosing interval. This facilitates the model to identify an MTD falling in the overdosing interval rather than stopping the trial.

In conclusion, the simulations performed illustrate that the model good and reasonable operating characteristics.

14.5.4 Statistical details for the Phase II part

A Bayesian approach will be used in the Phase II in order to estimate ORR for the NRAS mutant populations and to provide inferential statements based on the uncertainty of this quantity.

A Beta prior distribution that reflects the amount of uncertainty around the ORR before starting the phase II has been selected for the population to be enrolled in the phase II part NRAS mutant melanoma). Given that the Response rates to single agent therapies in NRAS mutant patients range between 15-25% (see Section 2.1), the prior mean ORR is conservatively set to be equal to 0.20 and the unimodal Beta prior distribution is constrained to be minimally informative. This leads to the following parameters for the Beta prior distribution:

- a = 0.25.
- b = 1.

At completion of the study the prior distribution will be updated taking into account all of the data available from the evaluable NRAS mutant patients at RP2D. Once updated, the posterior distribution summarizes the probability that the true ORR at the RP2D lies in the categories specified in Section 10.4.2.

The criteria defined to declare efficacy are provided in Section 10.4.2 and sample size justification is provided in Section 10.8.