NOVARTIS

Clinical Development

INC280

Protocol CINC280X2205 / NCT02276027

A Phase II, open label, multiple arm study of single agent AUY922, BYL719, INC280, LDK378 and MEK162 in Chinese patients with advanced non-small cell lung cancer (NSCLC)

Document type	Amended Protocol Version
EUDRACT number	Not applicable
Version number	07 (Clean)
Development phase	II
Document status	Final
Release date	22-May-2019

[redacted]

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List of abbreviations

ASCO	American Society of Clinical Oncology
ADA	American Diabetes Association
ADL	Activities of Daily Living
ADME	Absorption, Distribution, Metabolism and Excretion
AE	Adverse Event
AhR	Aromatic hydrocarbon Receptor
Akt	see PKB
ALT	Alanine aminotransferase/ glutamic pyruvic transaminase/ GPT
ALK	Anaplastic Lymphoma Kinase
ALP	Alkaline Phosphatase
AMI	Acute Myocardial Infarction
AST	Aspartate aminotransferase/ glutamic oxaloacetic transaminase/ GOT
AUC	Area Under the concentration-time Curve
BCRP	Breast Cancer Resistance Protein
BP	Blood Pressure
CFDA	China Food and Drug Administration
CI	Confidence Interval
CK	Creatine Kinase
CL	Clearance
Cmax	Maximum plasma concentration
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CSR addendum	An addendum to Clinical Study Report (CSR) that captures all the additional information that is not included in the CSR
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
CVA	Cerebrovascular Accident
CYP	Cytochrome P450
DCR	Disease Control Rate
DDI	Drug Drug Interaction
DILI	Drug Induced Liver Injury
DLT	Dose Limiting Toxicity
DTIs	Direct Thrombin inhibitors
ECG	Electrocardiogram
EGFR	Epidermal Growth Factor Receptor
EML4-ALK	Echinoderm microtubule associated protein like 4-anaplastic lymphoma kinase
ERG	Electro-Retinograms
FAS	Full Analysis Set
FIH	First-in-Human
FPG	Fasting Plasma Glucose
GGT	Gamma-glutamyl Transpeptidase
GLP	Good Laboratory Practice

[redacted]

HbA1c	Glycosylated Hemoglobin
HGF	Hepatocyte Growth Factor
HSP90	Heat Shock Protein 90
i.v.	intravenous
IC50	Concentration producing 50% inhibition
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
ILD	Interstitial Lung Disease
IRB	Institutional Review Board
IN	Investigator Notification
LFT	Liver Function Tests
Ki	Metabolic inhibition rate constant
Kinact	Maximal inactivation rate
LBBB	Left Bundle Branch Block
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantitation
LPLV	Last Patient Last Visit
LVEF	Left Ventricular Ejection Fraction
MAP	Meta Analytical Predictive
MDR	Multi-drug Resistance
MEK	Mitogen-activated protein (MAP) Kinase
MRP	Multidrug resistance-associated protein
MTD	Maximum Tolerated Dose
mTOR	Mammalian Target of Rapamycin
NSCLC	Non-Small Cell Lung Cancer
OATP	Organic anion-transporting polypeptide
ORR	Objective Response Rate
OS	Overall Survival
PAS	Pharmacokinetic Analysis Set
PFS	Progression Free Survival
P-gp	P-glycoprotein
PI3K	Phosphatidylinositol-3-Kinase
PIK3CA	Gene which encodes the p110alpha catalytic subunit of PI3K
PK	Pharmacokinetics
PD	Pharmacodynamics
PKB	Protein Kinase B
PPS	Per-Protocol Set
PR	Partial Response
PTX	Patient derived tumor xenograft
PXR	Pregnane X Receptor
Racc	Accumulation ratio
RAP	Report and Analysis Plan
RAS/RAF/MEK	mitogen-activated and extracellular signal–regulated kinase
RBBB	Right Bundle Branch Block
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors

[redacted]

RP2D	Recommended Phase II Dose
R Value	ALT/ALP in x ULN
RVO	Retinal Vein Occlusion
SAE	Serious Adverse Event
SCC	Squamous cell carcinoma
SD	Stable Disease
SEC	Safety Event Categories
T1/2	Terminal elimination half-life
TdP	Torsades de Pointes
TKI	Tyrosine Kinase Inhibitors
Tmax	Time to reach peak plasma concentration
TTP	Time to Progression
UGT	UDP-glucuronosyltransferase
ULN	Upper Limit of Normal
VEGFR	Vascular Endothelial Growth Factor Receptor

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Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q28 days)
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
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, 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
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 a patient permanently discontinues study treatment for any reason
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points
Withdrawal of Consent	Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact

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Amendment 7 (22-May-2019)

Amendment rationale

The main purpose of this amendment is to add the option for patients still on study treatment at the time of study end to transfer into another Novartis study.

In addition, the definition of end of the study has been clarified to provide sufficient data for analysis of secondary efficacy objectives.

Typographical errors and inconsistencies have been corrected as needed throughout the document.

Study Update:

The enrollment of this study has been halted since 01-Aug-2017 due to difficulty in identifying patients who met the eligibility criteria of the study. A total of 66 patients have been treated on the study with BYL719, INC280, LDK378 or MEK162. As of 01-Mar-2019, 8 patients are ongoing in LDK378 arm and have been on treatment for more than 40 cycles. One of the 8 patients achieved stable disease and the other patients achieved partial response.

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 underline for insertions.

List of Abbreviations: Abbreviations deleted for Investigator-Initiated Trial, Interactive Response Technology, Maximal inactivation rate, Red Blood Cells, Standard Operating Procedure and Volume of distribution at Steady State. Definition of abbreviation for MAP was updated.

Section 4.1 was updated to include the option to transfer patients to another Novartis study.

Sections 4.3 and 7.1.6 were updated to correctly reflect the definition of end of study.

IRBs/IECs

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.

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Amendment 6 (26-Jan-2017)

CINC280X2205 started enrollment on 20 January 2015. As of 15 November 2016, a total of 50 patients have been treated on the study with BYL719, INC280, LDK378 or MEK162.

The main purpose of this amendment is to update the protocol with new recommendations for BYL719 AE management and dosing administration, which were published in the most recent Investigator's Brochure.

The modifications to AE management are based on a program-wide assessment and advisory board input regarding BYL719 induced hyperglycemia and skin toxicity. The inclusion/exclusion criteria as well as management guidelines have been modified in this protocol, based on developed guidance from this program review. These recommendations apply to the BYL719 arm and include: a modification to exclude patients with HbA1c $\geq$ 6.5%; updated treatment guidance with regard to hyperglycemia, skin toxicity, and elevated transaminases.

The modifications to BYL719 dosing administration are based on clinical data from a food effect study and drug-drug interaction study. Based on these data, the protocol has been updated to include required administration of BYL719 with food and the removal of a restriction on administration of acid reducing agents. In addition, the amendment has been updated to:

- Allow central review for ECGs for comparison of local ECG analysis;
- Allow patients with overlapping molecular alterations to be enrolled;
- Remove the coagulation test during pre-screening as patients are expected to be monitored for bleeding risk during biopsy as per local practice;
- Implement new strength of 150mg INC280 tablet depending on the availability of the supplies and following the regulatory requirements;
- Increase the minimal patient number for PK sample collection for BYL719 arm to get more knowledge about the PK profile for BYL719 considering this is the first study for BYL719 in lung cancer. Specify the minimal patient number for PK sample collection for INC280 arm as both capsule and tablet have been used in this arm and only one patient was treated with capsule.
- Make other minor clarifications/ editorial changes which are included in the list of changes below.

Changes to the protocol

- Protocol summary and Section 5.1 have has been updated to include patients with lung squamous cell carcinoma for BYL719 arm to ensure the patient population is consistent with the one in the Section 5.2.
- Section 2.1 has been updated to correct the year of publication for one reference.
- Section 5.2 has been updated to clarify the process to enroll patient with overlapping molecular alterations tested in the study.
- Section 5.3 has been updated to exclude female patients with a QTcF>460 msec for BYL719 arm and to exclude patients with HbA1c $\geq$ 6.5% for BYL719 arm.

[redacted]

- Section 6.1.1 BYL719 dosing instructions and recommendations have been updated based on the results of a food effect and ARA DDI study.
- Section 6.2.1 has been reorganized and updated to specify the restriction of second dose reduction only applies to recurrent Grade 3/4 toxicity.
- Section 6.2.2, Table 6-3 has been moved to Section 14.3.2 to combine with the follow up guideline for liver abnormality for INC280 arm.
- Section 6.2.3 has been updated to include general measures to minimize risks to the patients. Management of Pneumonitis for BYL719 has been removed to Section 14.3 to ensure all the risk management guideline is included in the same section. Dose modification guideline for other AEs for LDK378 arm has been incorporated into the Table 14-8.
- Section 6.3.1 has been updated to include the permitted concomitant medications for BYL719 arm.
- Section 6.3.2 has been updated to include new permitted concomitant mediations used with caution for BYL719 arm and to add herbal medication as concomitant medications used with caution for all the arms.
- Section 6.3.3 has been updated to include the other anticancer therapy as the prohibited concomitant medication. Restriction of use ARA in BYL719 arm has been removed. CYP2C8/9 substrate with NTI has been moved to the permitted medication used with caution. Herbal medication has been clarified to be prohibited for disease treatment for all the arms.
- Section 6.5.2, Table 6-3 has been updated to add 150mg as a new strength for INC280.
- Section 7.1, Table 7-1 has been updated to remove the coagulation test during molecular screening. Apart time between triplet ECGs has been updated. And the reference table for the PK analysis has been corrected.
- Section 7.1.2 has been update to clarify that standard care of assessment performed before written inform consent obtained can be used considering it was within the screening window.
- Section 7.2.2.6 has been updated to introduce the potential central ECG review. Update of the apart time between triplet ECGs has been reflected in this section.
- Section 7.2.3.1 has been updated the minimal patient number for PK sample collection for each arm.
- Section 8.2.1 has been updated to clarify the protocol exempt SAE.
- Section 9.4 has been updated to reflect the potential use of central ECG review.
- Section 10 has been corrected the number of treatment arms.
- Section 10.5.2.4 has been updated to include the central ECG data in the final analysis.
- Section 11.5 has been updated to align with the Novartis publication guidance.
- Section 13 has been added with new references.
- Section 14.2, Table 14-6 has been updated to provide more dose modification guidance for hyperglycemia and skin toxicity and to update dose modification guidance on diarrhea, liver abnormality, cardiac events, stomatitis, and in case of acute pancreatitis for BYL719 arm.

[redacted]

- Section 14.2, Table 14-8 has been updated to correct the administration error and to add the general management guidance for other AEs.
- Section 14.3.1 has been added the skin toxicity, amylase/ lipase evaluation, liver toxicity as the selected toxicity for BYL719 and provided more guidance to manage hyperglycemia, skin toxicity and diarrhea.
- Section 14.3.2 has been updated to reflect the move of INC280 follow up of selected toxicity.
- Section 14.3.3 has been updated to refer the DILI follow up guidance for LDK378 arm to the one for INC280 arm.
- Section 14.3.5 has been updated with new reference added.
- Section 14.4 has been updated to reflect the changes with respect to the co-administration CYP2C8. CYP2C9, CYP3A4 and BCRP.

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IRB/IEC/HA

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.

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Amendment 5 (01-Jul-2016)

Amendment rationale

The CINC280X2205 study started enrollment on 20 January 2015. As of 23 May 2016, a total of 40 patients have been treated in the study with BYL719, INC280, LDK378 or MEK162. The enrollment for LDK378 arm was completed on 15-Apr-2016 because the sample size as defined in the protocol was reached.

The main purpose of this amendment is to update the concomitant medication information for INC280 treatment arm and LDK378 treatment arm, and to clarify the QT interval correction method for LDK378 treatment arm.

Amendment Rationales for INC280 arm:

- Based on new PK data it is suggested that the concomitant use of Proton Pump Inhibitors (PPIs) is unlikely to impact the efficacy of INC280, therefore the PPI restriction can be removed from this protocol for patients requiring PPI gastric protection treatment. Moreover, requirements on other acid reducing agents (gastric acid modulators and H2 receptor antagonists) can also be removed.
- The list of prohibited and to be used with caution medications for INC280 has also been updated based on the latest internal DDI guidance.

Amendment Rationale for LDK378 arm:

- For clarification purpose, to ensure the QT correction method is consistent during the study, ECG assessment and dose modification guidance has been updated to specify that QTcF would be used to monitor QT prolongation.
- The list of permitted, prohibited and to be used with caution medications for LDK378 has been updated based on the latest internal guidance for LDK378 treatment. Non-enzyme inducing anti-epileptic drugs and herbal medications have been added as the prohibited concomitant medications. Enzyme inducing anti-epileptic drugs, bisphosphonate and denosumab have been added as permitted concomitant medications. Corticosteroid has been added as the concomitant medications to be used with caution. Palliative radiotherapy and palliative surgery have been added as allowed concomitant treatments.

Changes to the protocol

Section 1.2.2.2.2: Clinical pharmacokinetics has been updated with new PK data for INC280.

Section 6.3.1: PPIs and other acid reducing agents have been added as the permitted concomitant medications for INC280. Enzyme inducing anti-epileptic drugs**,** bisphosphonate and denosumab have been added as permitted concomitant medications for LDK378.

Section 6.3.2: Corticosteroid has been added as the concomitant medications to be used with caution for LDK378. Palliative radiotherapy and palliative surgery have been added as allowed concomitant treatments for LDK378. Restrictions on acid reducing agents (gastric acid modulators and H2 receptor antagonists) have been removed for INC280.

Section 6.3.3: Restriction on PPIs has been removed for INC280 based on new PK data. CYP2C8 substrate with narrow therapeutic index (NTI) has been removed for LDK378 as

[redacted]

LDK378 is not a potent inhibitor of CYP2C8. Investigational therapies and anti-cancer therapies except the study treatment and those listed in the Section 6.3.2 have been clarified to be prohibited concomitant therapies.**Table 7-4 INC280 arm:** Local clinical laboratory parameters collection plan has been updated to include the required laboratory evaluations for potential drug-induced liver injury cases.

Section 14.3.2: Follow-up evaluations for selected hepatic toxicities have been updated to make it consistent with Table 6-3. And R value definition has been updated in the follow up of potential DILI case section.

Section 7.2.2.6.1: Text has been added to clarify that QTcF will be used to correct QT interval during the treatment**.**

Table 14-8 LDK378 arm: Text has been added to clarify that QTcF will be used as the correction method for the monitoring of QT prolongation.

Section 14.4: Guidance has been added for handling the situation if a medication is listed both in Table 14-12 and Table 14-13.

Table 14-12: The sensitive CYP2D6 substrate has been removed as it is not applicable to any arm. And PPIs have been added to ensure it consistent with the Section 6.3.2.**Table 14-13**: CYP2D6 substrates with NTI and P-gp transporters with NTI have been removed as they are not applicable to any arm. CYP2C8 substrate with NTI and CYP2C9 substrate with NTI have been added to ensure the information in Table 14-13 is consistent with the Section 6.3.3. Additionally, each prohibit concomitant medication has been specified with its applicable treatment arm(s).

Table 14-14: Medications with known risk of QT prolongation have been updated.

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Amendment 4

Amendment rationale

The main purpose of this amendment is to include squamous cell carcinoma patients into the BYL719 arm and to update the dose modification guidelines, safety monitoring plan and certain inclusion/exclusion criteria for INC280, LDK378 and MEK162 treatment arms based on available and current information. For the patient population, the limitation of no more than two prior lines of antineoplastic was removed providing treatment opportunities for those patients with advanced lung cancer disease in the late setting, considering recent changes of treatment landscape in lung cancer. This amendment also introduces the possibility of utilizing a central laboratory for molecular prescreening purposes. The rationale for modification of each arm of the study is listed as below.

Main Changes in BYL719 arm:

- PIK3CA-mutated non-small cell lung cancer (NSCLC) represents a clinically and genetically heterogeneous subgroup in adenocarcinomas as well as in squamous cell carcinomas (SCC) with a higher prevalence of these mutations in SCC (8.9% vs 2.9% comparing with adenocarcinoma) (Scheffler et al. 2015). PIK3CA copy-number gains also occur in lung cancers, with higher frequency in squamous cell carcinomas (Yamamoto H et al, Cancer Res. 2008; Kawano O et al, Lung Cancer. 2007). PIK3CA mutation/amplification may represent a good predictive feature for the clinical application of specific PI3K inhibitors in SCC lung cancer patients (Bonelli MA et al. Mol Cancer Ther. 2015 Aug). Internal Patient derived tumor xenograft (PTX) data showed that 3 out of 4 PIK3CA mutation lung squamous cell carcinoma cell line responded (2 stable and 1 partial response, then progress) to the BYL719 single agent treatment. Based on his, the inclusion criteria of BYL719 arm is expanded from adenocarcinoma NSCLC patients to adenocarcinoma or squamous cell carcinoma NSCLC patients.

Main changes in INC280 arm:

- This protocol amendment provides additional information and guidance to investigators for the management of liver toxicities. After the cut-off date of the current INC280 Investigator's Brochure (28-Sep-2014), a female patient experienced a serious, unexpected, possibly related adverse event of abnormal liver function tests during treatment with a combination of INC280 and gefitinib while enrolled in the CINC280X2202 study. This adverse event met the lab criteria of Hy's Law and the hepatotoxicity could not be attributed solely to either drug alone or to the combination. Therefore, clarifications in the dose modification guidelines in case of liver toxicity and updated rules with regards to study treatment discontinuation for events that meet the Hy's Law criteria are added. Furthermore, other updates are being implemented in this protocol amendment as described below:
- Based on the preclinical data which suggest photosensitization potential for INC280, precautionary measures against ultraviolet exposure are being included in this amendment, in addition to the information provided in the current INC280 Investigator's Brochure.
- Based on the recent preliminary data from the ongoing clinical studies with INC280, the definition of c-MET positivity is updated. Single agent INC280 showed preliminary

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antitumor activity in patients with NSCLC. As of 21-Mar-2014, 3 out of 6 patients had a confirmed partial response; all patients had high c-MET status by IHC or fluorescence in situ hybridization (FISH) (Bang et al 2014). Two of 3 patients had c-MET mutations. Moreover, as of 21-Mar-2014, in the combination study of INC280 plus gefitinib, partial responses were seen in 8 out of 46 (17%) evaluable NSCLC patients. All responders had high c-MET status (analyzed by IHC or FISH): patients with MET gene copy number ≥ 5 demonstrated an overall response rate of 40% (n=8/20) and patients with c-MET IHC intensity score 3+ demonstrated an overall response rate of 33% (n=7/21). No responses have been observed in patients with c-MET IHC intensity score 2+ or low MET gene copy number (< 5) (Wu et al 2014). Based on these preliminary data on the antitumor activity of INC280 as a single agent and in combination with gefitinib in NSCLC patients, the definition of the c-MET positive status in this study will be updated for patients with c-MET IHC intensity score 3+ in $\geq 50\%$ of tumor cells or c-MET IHC intensity score 2+ in $\geq 50\%$ of tumor cells and MET gene copy number ≥ 5 as detected by FISH.

- To clarify the initial dosage and dose modification schedule for INC280 tablet formulation.

Main changes in LDK378 arm:

Under this amendment, a consistent approach is being implemented across ongoing studies with LDK378 to monitor and manage safety signals identified as the clinical experience with LDK378 has grown. Specifically, changes are made that address hepatic toxicity, pancreatitis and pneumonitis.

- to exclude patients with history of pancreatitis or history of increased amylase or lipase that was due to pancreatic disease
- to include additional dose modification and follow-up monitoring language for patients who may experience pancreatic enzyme elevations in the absence of clinical symptoms
- to update dose modification language and the guidelines for the management of hepatic toxicity
- 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), study treatment must be permanently discontinued
- to update adverse events of special interest including hepatotoxicity, interstitial lung disease/pneumonitis, QT interval prolongation, bradycardia, hyperglycemia, gastrointestinal toxicity (nausea, vomiting and diarrhea) and pancreatitis (including lipase and amylase elevations).
- Hyperglycemia has also been observed in patients treated with LDK378. Patients with abnormally high fasting glucose levels are now excluded from participating in this study. For consistency across the LDK378 program clinical trials, other changes as outlined below have been made to dose modifications for patients who experience toxicity.

Main changes in MEK162 arm:

To clarify the dose modification guidelines and to align with other MEK162 ongoing studies, specifically for retinal events, left ventricular systolic dysfunction and creatine kinase (CK) elevation. The recommended dose modifications were also modified and clarified for: other eye disorders, liver-related AEs, QT prolongation and rash.

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- To modify the grading criteria and dose modification for retinal events
- To clarify the dose modification table for left ventricular systolic dysfunction
- To clarify the guidance for monitoring and dose modification for CK elevation

Changes to the protocol

1. Section 1.2.2.2: INC280 clinical safety: the clinical safety section for INC280 has been updated with the most recent information based on the current INC280 Investigator's Brochure (edition 5.2) including the description of the event of abnormal liver function tests meeting the criteria of Hy's Law.
2. Section 1.2.3: updated the FDA and European Commission approved indication and information of LDK378 (ZYKADIA™)
3. Section 1.2.3.2: updated to delineate overall Adverse Event occurrence and to denote adverse events of interest for LDK378 arm.
4. Section 1.2.4.2.1: updated the clinical information according to current NAME COMPOUND IB edition 11.
5. Section 2.3 and 6.1: updated the initial dosage for INC280 tablet formulation
6. Section 4.1, section 5.1 and section 7.1.1: introduced the possibility of using central laboratory for molecular prescreening purpose.
7. Section 4.3: clarified the definition for end of study.
8. Section 5.2- to include squamous cell carcinoma patients into the BYL719 arm
9. Section 5.2- INC280 arm: updated inclusion criteria 8 to update the c-MET positive definition.
10. Section 5.3- Exclusion criterion 9 has been updated to modify bilirubin excluded values at screening/baseline.
11. Section 5.3- LDK378 arm: updated exclusion criteria 27-34, and 39-40 with further laboratory exam and to exclude patients with significant pancreatic history for safety.
12. Section 5.3-MEK162 arm: included history of Gilbert's syndrome
13. Section 6.1.1: Instructions for administration of INC280: precautionary measures against ultraviolet exposure have been added.
14. Section 6.1.1: Patients who have disease progression and have evidence of clinical benefit, such as disease shrinkage at other sites or symptomatic improvement, may continue treatment with BYL719, INC280, LDK378 and MEK162. In addition, BYL719, INC280, LDK378 and MEK162 treatment may be temporarily interrupted to permit local therapy for symptomatic metastases after disease progression has been documented. Patients who continue on treatment after disease progression should discontinue study treatment once they are no longer deriving benefit as assessed by the investigator.
15. Section 6.2: updated the dose modification schedule for INC280 tablet formulation.
16. Section 6.2: updated the dose modification guideline and added the general guideline for unlisted toxicity of LDK378
17. Section 6.3.2: update the medications to be used with caution for INC280
18. Section 6.3.2: added UGT1A1 inhibitors and inducers as permitted concomitant medication used with caution for the MEK162 arm

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19. Section 6.5.2: added 100mg INC280 tablet formulation for clinical use.
20. Section 7.1.4.1: provided further clarity for criteria for premature patient withdrawal.
21. Section 7.1.7: added the description to clarify the situation for withdrawal of consent.
22. Section 7.1.5: added the description to clarify the situation for lost to follow up.
23. Section 7.2.2.5: updated the local clinical chemistry laboratory parameters adding serum amylase, serum lipase and fasting plasma glucose
24. Section 14.2, table 14-7, Dose modification guideline for INC280: the recommended dose modifications for INC280 in case of hepatic toxicities have been updated.
25. Section 14.2, table 14-8, Dose modification guideline for LDK378: provided additional clarity and parameters for study drug dose modifications, discontinuation, with special focus on pneumonitis, hepatic, renal and pancreatic toxicities
26. Section 14.2, table 14-9, Dose modification guideline for MEK162 and table 14-10, grading of retinal detachment: provided additional clarity and parameters for study drug dose modifications, discontinuation, with special focus on retinal events, hepatic, cardiac and skin toxicities. To add the modified grading definition of retinal detachment table for improved accuracy grading of any associated retinal events. This revised table is adapted from the NCI CTCAE, Version 4.03 Grading of Retinopathy.
27. Section 14.3.2: updated INC280 guideline for the follow-up of laboratory liver abnormalities
28. Section 14.3.3: updated LDK378 Guidelines for the follow-up of laboratory hematologic abnormalities, laboratory liver abnormalities, laboratory renal abnormalities, laboratory pancreatic abnormalities, guideline for monitoring pneumonitis and guideline for treatment of hypophosphatemia.
29. Section 14.4: updated with current information for concomitant medications prohibited or used with caution, including UGT1A1 inhibitors and inducers for the MEK162 arm

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IRB/IEC/HA

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Amendment 3

Amendment rationale

The purpose of this amendment is to remove the AUY922 treatment arm from the study and to include guidelines for the management of pneumonitis in the BYL719 treatment arm of the study.

Novartis has announced that all development work on the AUY922 program has been ceased based on available safety and efficacy clinical data. Therefore, the AUY922 treatment arm will be removed from this study as well.

Changes to the protocol

Deletion of the AUY922 relevant paragraphs from Section 1.2.1, Section 2.1, Table 3-1, Figure 4-1, Section 5.2, Section 6.1, Section 6.3, Section 7.1, Table 7-5, Table 7-6, Table 7-11, Section 10.4.2, Table 10-1, Table 10-3, Table 10-4, Table 14-6, Section 14.3.1.

Addition of Section 6.2.3 Management of pneumonitis and addition of guidelines for the management of pneumonitis to Table 14-7, Criteria for interruption and re-initiation of BYL719 treatments.

IRB/IEC

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Amendment 2

Amendment rationale

The main purpose of this amendment is to update the safety monitoring plan as recommended by the health authority, CFDA, for AUY922 and INC280 arms of the protocol.

Changes to the protocol

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

Section 5.3 exclusion criteria 30, has been updated to exclude the patients with highly suspicious pulmonary fibrosis or interstitial lung disease.

Section 6.1.1 has been updated to explain the criteria to switch INC280 formulation from capsules to tablets.

Section 6.2.1 has been updated to clarify the patient discontinuation criteria for AUY922 arm.

Section 7.2.2.6.2 and table 7-5, has been updated to add the unscheduled ECG visit into the cardiac safety monitoring plan for AUY922 arm.

Section 7.2.2.7, has been updated to add the unscheduled ophthalmologic exams into the ophthalmologic safety monitoring plan for AUY922 arm.

Section 7.2.3.1 has been updated to add the unscheduled PK sample collection correlated with the unscheduled ECG visit.

IRB/IEC/HA

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.

[redacted]

Amendment 1

Amendment rationale

The main purpose of this amendment is to refine the patient criteria for patients enrolled into the AUY922, BYL719, and INC280 arms, based on recent new data.

For AUY922 arm, the inclusion criteria is refined from EGFR mutation to only EGFR exon 20 insertion mutation based on the current ongoing trial CAUY922A2206 and CAUY922A2207 interim analysis results. According to preliminary clinical efficacy data in CAUY922A2206, the anti-tumor activity of AUY922 single agent has been observed primarily in the exon 20 insertion mutation population. Since the exon 20 insertion in EGFR is a known intrinsic/ primary resistance mechanism to EGFR tyrosine kinase inhibitors (TKIs), the inclusion criteria for prior treatment with TKIs is now removed. In addition, this patient population represents a high unmet medical need among NSCLC patients.

For BYL719 arm, the inclusion criteria is further clarified for PIK3CA gene amplification as copy number ≥4 which was not defined in the current protocol.

For INC280 arm, the inclusion criteria is restricted from cMET FISH (fluorescence in situ hybridization) gene copy number of ≥5 or IHC (immunohistochemistry) staining 2+ or 3+ ≥ 50% tumor cells to only IHC staining 3+ ≥50% tumor cells with exploration of c-MET mutation and amplification retrospectively. The preliminary data from the single agent INC280 study, CINC280X2102, suggested that efficacy is restricted to the patient population with EGFRwt and high MET status. As of 21 March 2014, 3 out of 6 patients had confirmed PR; all patients were EGFRwt and had high MET status by IHC or FISH (Bang Y-J et al 2014). Two of three patients had cMET mutations. The amended criteria is to keep consistency with the ongoing CINC280X2102 study.

For the pharmacokinetics (PK) section, the amendment is mainly to harmonize and clarify the procedures by reducing the PK samplings and optimizing the timing point without major changes, which will be in favor of patients and simplified the procedure in clinical site operation.

Additional modifications/ updates to the protocol include:

To exclude EGFR mutation patient with concurrent MET amplification/overexpression and/ or PIK3CA mutation/ amplification for AUY922 arm according to available data.

To add a note for INC280 tablets recommended dosing regimen information and dose reduction steps in study treatment section which was not defined in the current protocol.

To exclude the patient has history of interstitial lung disease or interstitial pneumonitis in LDK378 arm according to available safety information and to comply with health authority's request.

To update and clarify the fasting time for BYL719/INC280/LDK378 arms based on current available clinical pharmacological information.

[redacted]

To remove the fasting requirement for MEK162 arm based on the food effect studies, CMEK162A2103 and ARRAY studies, which suggested no need for specification of food intake for MEK162 administration.

To update and clarify the permitted and prohibited medication section and also align with currently available information for compounds in all arms.

To remove the C1D1 PK collection for AUY922/INC280/LDK378/MEK162 arms and modify several PK collection time points without major changes because full human PK profiles are available from previous studies and less/sparse sampling will serve the purpose of PK characterization [redacted] in this study.

To implement the safety data and efficacy data reviewing plan for AUY922, BYL719 and MEK162 as ongoing basis in safety monitoring and reporting section.

To update the parameters of statistical model based on available AUY922 efficacy data.

To update the criteria for interruption and re-initiation guideline for pulmonary toxicity of LDK378 arm according to available safety information.

Additional editorial changes have been made throughout the document in order to increase consistency and clarity.

Changes to the protocol

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

Section 1.2 has been updated with current clinical trial data in AUY922 arm and with new information of food effect study in MEK162 arm.

Section 2.1 has been updated with the rationale and relevant reference for selecting patient population of EGFR exon 20 insertion mutation in AUY922 arm.

Section 2.3 has been updated with current information of INC280 arm for tablet formulation.

Section 3 Table 3-1 has been updated to remove the PK parameter Racc as C1D1 PK will not be obtained.

Section 4 Figure 4-1 has been updated to align with the new molecular alteration criteria.

Section 5.2 inclusion criteria 7 for AUY922 arm has been modified and changed from EGFR gene mutation population to EGFR gene exon 20 insertion mutation.

Section 5.2 inclusion criteria 8 and 9 for AUY922 arm were removed. Since the EGFR exon 20 insertion mutation is one of the known intrinsic resistance mechanisms to EGFR tyrosine kinase inhibitors (TKIs), the required TKI as prior treatment is removed from inclusion criteria. Section 5.2 inclusion criteria 10 for BYL719 arm has been further clarified for the molecular amplification with PIK3CA gene copy number ≥ 4.

Section 5.2 inclusion criteria 11 for INC280 arm has been changed as IHC 3+ in $\geq$ 50% of tumor cells.

[redacted]

Section 5 inclusion criteria note was modified with removing "the patients who have EGFR mutation and concurrent with cMET amplification/ overexpression or PIK3CA mutation/ amplification".

Section 5 exclusion criteria 19 for AUY922 arm was removed to align with inclusion criteria 7, 8, and 9 changes in the protocol

Section 5 exclusion criteria 36 for LDK378 arm was added to exclude the patients with a history of interstitial lung disease or interstitial pneumonitis.

Section 6.1.1, Table 6-1 has been updated with the dosing regimen information for tablet formulation of INC280 arm, and the fasting time for BYL719/INC280/LDK378 arms was updated in section 6.1.1 to align with current information for these compounds. For MEK162 arm, the fasting requirement is removed based on current data of MEK162.

Section 6.2.1, Table 6-2 has been clarified for the dose reduction steps for INC280 arm.

Section 6.3.2 and 6.3.3 has been modified and updated for the permitted concomitant therapy requiring caution and prohibited concomitant therapy to align with available data of all arm compounds.

Section 6.5.2, Table 6-3 the available tablet strength of 50mg INC280 was added.

Section 7.1.1 was removed of the requirement of post-TKI treatment tumor sample collection to align with the inclusion criteria 7 changes.

Section 7.1.4.1 was clarified the definition of criteria for premature patient withdrawal and to align with the clinical database set up.

Section 7.2.2.6, Table 7-5 was clarified with the ECG collection time points.

Section 7.2.3.1, Tables 7-6 to 7-15 were modified to remove C1D1 PK collection in AUY922, INC280, LDK378, MEK162 arms and less/sparse PK sampling in all tables. These updates were for harmonization of the PK collection schedule in AUY922/INC280/LDK378/MEK162 arms without major changes substantially.

Section 7.2.3.2 was added with PK analysis of the major AUY922 metabolite BJP762.

[redacted]

Section 8.6 to indicate the safety and efficacy data review plan in the protocol. The monitoring of patient data will provide the basis to Novartis for next steps considering efficacy and safety data.

Section 10.4.2 to update the most current efficacy data for AUY922 arm and Table 10-1 with parameter of prior distributions and thresholds for posterior distribution of ORR.

Section 10.5.3, Table 10-2 several PK parameters were simplified.

Section 10.7 to indicate the safety and efficacy data review plan in the protocol and align with the Section 8.6.

Section 10.8, Table 10-3 and 10-4 to update clinically relevant efficacy category (Ri) and probability to align with the updated parameter in Section 10.4.2.

Section 13 to add three new publications as references.

[redacted]

Section 14, Table 14-9 to update the dose interruption and re-initiation guideline for pulmonary toxicity in LDK378 arm.

Section 14, Appendix 3, Appendix 4 and Appendix 5 were clarified and updated with permitted concomitant medication requiring caution, prohibited concomitant medication, and drugs with risk of TdP/QT prolongation, respectively.

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation. The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Protocol summary:

Protocol number	CINC280X2205
Title	A Phase II, open label, multiple arm study of single agent AUY922, BYL719, INC280, LDK378 and MEK162 in Chinese patients with advanced non-small cell lung cancer (NSCLC)
Brief title	n/a
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to evaluate the anti-tumor activity of single agent BYL719, INC280, LDK378 and MEK162 in advanced NSCLC patients carrying specific molecular alterations. There is a great unmet medical need in NSCLC patients with advanced or metastatic disease. Novel approaches using targeted therapeutic agents for these patient populations with molecular characterization could potentially identify subsets of advanced NSCLC patients who would benefit from targeted kinase inhibition. Study treatments, BYL719, INC280, LDK378 and MEK162, which target PIK3CA, c-MET, ALK/ROS1 and MEK respectively, have shown promising data in either preclinical or clinical lung cancer settings.
Primary Objective	To investigate the anti-tumor activity of single agent BYL719, INC280, LDK378 and MEK162
Secondary Objectives	**Objective 1**: To further assess the clinical activity of single agent BYL719, INC280, LDK378 and MEK162 **Objective 2**: To characterize the safety and tolerability of single agent BYL719, INC280, LDK378 and MEK162 **Objective 3**: To characterize the pharmacokinetic profiles of single agent BYL719, INC280, LDK378 and MEK162
Study design	This is a Phase II, multiple arm, open-label study of single agent BYL719, INC280, LDK378 and MEK162. This study will enroll 20-25 advanced NSCLC patients to each treatment arm according to their molecular alterations. Each treatment arm is independent from one another and will be analyzed separately.
Population	The study will enroll patients who have histologically or cytologically confirmed advanced (stage IIIB or stage IV) lung adenocarcinoma (all treatment arms) or lung squamous cell carcinomas (BYL719 arm only), who have failed prior treatment or patients who are deemed unsuitable for chemotherapy in the investigator's opinion.
Key Inclusion criteria	Patients eligible for inclusion in this study have to meet all of the following criteria: Written informed consent must be obtained prior to any screening procedures. 1. Patients must be 18 years or older and able to sign Informed Consent. 2. Histologically or cytologically confirmed advanced (stage IIIB or stage IV) lung adenocarcinoma. For BYL719 treatment arm, the histologically or cytologically confirmed advanced (stage IIIB or stage IV) lung adenocarcinoma or lung squamous cell carcinoma. 3. Patients who have failed at least one prior anticancer treatment regimen or patients who are deemed unsuitable for chemotherapy in the investigators opinion (including patients who refuse chemotherapy) Note: Chemotherapy administered as adjuvant treatment more than six months prior to study enrollment is not considered a prior line of therapy for purposes of this study. 4. Measurable disease according to RECIST v.1.1 (Irradiated lesions are not considered measurable unless they have clearly progressed since radiotherapy) 5. ECOG performance status ≤ 2 6. Patients must be suitable and willing to undergo mandatory biopsy according to treating institution's guidelines and requirements for such procedure if there is no archival biopsy available.

[redacted]

	In addition, patients eligible for each treatment arm must meet the criteria for the respective arm.
Key Exclusion criteria	Patients eligible for this study must not meet any of the following criteria: 1. Symptomatic CNS metastases which are neurologically unstable or requiring increasing doses of steroids within the 4 weeks prior to study entry to control their CNS disease 2. Radiation therapy within ≤ 4 weeks prior to study entry, with the exception of limited field palliative radiotherapy for bone pain relief. Any persistent side effect of prior radiotherapy must be resolved to ≤ CTCAE grade 1 prior to the first dose of study treatment. 3. Any other malignancies within the last 5 years before study entry, except for adequately treated carcinoma in situ of cervix, basal or squamous cell skin cancer 4. Major surgery ≤ 2 weeks prior to study entry or who have not recovered from side effects of such therapy 5. Patients must not have received previous anti-cancer therapies ≤ 4 weeks prior to the first dose of study treatment except: • ≤6 weeks for nitrosoureas and mitomycin • ≤5 half-life of continuous or intermittent small molecule therapeutics or investigational agents (or ≤ 4 weeks when half-life is unknown), and have not recovered from the side effects of such treatment (CTCAE grade ≤ 1) prior to the first dose of study treatment, except for alopecia. 6. Any of the following laboratory values at baseline: • Hemoglobin < 9 g/dL (SI Units: 90 g/L) • Platelet count <100 x 109/L • Absolute neutrophil count (ANC) < 1.5 x 109/L • Serum albumin < 2.5 g/dl • Total bilirubin > 1.5 x upper limit of normal (ULN) • AST/SGOT or ALT/SGPT > 3 x upper limit of normal (ULN) or > 5.0 x ULN if liver metastases are present • Serum creatinine > 1.5 x ULN or calculated creatinine clearance by Cockcroft-Gault formula < 50 mL/min • Serum calcium, potassium and magnesium<LLN Patients eligible for each treatment arm must not meet criteria for respective arm.
Investigational and reference therapy	BYL719, INC280, LDK378, MEK162
Efficacy assessments	• ORR • OS • PFS • DCR • Duration of overall response per RECIST v1.1
Safety assessments	• Frequency/severity of AEs and SAEs • Laboratory abnormalities • Dose interruptions and dose reductions
Other assessments	• PK parameters [redacted]
Data analysis	A Bayesian approach will be used to estimate ORR and to provide inferential statements for each treatment arm. Bayesian decision rules will be used to define clinically and statically significant anti-tumor activity. At the time of analysis of each treatment arm the respective prior distribution will be updated with all available data from patients in the respective FAS. All data will be listed and summarized when appropriate.
Key words	non-small cell lung cancer, NSCLC, stage IIIB or stage IV

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Lung cancer is a common type of cancer that affects men and women around the globe. In 2012, there were an estimated 160,000 deaths in the US (Siegel et al 2012) and 262,000 in the European Union (Malvezzi et al 2012). In China in 2005, there were 497,908 new cases and 428,936 deaths, the highest for any malignant tumor (Wu 2007). Non-small cell lung cancer (NSCLC) is the most common type of lung cancer that accounts for roughly 85% of all cases with approximately 70% of these patients presenting with advanced disease (Stage IIIB or Stage IV) at the time of diagnosis (Alvarez 2007, Ruiz 2008).

Platinum-based chemotherapy is the standard first-line treatment for patients with advanced NSCLC (Sandler et al 2006). These platinum based two drug cytotoxic combinations (doublets) include cisplatin/paclitaxel, cisplatin/vinorelbine, cisplatin/gemcitabine, cisplatin/docetaxel, and carboplatin/paclitaxel. Pemetrexed plus platinum chemotherapy in the first-line setting lead to a significant survival advantage for advanced non-squamous NSCLC patients compared with other platinum-based regimens (Richey et al 2012). Adding anti-vascular endothelial growth factor receptor (VEGFR) monoclonal antibody Bevacizumab(Avastin®) to carboplatin/paclitaxel has been shown to improve progression free survival (PFS) and overall survival (OS) by two months (Sandler et al 2006). In a multi-center randomized phase III study Sandler and colleagues showed that the PFS and OS for patients receiving Bevacizumab plus carboplatin and paclitaxel was 6.2 months and OS 12.3 months, respectively compared to 4.5 months and 10.3 months for patients receiving carboplatin and paclitaxel only.

During the last few years, improved knowledge of NSCLC biology led to the identification of molecular events crucial for malignant transformation and cancer cell survival. These aberrant molecular events are critical oncogenic drivers and, therefore, represent potential therapeutic targets (Gettinger et al 2011). As a result, new targeted treatment options are evolving. Erlotinib and gefitinib, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), have been approved for the treatment of NSCLC patients with tumors harboring activating mutations in the EGFR gene (Gettinger et al 2011). Recently completed phase III studies have confirmed that patients with EGFR mutations should receive EGFR TKI gefitinib or erlotinib as first line treatment (Mok 2009, Maemondo 2010, Zhou 2011, Rosell 2012). These studies showed a PFS of 9 to 13 months in first-line patients with advanced disease and EGFR mutations when treated with EGFR TKI. The PFS for patients in these studies randomized to receive chemotherapy was 4-6 months. The overall response rate (ORR) in patients receiving EGFR TKI ranged from 71% to 82%. The frequency of EGFR mutations is more common in patients of Asian descent (around 30-40%) in comparison to Caucasian patients (around 10-15%) (Sequist and Lynch 2008), however there is no indication that patients respond differently to EGFR TKI based on ethnicity.

[redacted]

The discovery of anaplastic lymphoma kinase (ALK) rearrangement in NSCLC in 2007 (Soda et al 2007) represents another important milestone in the era of molecular targeted therapy in NSCLC. Most recently remarkable responses, similar to EGFR TKIs, have been observed with crizotinib, a dual ALK and c-MET inhibitor in patients that harbor the echinoderm microtubule associated protein like 4-anaplastic lymphoma kinase (EML4-ALK) transfusion gene. Crizotinib was associated with clinically meaningful response rates of 50% and 61% in two single-arm trials in 255 patients with locally advanced or metastatic ALK-positive NSCLC (Ou et al 2011). Based on these data, crizotinib received approval for the treatment of ALK-rearranged NSCLC. As of May 2012, crizotinib is approved in several countries including but not limited to US, Japan and Switzerland. In the completed phase I first in human study, a potent new inhibitor, LDK378 showed 75% ORR in advanced ALK activated NSCLC patients, and exhibited potent antitumor activity in both Crizotinib naïve and treated populations (Shaw et al 2013).

However, despite the dramatic responses to such inhibitors, most patients ultimately have a relapse. Moreover, in addition to EGFR and ALK, other molecular alterations such as amplifications of c-MET, mutations of PIK3CA, the gene encoding for phosphatidylinositol-3-kinase (PI3K) alpha, and mutations of KRAS have been found in NSCLC. The management of advanced NSCLC has evolved into subtyping each tumor based on driver oncogenic events involving targetable kinase. Novel approaches using targeted therapeutic agents for these patient populations with molecular characterization may identify subsets of advanced NSCLC patients who would benefit from targeted kinase inhibition.

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

1.2.1 Overview of BYL719

BYL719 is an oral α-specific class I PI3K inhibitor. It potently inhibits p110α (both wild type and mutations) but less strongly the β, δ, and γ isoforms of PI3K. BYL719 is also highly selective for PI3K alpha and does not act against Vps34 and mammalian target of rapamycin (mTOR). For further details, refer to the current version of the IB [BYL719 Investigator's Brochure].

1.2.1.1 Non-clinical experience

1.2.1.1.1 Non-clinical pharmacodynamics

The potency and selectivity of BYL719 is confirmed at the cellular level in mechanistic and relevant tumor cell lines. BYL719 potently inhibits p110α cellular activity (Concentration producing 50% inhibition (IC_{50})=74 nM) and shows significant selectivity against the p110β and p110δ isoforms (above 15-fold). Its biological activity correlates with inhibition of various PI3K/Akt downstream signaling pathway components. *In vivo*, BYL719 shows dose and time-dependent inhibition of the PI3K/Akt pathway in relevant tumor xenograft models (p110α-mechanistic model and p110α-mutant xenograft models) in nude mice and rats.

[redacted]

1.2.1.1.2 Non-clinical pharmacokinetics and metabolism

In all species, the compound was rapidly absorbed with Tmax occurring between 0.5-2.0 h. Oral bioavailability was moderate in rats after suspension dosing and complete in mice and dogs after a single dose of BYL719 as a solution. In rat ADME study, the drug related radioactivity was rapidly distributed to almost all tissues, but not the brain. The highest tissue exposure after dosing was found in the liver, bile, harderian gland, hair follicles, tactile hair, and in the preputial gland. Drug related radioactivity was also found in melanin containing tissues such as the choroid and ciliary body of the eye but declined with time.

BYL719 showed low clearance compared to the hepatic blood flow in each species tested. The main biotransformation pathway that was observed consistently across species was hydrolysis of the proline amide moiety, which is the only metabolite that was detected in human and dog hepatocyte incubations.

After the oral administration of [^{14}C]BYL719 in rats, the drug-derived radioactivity underwent mainly biliary excretion with almost complete recovery at 7 days post-dose. Renal excretion of radioactivity was relatively low (11-15 %).

BYL719 showed reversible weak inhibition of CYP2C8, CYP2C9. The compound is also a strong time-dependent inhibitor of CYP3A4 *in vitro*. BYL719 is a substrate of BCRP and multi-drug resistence-1 (MDR-1) (low affinity) and showed very weak inhibition of MDR-1. No inhibition could be observed on BCRP- or MRP2-mediated transport. BYL719 is not considered a human pregnane X receptor (PXR) or aromatic hydrocarbon receptor (AhR) activator.

For more information, please refer to the current [BYL719 Investigator's Brochure].

1.2.1.1.3 Non-clinical safety and toxicology

Routine safety pharmacology and toxicology studies were conducted in rats and dogs. In addition, for exploratory studies, such as insulin/glucose tolerance tests, mice were also used. The majority of the observed toxicological effects of BYL719 were related to the pharmacological activity of BYL719 as a p110α specific inhibitor of PI3K pathway, such as an influence on insulin (and potentially glucose) homeostasis and the risk of increased blood pressure. The pharmacologically relevant toxicity was mainly observed at dosages close to or at MTD affecting the bone marrow and lymphoid tissue, pancreas, and some reproductive organs of both genders being the main target organs of the toxic effects. In dogs, epithelial effects were seen in the cornea; however, these effects were not dose-dependent. No ophthalmologic abnormalities, associated with BYL719 treatment, were observed in rats or in dogs. Clinical chemistry and histopathological changes in the pancreatic islets indicated an altered glucose metabolism, correlating with signs of insulin insensitivity as was also seen in the mouse insulin/glucose challenge test. All toxic events were reversible or showed a tendency to reversibility.

BYL719 did not show signs of QT prolongation, neurological or pulmonary toxicity; it did not show a phototoxic potential and was not genotoxic *in vitro*.

For more information, please refer to the current [BYL719 Investigator's Brochure].

[redacted]

1.2.1.2 Clinical experience

1.2.1.2.1 Clinical studies

As of the cut-off date of 20-May-2014, 543 patients have received BYL719 as a single agent or in combination with another treatment.

CBYL719X2101

BYL719 is being tested in a First-in-Human (FIH) Phase I dose escalation study [CBYL719X2101] in patients with advanced solid tumors carrying a mutation of the PIK3CA gene. Enrollment of the dose escalation phase of this study is completed. Dose levels from 30 mg qd to 450 mg qd have been tested. The single agent MTD was declared at 400 mg qd. A safety expansion cohort is currently ongoing at a dose of 400 mg qd. In parallel, a twice daily (bid) schedule is being investigated.

As of 15-Feb-2013, a total of 102 patients with advanced cancer have received at least one dose of BYL719 and have been evaluated for safety in study [CBYL719X2101]. A total 13 out of 102 evaluable patients experienced dose limiting toxicity, 8 after the qd and 5 after the bid regimen. Dose limiting toxicities (DLTs) included grade 3 or 4 hyperglycemia (9 patients), grade 3 nausea (3 patients), grade 3 vomiting (1 patient), grade 3 diarrhea (1 patient) and grade 3 hyperphosphatemia (1 patient).

Overall, 101 (99%) patients experienced AEs which were suspected to be related to BYL719. The most frequently reported treatment-related AEs, regardless of CTCAE grade and dose were hyperglycemia (49%), nausea (43%), decreased appetite (37%), diarrhea (35%), rash/hypersensitivity (34%), and asthenia/fatigue (34%). The most common treatment-related grade 3 or 4 AEs were hyperglycemia (25%), and rash (8%).

Partial tumor responses with single agent BYL719 were observed in 9 patients treated at daily doses $\geq$ 270 mg (4 confirmed, 5 unconfirmed). Median progression-free survival was 15.7 weeks (Gonzalez-Angulo et al 2013).

1.2.1.2.2 Clinical Pharmacokinetics

After oral administration, BYL719 is well absorbed. Median Tmax at the MTD dose (400 mg once daily) was 2 hours. Plasma concentrations of BYL719 generally declined in a mono-exponential manner. T1/2 after a 400 mg oral dose was 7 to 8 hours and generally appeared to be independent of dose and time. After once daily dosing, the drug was minimally accumulated. The median accumulation ratio (Racc) of BYL719 across all dose levels was calculated to be about 1.3, which is in agreement with the short half-life of BYL719.Steady-state BYL719 plasma levels can be expected to be reached at 2 to 3 days following onset of therapy in most patients.

A phase I study is also ongoing in Japanese solid tumor patients [BYL719X1101]. Preliminary PK analysis showed BYL719 exposure in Japanese patients was comparable to Western patients [BYL719X2101] at the tested dose levels of 90 mg, 180 mg, 270 mg, 350 mg and 400 mg qd.

For further details, refer to the current [BYL719 Investigator's Brochure].

[redacted]

1.2.2 Overview of INC280

INC280 is a small ATP competitive, reversible inhibitor of the c-MET receptor tyrosine kinase. The proto-oncogene c-MET encodes the high-affinity receptor for hepatocyte growth factor (HGF), which is the only known ligand for this receptor.

1.2.2.1 Non-clinical experience

1.2.2.1.1 Non-clinical pharmacodynamics

INC280 possesses potent inhibitory activity against the c-MET kinase *in vitro*. Potent activity (IC50 values: 0.2 - 2 nM) has been demonstrated in cell-based biochemical and functional assays that measure c-MET-mediated signal transduction, as well as c-MET-dependent cell proliferation, survival, and migration. In c-MET/HGF-driven xenograft mouse tumor models, oral dosing of INC280 demonstrated significant *in vivo* activity in blocking both c-MET phosphorylation and tumor growth.

1.2.2.1.2 Non-clinical pharmacokinetics and metabolism

After a single oral dose, INC280 was absorbed rapidly in rats and dogs (T_{max} < 1h). T_{max} in monkeys was longer and ranged from 2.7 to 7 h. The absolute oral bioavailability (F%) was low in dogs (28%), moderate in the rat (66%) and low to moderate in the monkey (24% to 44%).

INC280 is widely and rapidly distributed into all tissues. INC280 penetrated the normal blood-brain barrier with a brain tissue to plasma ratio of 0.1.

INC280 is predominantly metabolized by cytochromes P450 in human hepatic microsomes. CYP3A4 is the major P450 enzyme to metabolize INC280. *In vitro* CYP3A4 is the major liver CYP enzymes involved in oxidative metabolism of INC280 in human liver microsome (HLM) (~f_m 99.6%) with very low contribution from other enzymes (~0.4%).

Following *i.v.* administration of INC280 in rats and monkeys, less than 1% of total dose was excreted as parent drug in urine, suggesting that the renal pathway is not a significant route of elimination. In the rats ADME study, total radioactivity was primarily eliminated *via* biliary secretion.

INC280 showed inhibitory potency for CYP1A2, CYP2C8, CYP2C9, CYP2C19 and CYP3A4/5. Time-dependent (irreversible) inhibition by INC280 was observed for CYP1A2 and CYP3A4/5-mediated midazolam 1'-hydroxylation. Potential DDI due to inhibition of CYP1A2, 2C8, 2C9, 2C19 and 3A4/5 is possible at clinically relevant doses.

INC280 inhibits P-gp, MXR/BCRP, OATP1B1 and OATP1B3. INC280 may increase uptake of co-medications transported by ABC and SLC-transporters in the gastro-intestinal tract or decrease elimination of some drugs into the bile and/or urine.

For more information, please refer to the current [INC280 Investigator's Brochure].

[redacted]

1.2.2.1.3 Non-clinical safety and toxicology

Safety pharmacology studies with INC280 indicated that INC280 had no significant effects on central nervous system (CNS) and respiratory functions in rats, and no effects on cardiovascular function in monkeys.

The toxicology profiles of INC280 were characterized in single and repeat-dose studies in mouse, rat and Cynomolgus monkey. The repeat-dose studies revealed the following target organs or systems: kidneys, pancreas, CNS, and potentially the liver.

Detailed information is available in the latest version of the [INC280 Investigator's Brochure].

1.2.2.2 Clinical experience

As of 28-Sep-2014 (cut-off date of the INC280 Investigator's Brochure, edition 5.2), a total of 203 cancer patients have been treated in five clinical trials with INC280 as a single agent and a total of 103 cancer patients have been treated with INC280 in 5 different combination therapies with anti-cancer agents at various doses and in two formulations, capsule and tablet.

Single agent INC280 is generally tolerable (regardless of the dose), with the majority of the reported adverse events (AEs) being of mild or moderate severity (CTCAE grade 1 or grade 2). CTCAE grade 3 or grade 4 AEs suspected to be related to INC280 in single agent studies (regardless of the dose) included hypophosphatemia, peripheral edema, fatigue, increase in AST, ALT, GGT, amylase, blood bilirubin and lipase, vomiting, colitis ulcerative, lung infection, nausea, anemia, neutropenia, hypophagia, decreased appetite, hypoalbuminemia, maculo-papular rash, dehydration and lymphocyte decreased.

In the combination studies, the most frequent AEs suspected to be related to INC280 (regardless of the dose) were nausea and vomiting. CTCAE grade 3 and grade 4 AEs suspected to be related to INC280 (regardless of the dose) included most frequently: asymptomatic increase in amylase, increase in lipase, AST and ALT, nausea and vomiting. One SAE with fatal outcome, deteriorated cough and dyspnea, has been reported with a suspected causal relationship to INC280.

After the cut-off date of 28-Sep-2014, a female patient experienced a serious, unexpected, possibly related adverse event of abnormal liver function tests during treatment with a combination of INC280 and gefitinib while enrolled in the [CINC280X2202] study. Patient experienced concurrent elevations of total bilirubin >2×ULN and ALT/AST >3×ULN with alkaline phosphatase (ALP) <2×ULN. The patient permanently discontinued study drugs. The liver function alterations were reversible and improved after the discontinuation of both drugs. At the time of the follow-up Investigator Notification (IN), the outcome of the adverse event of abnormal liver function tests was reported as completely recovered. This patient met the criteria of Hy's Law and the hepatotoxicity could not be attributed solely to either drug alone or to the combination.

The recommended phase II dose (RP2D) of INC280 monotherapy and in combination therapy with gefitinib is 400mg BID in tablet formulation. The maximum tolerated dose (MTD) for single agent INC280 has not been defined.

[redacted]

1.2.2.2.1 Clinical studies

CINC280X2101

As of 28-Sep-2012, study INCB28060-101 (Novartis study code [CINC280X2101]), conducted by Incyte Corporation is a single agent Phase I FIH study designed to characterize safety, tolerability, pharmacokinetics, pharmacodynamics, and anti-tumor activity. A total of 45 patients have been treated on eleven dose cohorts. The highest doses tested were 300 mg bid and 400 mg qd. INC280 was well tolerated and the MTD has not been established.

CINC280X2102

[CINC280X2102] study is a Phase I dose escalation study in solid tumor with c-MET dysregulation conducted by Novartis.

As of June 26, 2013 INC280 600mg bid is the highest safe dose being evaluated in this study. 25 patients have been enrolled to six dose levels (100mg bid (4 patients), 200mg bid (5 patients), 250mg bid (4 patients), 350mg bid (3 patients), 450mg bid (5 patients), 600 mg bid (4 patients). In total three DLTs have been reported in this study, one CTCAE grade 3 total bilirubin increase at 250mg bid dose level, and two CTCAE grade 3 fatigue, one at 200mg bid and one at 450mg bid dose level.

In the highest dose level (600 mg bid) there were no DLTs reported. In addition, as of June 26, 2013 no grade 3 or 4 suspected AEs have been reported for this dose level. Five SAEs in one patient were reported for this cohort: hypercalcaemia (before dosing), fever (before dosing), influenza (before dosing), creatinine increase and hepatorenal syndrome. However, none of the SAEs were related to the study treatment.

Therefore, with consideration of clinical safety, PK data (Section 1.2.2.2.2), as well as preclinical PK/PD data, 600mg bid will selected for this phase II study.

The preliminary data from the single agent INC280 study, CINC280X2102, suggested that efficacy is restricted to the patient population with EGFRwt and high MET status. As of 21 March 2014, 3 out of 6 patients had confirmed PR; all patients were EGFRwt and had high MET status by IHC or FISH (Bang Y-J et al 2014). Two of three patients had cMET mutations. Therefore, this study will select the high MET status as inclusion criteria.

CINC280X2202

[CINC280X2202] is a Phase Ib/II study in combination with gefitinib in adult patients with EGFR mutated, c-MET-positive NSCLC who have progressed after EGFR inhibitor treatment.As of June 26, 2013, twenty six patients were treated in five dose cohorts (100mg qd, 200mg qd, 400mg qd, 800mg qd, 200mg bid) of INC280. No DLT has been observed. Two patients have reported confirmed PRs, one in 200 mg qd cohort and the other in 400 mg qd cohort.

1.2.2.2.2 Clinical Pharmacokinetics

By the cut-off date of June 26, 2013 twenty one patients from [CINC280X2102] study have evaluable PK data on C1D1 and C1D15 from 100 mg bid to 600 mg bid. Three patients at

[redacted]

600mg bid have evaluable PK data. INC280 exposure is increasing by dose with moderate to high inter-subject variability. After oral administration, absorption of INC280 is fast. Median Tmax ranges from 1 to 4 hours. Observed terminal half-life is averaged of 2.9 to 7.78 hours. The mean steady state AUC0-12h at 350 mg bid, 450 mg bid and 600 mg bid are 20116, 17077 and 37142 ng*h/mL, respectively. Steady state Ctrough concentration at 600 mg bid is about 35 fold of in vivo IC90 for p-c-MET inhibition measured from preclinical S114 xenograft model.

INC280 exhibited a pH-dependent solubility profile with a low solubility at high pH level. A study to evaluate the effect of long acting proton pump inhibitor on the PK of a single dose INC280 tablet (600 mg) was completed in healthy volunteers [CINC280A2101]. Daily treatment of 20 mg rabeprazole for 4 days resulted in a modest reduction in the extent of INC280 absorption with a 25.2% decrease in AUCinf and a 37.5% decrease in Cmax. Considering the 42% and 65% variability in AUC observed in patient single agent studies [CINC280X2102] and [CINC280X1101], a decrease of 25% in AUC when administered with PPI is considered not significant. The impact on the 12 hour post-dose concentration of INC280 (defined as trough concentration for BID dosing) was small with ~7% reduction after rabeprazole treatment. Preliminary data in NSCLC patients [CINC280X2202] suggested that anti-tumor activity is correlated more with Ctrough than AUC and Cmax.

For further details, refer to the current [INC280 Investigator's Brochure].

1.2.3 Overview of LDK378

LDK378 (ceritinib) is an orally available ALK inhibitor. LDK378 is an approximately 20-fold more potent ALK inhibitor than crizotinib, it is more selective for ALK and does not inhibit MET.

In addition, LDK378 (ceritinib) shows potent antitumor activity in crizotinib-resistant animal models (as described below), and the efficacy seen in the ongoing Phase I clinical trial in patients (with and without previous crizotinib therapy) led to the approval of LDK378 (ceritinib) by the FDA under the trade name ZYKADIA™ on 29-Apr-2014 for the following indication:

- ZYKADIA™ is indicated for the treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib.

This indication is approved under accelerated approval based on tumor response rate and duration of response. An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Furthermore, the European Commission approved ZYKADIA on 06-May-2015 for the following indications:

- ZYKADIA is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib.

[redacted]

1.2.3.1 Non-clinical experience

1.2.3.1.1 Non-clinical pharmacodynamics

LDK378 inhibits autophosphorylation of ALK, ALK-mediated phosphorylation of downstream signaling proteins, and proliferation of ALK-dependent cancer cells both *in vitro* and *in vivo*. LDK378 is approximately 20-fold more potent than crizotinib in enzymatic inhibition assays of the ALK kinase activity (IC50 of 0.15 nM for LDK378 and 3 nM for crizotinib).

1.2.3.1.2 Non-clinical pharmacokinetics and metabolism

LDK378 showed delayed absorption with T_{max} of 7 to 13 hours across animal species. Good oral bioavailability (48-58%) was observed in the mouse, rat and monkey when administered as a solution or suspension under fasted condition.

In rat ADME study, the tissue distribution of the radioactivity was extensive where most of the tissue/matrices had higher exposure than that of blood, except eye, brain and spinal cord. LDK378 derived radioactivity had low distribution into the brain with an AUC_{last} brain/blood ratio of 0.11.

CYP3A4/5 is the major hepatic enzyme metabolizing LDK378 in a human *in vitro* system.

In rats, nearly 100% of LDK378-related radioactivity was eliminated *via* the feces, and renal excretion was minor, accounting for <1% of the dose.

The compound is a time-dependent CYP3A4/5 inhibitor, and a potent reversible inhibitor of CYP2A6, 2B6, 2C8, 2C9 and 3A4/5. These data suggest a high potential of drug-drug interaction between LDK378 and compounds metabolized by these CYP isoforms if sufficiently high concentrations of LDK378 are achieved. LDK378 is likely a P-gp, but not BCRP or MRP2 substrate. It does not inhibit P-gp, BCRP or MRP2 up to 1.5 µM *in vitro*.

For more information, please refer to the current [LDK378 Investigator's Brochure].

1.2.3.1.3 Non-clinical safety and toxicology

LDK378 was evaluated for safety in 2- and 4-week studies in rats and monkeys. The toxicities induced by LDK378 were systemic inflammation, gastrointestinal, liver (bile duct) and pancreas.

Detailed information is available in the latest version of the [LDK378 Investigator's Brochure].

1.2.3.2 Clinical experience

1.2.3.2.1 Clinical studies

CLDK378X2101

A FIH dose escalation phase I study of LDK378, [CLDK378X2101], is ongoing in patients with malignancies characterized by genetic alterations of ALK. As of 31-Oct-2013, 304 patients have been treated with LDK378 on the first-in-human study [CLDK378X2101].

[redacted]

Patients have been treated on a once daily schedule at the following dose levels: 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg and 750 mg. The MTD in adult patients is 750 mg qd, dosed once daily.

Gastrointestinal toxicities including diarrhea, nausea, and vomiting were the most common adverse events, occurring in 72.7%, 72.7% and 55.5% of patients, respectively. Other adverse events occurring in more than 20% of patients included fatigue (30.9%), abdominal pain (27.3%), decreased appetite (25.9%), ALT increase (25.0%) and constipation (21.4%). The incidence of grade 3-4 AEs, regardless of study drug relationship was <10% for all AEs except ALT increase (26.7%). The incidence of grade 3-4 AEs, regardless of study drug relationship was <5% for all AEs except AST increase (8.2%), diarrhea (5.9%), hyperglycemia (5.5%), lipase increase (5.1%), and blood alkaline phosphatase (ALP) increase (5.1%). Preliminary ECG data from 220 patients treated at doses of 50-750 mg suggest that LDK378 may have an effect on the QT interval.

One patient (700 mg QD dose; <1%) had a QTc > 500 msec and 2 (1.6%) patients (1 at 700 mg QD dose, 1 at 750 mg QD dose) had an increase of > 60 msec from baseline QTc. Pneumonitis or interstitial lung disease has been reported as an SAE in four patients.

Adverse events of special interest to be monitored for LDK378 (ceritinib) have also been identified and include: hepatotoxicity, interstitial lung disease/pneumonitis, QT interval prolongation, bradycardia, hyperglycemia, gastrointestinal toxicity (nausea, vomiting and diarrhea) and pancreatitis (including lipase and amylase elevations). For additional details, refer to the current [LDK378 Investigator's Brochure].

Among 114 response-evaluable patients with at least 18 weeks of follow-up prior to 28 Feb, 2013, or who discontinued study earlier, and were treated with LDK378 doses of 400 mg qd or higher, 66 (58%) patients have responded (Shaw et al 2013). In addition, the response rate to LDK378 is similar regardless of prior ALK inhibitor therapy. In patients with NSCLC treated at ≥400 mg qd, who had previously received crizotinib, the response rate was 57%, and in those who had not previously received crizotinib it was 60%. The median duration of response in patients who responded and were treated at ≥400 mg qd was 8.2 months (95% CI: 6.9, not estimable), and 71% had a duration of response of 6 months or longer.

1.2.3.2.2 Clinical Pharmacokinetics

Based on preliminary clinical pharmacokinetic (PK) data, the apparent $T_{1/2}$ of LDK378 is approximately 31-39 hours across the dose range of 400-750 mg. Following oral administration, the median time to maximal concentration is approximately 6 hours. With multiple daily dosing, the accumulation ratio (Racc) ranged from 4-7 fold. Evaluation of trough concentrations following repeated daily administration suggested that the steady-state of LDK378 was achieved by approximately Cycle 1 Day 15 and remained relatively stable after cycle 1. The PK profile of LDK378 supports once daily dosing.

Preliminary PK analysis from [CLDK378X2101] and [CLDK378X1101] reveals similar PK profile among Caucasian and Japanese from 300 to 750 mg dose level.

For further details, refer to the current [LDK378 Investigator's Brochure].

[redacted]

1.2.4 Overview of MEK162

MEK162, previously named ARRY 438162, is a potent and selective allosteric, ATP-uncompetitive inhibitor of MEK. For further details, refer to the current version of the IB [MEK162 Investigator's Brochure].

1.2.4.1 Non-clinical experience

1.2.4.1.1 Non-clinical pharmacodynamics

The biological activity of MEK162 has been evaluated in vitro (both enzymatic and cell culture assays) and in vivo in mouse xenograft studies. MEK162 potently inhibits MEK in both biochemical assays using purified protein, and in cells. MEK162 has demonstrated robust, but selective, growth inhibitory activity in a wide variety of cancer cell lines. In a collection of ~500 genetically annotated cell lines, MEK162 showed anti-proliferative activity preferentially in cells harboring activating mutations of the MAP kinase pathway (e.g. BRAF, NRAS and KRAS), and in particular, activating mutations in BRAF and NRAS. In vivo, MEK162 has demonstrated dose dependent tumor growth inhibition in various subcutaneous tumor transplants harboring BRAFV600E mutations (HT29, COLO205, A-375) as well as activating mutations in both NRAS (Hs. 944T) and KRAS (MiaPaCa2, A549, LoVo, Calu6). These data suggest that MEK162 may provide a potential therapeutic benefit in cancer indications harboring these mutations.

1.2.4.1.2 Non-clinical pharmacokinetics and metabolism

In the rat and monkey ADME study, after oral dosing of MEK162, the average absorption in both species was moderate (49%). The rate of absorption was fast (T_{max} ranged from 0.33 - 0.67h).

In rat ADME study, drug-derived radioactivity was absorbed and widely distributed to most tissues. The highest concentrations were located in the excreta (over a 24-hour time period for both strains) and included the gastrointestinal contents, bile and urine. There was no evidence of meaningful CNS penetration.

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%). 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). *In vitro*, the relative contributions of the glucuronidation, hydrolysis, or the oxidative pathway (AR00426032), to overall MEK162 metabolism in human hepatocytes were 45.1%, 5.1% and 2.4%, respectively. UGT1A1 was shown to be the major contributor (90%) to the formation of the direct glucuronide in human liver microsomes (HLM). UGT1A3 and UGT1A9 contributed 3% and 7% respectively to the glucuronidation activity.

MEK162 potently inhibits CYP2B6 and weakly inhibits CYP1A2 and 2C9. It is not a time dependent inhibitor of CYP1A2, CYP2C9, CYP2D6 and CYP3A. *In vitro* evidence also suggests that MEK162 induces CYP3A.

For more information, please refer to the current [MEK162 Investigator's Brochure].

[redacted]

1.2.4.1.3 Non-clinical safety and toxicology

The toxicological evaluations of MEK162 include single dose, and 28-day and 6-month repeat-dose studies in Sprague Dawley rats and 28-day and 9-month repeat-dose studies in cynomolgus monkeys. In all of the good laboratory principle (GLP) toxicology studies conducted, there was no significant effect of MEK162 on vital signs, coagulation parameters, complement, organ weights or urinalysis parameters with doses up to 100 mg/kg in rats and 10 mg/kg in monkeys.

Safety pharmacology studies were conducted to assess the effects of MEK162 on key organ systems (cardiovascular, respiratory, neurobehavioral, renal and gastrointestinal function). Rats received single oral doses of 10, 30 or 100 mg/kg and monkeys were given single oral doses of 1, 3 and 10 mg/kg. There were no significant in vivo safety findings at doses up to 100 mg/kg in rats and 10 mg/kg in monkeys in any of these studies. In the in vitro hERG channel assay, MEK162 was evaluated at concentrations up to 30 µM and demonstrated 30% inhibition at 30 µM (again, in vivo cardiovascular telemetry study showed no effects).

Detailed information is available in the latest version of the [MEK162 Investigator's Brochure].

1.2.4.2 Clinical experience

1.2.4.2.1 Clinical studies

As of 07-January-2015, a total of 2430 healthy subjects and patients have been enrolled in MEK162 studies and 1945 of whom have received at least one dose of MEK162, either as a single agent or in combination and have been evaluated for safety, including 204 healthy subjects, 6 liver dysfunction patients, 164 patients with rheumatoid arthritis and 1571 patients with advanced cancer. For further details, refer to the current version of the IB [MEK162 Investigator's Brochure].

ARRAY-162-111

The ongoing clinical study ARRAY-162-111 is an open-label dose-escalation study in patients with advanced solid tumors with expansion cohorts in patients with biliary cancer or KRAS- or BRAF-mutant metastatic colorectal cancer. As of 07-January-2013, enrollment is closed and a total of 93 patients have received at least 1 dose of MEK162. Four dose levels were evaluated: 30 mg bid, 45 mg bid, 60 mg bid and 80 mg bid. Two of 4 patients receiving 80 mg bid experienced DLTs (grade 3 chorioretinopathy and grade 3 dermatitis acneiform despite maximal treatment measures), thus the 80 mg bid dose was declared non tolerable. Seven patients were enrolled at 60 mg bid and no DLTs were observed; therefore, 60 mg bid was declared the MTD. Additional DLTs observed in the expansion cohorts have included grade 3 pneumonia and grade 3 blood creatine kinase (CK) increased (one patient each at the 45 mg bid dose level) and grade 3 mucosal inflammation and grade 3 generalized edema (one patient each at the 60 mg bid dose level). The recommended dose for the planned Phase III studies is 45 mg bid.

[redacted]

Fifteen out of 93 patients (16%) experienced at least one grade 3 or 4 AE suspected to be treatment related. The most common treatment-related grade 3 or 4 AEs were blood CK increased, rash, dermatitis acneiform, hypokalemia and generalized edema. Most of the CK elevations were asymptomatic and reversible.

Retinal/visual events (combined term of retinal and visual events of chorioretinopathy, vision blurred, photopsia, retinopathy, retinal detachment, visual impairment, macular edema, chorioretinal disorder, maculopathy, metamorphopsia, photophobia, retinal ischemia, retinal telangiectasia, venous stasis retinopathy and xanthopsia) were reported in 27/93 (29%) of patients, all of which were considered treatment-related events. In all but one patient (grade 3 at 80 mg bid) these events were grade 1 (14%) or grade 2 (14%) in severity. To date, these retinal events have been reversible in all patients upon discontinuation or dose reduction of MEK162.

Cardiac events (combined term of cardiac events of syncope, ejection fraction decreased and cardiomyopathy) were reported in 6/93 (6%) of patients, of those 1/93 (1%) were considered treatment related.

As of 07-January-2013, among 93 patients treated, stable disease was observed in 33 (35%), with a median duration of 3.9 months.

CMEK162X2201

[CMEK162X2201] is a phase II study assessing the safety and efficacy of MEK162 in patients with locally advanced unresectable and metastatic BRAF and NRAS mutated melanoma.

As of 07-January-2013, a total of 106 patients have received at least 1 dose of MEK162. Forty six out of the total 106 enrolled patients (43%) experienced at least one grade 3 or 4 AE suspected to be treatment-related. The most common treatment-related grade 3 or 4 AEs were CK increased (20/106), dermatitis acneiform (4/106) and diarrhea (3/106). The majority of the CK elevations were asymptomatic, 13/38 patients with CK elevations also experienced myalgia, muscular weakness or musculoskeletal pain which was judged to be related to MEK162. Central serous retinopathy like events were reported by 40/106 (38%) patients regardless of relationship to MEK162 including grade 3 or 4 events in 3/106 (3%) of patients. These events included retinopathy (13/106), blurred vision (9/106), retinal edema (8/106), generalized eye disorder (4/106), vitreous floaters (4/106), retinal detachment (3/106), retinal epitheliopathy (3/106), visual impairment (3/106). Most Central serous retinopathy like events were grade 1, transient in nature and resolved without treatment modification, after dose reduction, or after interruption of treatment. Cardiac events regardless of relationship to MEK162 were reported by 4/106 (4%) patients. All were grade 3.

Among the 35 patients evaluable for efficacy with mutant BRAF melanoma at 45 mg bid, 2 confirmed and 6 unconfirmed partial responses and 14 patients with stable disease were recorded. There were 23 patients with BRAF mutant melanoma treated at 60 mg bid were evaluable for efficacy, 3 patients with confirmed partial responses and 1 with unconfirmed partial response and 6 patients with stable disease were reported. There were 35 patients with NRAS mutant melanoma treated at 45 mg bid evaluable for efficacy, 6 confirmed and 2 unconfirmed partial responses and 15 patients with stable disease were recorded.

[redacted]

1.2.4.2.2 Clinical pharmacokinetics

In healthy subjects and patients with rheumatoid arthritis, the analysis of PK data was done using model independent methods only. These analyses suggested that absorption was rapid, there was extensive distribution and that the apparent terminal half-life was short. Contrary to expectation, given the short half-life, accumulation greater than that predicted by linear PK was observed. Overall when given bid, accumulation was around 1.5 to 1.7 fold. This apparent non-linearity in the PK of MEK162 may have been related to a combination of a relatively high LOQ of the assay used (5 ng/mL) and the schedule of blood collection for PK used. In order overcome these limitations and to fully characterize the PK of MEK162 in cancer patients a model based analysis was conducted using a population PK method. MEK162 PK was best described by a two compartment disposition model with first-order elimination and first order absorption with a lag time. The estimated between subject variability on apparent clearance (CL/F) was moderate (44%) and very high (~150%) for the apparent central volume of distribution (Vc/F) and apparent peripheral volume of distribution (Vp/F). The covariate effect of dose on relative bioavailability was identified as significant (at an $\alpha = 0.001$ significance level). Relative to the 45 mg dose, the bioavailability of the 30 mg dose level is 120%; while the relative bioavailability of 60 mg and 80 mg doses were 88% and 77% This dose dependence was not seen using model independent methods but most likely represents either solubility limited absorption of MEK162 or the impact of P-gp or a combination of the two. Based on the PK parameters estimated in this analysis when administered bid, MEK162 steady state is reached around Day 15 and the accumulation is around 1.7 fold which is consistent with observation.

PK properties of MEK162 were in general consistent across ethnicities.

The effect of food on the PK of MEK162 was assessed in a definitive food effect study [CMEK162A2103] and clinical study [ARRAY-162-104]. The results of [CMEK162A2103] study showed that although the mild effect of food on the absorption kinetics of MEK162 was observed, it however is concluded not clinically relevant. There is no need for specification of food intake for MEK162 administration. Data from the two studies suggested that cancer patients do not need to be fasted when taking MEK162.

2 Rationale

2.1 Study rationale and purpose

Oncogenic signaling pathways commonly dysregulated in lung cancer involve activation of a receptor tyrosine kinase, including EGFR and MET, at the cell surface by ligand binding and receptor homodimerization or heterodimerization leading to autophosphorylation of the intracellular tyrosine kinase domain, which in turn triggers multiple signal transduction cascades including the RAS/RAF/MEK (mitogen-activated and extracellular signal–regulated kinase kinase) and PI3K/AKT/mTOR pathways (Larsen et al 2011). These aberrant pathways provide a wealth of new possibilities for targeted therapeutics.

[redacted]

Figure 2-1 Molecular abnormalities in human lung adenocarcinoma

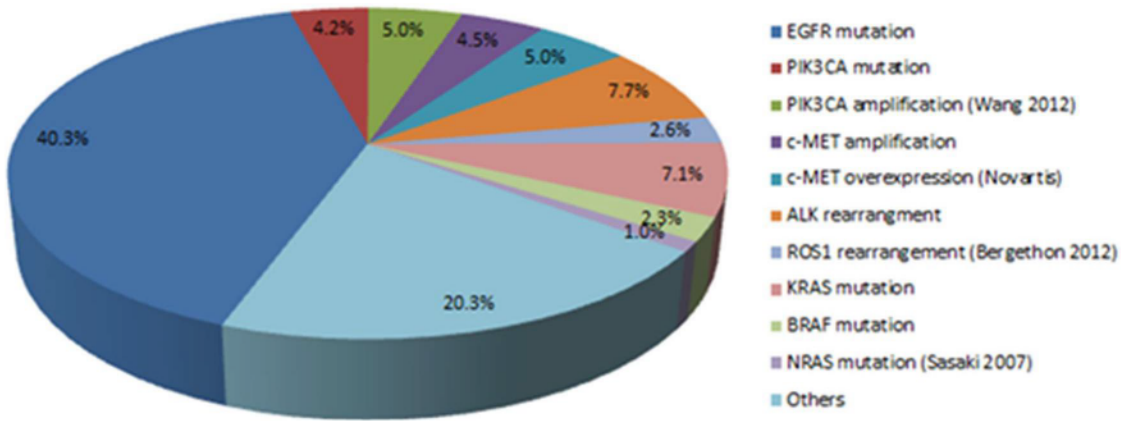


Figure 2-1 shows some of the common molecular abnormalities in human lung adenocarcinoma and the signaling pathway at which study treatment proposed in this study are targeting. The frequencies of these oncogenic driver genes found in adenocarcinoma including EGFR, PIK3CA, c-MET, ALK/, ROS1 and KRAS/NRAS/BRAF have been reported to be 40.3%, 9.2%, 9.5%, 10.3% and 10.5%, respectively, based on data from Guangdong Lung Cancer Institute, China (An et al 2012) and other publications (Wang et al 2012, Sasaki et al 2007, Bergethon et al 2012).

The purpose of this study is to evaluate the anti-tumor activity of single agent BYL719, INC280, LDK378 and MEK162 in advanced NSCLC patients carrying specific molecular alterations. In addition, this study is testing the modern paradigm of allocating patients to specific treatment arm based on their individual genetic profile. Most lung adenocarcinoma patient populations with molecular characterization could receive targeted treatment and potentially benefit from targeted kinase inhibition.

The rationale for each of the study treatments is outlined below:

BYL719

Recent studies have shown that the PI3K signaling cascade is frequently overactivated in human cancer (Vivanco 2002, Altomare 2005, Carnero 2010), and is playing a critical role both in the initiation and progression of NSCLC (Memmott 2010, Xu 2010). PIK3CA copy number gain has been reported in 6.2% adenocarcinoma lung cancer (Yamamoto 2008) The pre-clinical data demonstrated that BYL719 exhibits strong antitumor effects at well tolerated doses in the PIK3CA mutated lung cancer models such as NCI-H596, HLUX1834, HLUX2042 and HLUX3029 subcutaneous xenograft model *in vivo*. Clinical experience with BYL719 in NSCLC is limited so far. Treatment with BYL719, alpha-specific PI3K inhibitor may represent an important therapeutic option for patients with molecular alteration (mutation or amplification) of PIK3CA. PIK3CA-mutated Non-small cell lung cancer (NSCLC) represents a clinically and genetically heterogeneous subgroup in adenocarcinomas as well as in squamous cell carcinomas (SCC) with a higher prevalence of these mutations in SCC (8.9% vs 2.9% comparing with adenocarcinoma) (Scheffler et al. 2015). PIK3CA copy-number gains also occur in lung cancers, with higher frequency in squamous cell carcinomas (Yamamoto H 2008; Kawano O 2007). PIK3CA mutation/amplification may represent a good predictive feature for the clinical application of specific PI3K inhibitors in SCC lung cancer patients (Bonelli MA et al. 2015 Aug).

[redacted]

INC280

MET is involved in many mechanisms of cancer proliferation and metastasis. MET overexpression and genetic alterations play a role in the pathogenesis of several tumors, including lung cancer (Sattler et al 2011). A striking correlation between amplification of the c-MET gene and response to c-MET inhibitors has been observed in rare cancer cell lines originating from lung and other tissues (Lutterbach 2007, McDermott 2007). A randomized phase II trial with MetMAb showed a nearly doubling (from 6.4 to 12.4 weeks) in progression free survival (hazard ratio=0.56, 95% CI=0.31-2.02, p=0.05) with MetMAb plus erlotinib versus erlotinib alone in patients with previous treatment for advanced NSCLC and whose tumors express high c-MET levels assessed by IHC (Spigel et al 2011). INC280, a highly selective and potent c-MET inhibitor, is expected to have therapeutic effect in patients whose tumors bear aberrations in this pathway.

LDK378

ALK rearrangements, similar to other oncogenic drivers such as mutant EGFR and oncogenic RAS, are generally mutually exclusive. Currently, crizotinib is the only therapy approved specifically for this small subset of patients with ALK positive NSCLC. Crizotinib is also effective in ROS1 translocation patients (Shaw et al 2012). The investigation of ALK-targeted therapies that may have differential characteristics versus crizotinib in terms of resistance mechanism, clinical activity and/or safety profile and that may represent alternative and/or complimentary therapeutic options is warranted. LDK378 is a novel inhibitor of ALK that, in preclinical studies, was found to be more potent and specific (i.e. does not inhibit other kinases, such as MET) than crizotinib, and is active against mutated versions of ALK that are known to confer resistance to crizotinib. In the ongoing phase I first in human study, LDK378 exhibited potent antitumor activity in both crizotinib naïve and treated populations. LDK was designated as breakthrough therapy by FDA on 6-March-2013.

MEK162

KRAS is one of the most frequently mutated oncogene in NSCLC, with mutations detected in about 30% of tumors in white people (Davies et al 2002, Malumbres 2003). KRAS mutations also predict for absence of benefit from EGFR tyrosine kinase inhibitors, are a negative prognostic factor for survival (Mitsudomi et al 2007; Mascaux et al 2005). Although KRAS mutations were identified in lung cancer nearly 20 years ago, no approved therapies exist for KRAS mutant NSCLC and few trials have specifically addressed this population of patients. Up to now, direct inhibition of KRAS has proven clinically challenging (Santos et al 1984; Blumenschein et al 2005). Efforts to inhibit mutant KRAS in NSCLC have therefore targeted effector proteins downstream in the RAS-RAF-MEK-ERK (MAPK) signalling pathway. The MAPK pathway converges at the MEK1/MEK2 (also known as MAP2K1 and MAP2K2) kinases, for which the only known substrates are the ERK1/ERK2 (also known as MAPK3 and MAPK1) kinases. MEK inhibition is expected to block ERK signaling irrespective of the upstream signaling (Janne et al 2013). Therefore, MEK represents a compelling target for the treatment of cancer and its inhibitor MEK162 may inhibit growth-stimulatory signals from a number of diverse sources. The first study to demonstrate the clinical benefit for patients with KRAS mutant NSCLC is a phase II, randomized trial with selumetinib, an inhibitor of MEK.

[redacted]

Selumetinib showed improvement in median OS by 4.2 months when added to docetaxol (9.4 months vs 5.2 months), and improvement in median PFS by 3.2 months (5.3 months vs. 2.1 months), 16 (37%) patients in the selumetinib group and none in the placebo group had an objective response (Janne et al 2013).

2.2 Rationale for the study design

The study is designed as a Phase II, multiple arm, open-label study in advanced NSCLC patients who have failed prior treatment, and must not have received more than two prior lines of antineoplastic therapy. These patients, who currently have no effective therapeutic options, will be allocated to a specific treatment arm according to their characterized molecular alterations, after the molecular pre-screening which can optimize the patient selection.

The multiple arm design was chosen, with objective response rate (ORR) as primary endpoint, to evaluate the efficacy of single agent BYL719, INC280, LDK378 and MEK162 in advanced NSCLC patients. In addition, safety, tolerability, PK and gene alterations that may be related with resistance will also be evaluated for each agent.

Protocol will be amended if new non-overlapping target(s) and compound(s) are identified and considered to be added as independent arm(s) in the future.

For each treatment arm the sample size was calculated based on a Bayesian approach using either a minimally informative prior (BYL719, INC280 and MEK162) or an informative prior using relevant historical data (LDK378). The proposed sample size will allow detecting with high likelihood statistically and clinically relevant anti-tumor activity.

2.3 Rationale for dose and regimen selection

The selection of the doses (750mg qd for LDK378, 45mg bid for MEK162) are based on MTD or RP2D identified (Section 1.2). The same MTD or RP2D for LDK378 and MEK162 are established in phase I studies in Japan.

For BYL719, 400 mg qd was the MTD identified in its FIH study. However, further data showed that 350 mg qd is better tolerated, and 350 mg qd has been declared as RP2D for Japanese population. Therefore, 350 mg qd will be used in this study.

For INC280, RP2D of 600 mg BID has been established with capsules. To improve convenience of study drug administration for the patients, INC280 tablet formulation was developed with higher dosage strengths and evaluated in [CINC280X2102], [CINC280X1101] and [CINC280X2202] studies. Preliminary PK data showed that mean AUC and Cmax at steady-state following administration of INC280 tablets at 400 mg BID was higher than that following capsules at 600 mg BID (RP2D in [CINC280X2102]), but in the range considering the CV%. Based on the tablet PK and safety data from these studies, the dosage of INC280 at 400 mg BID in tablet has been declared as RP2D in CINC280X2102 study. 400 mg bid is therefore the dose of tablet formulation in this study.

[redacted]

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		
To investigate the anti-tumor activity of single agent BYL719, INC280, LDK378 and MEK162	ORR per RECIST v1.1	Refer to Section 10.4
Secondary		
To further assess the clinical activity of single agent BYL719, INC280, LDK378 and MEK162	OS, PFS, DCR, duration of overall response per RECIST v1.1	Refer to Section 10.5.1
To characterize the safety and tolerability of single agent BYL719, INC280, LDK378 and MEK162	Frequency/severity of AEs and SAEs; laboratory abnormalities Dose interruptions and dose reductions	Refer to Section 10.5.2
To characterize the pharmacokinetic profiles of single agent BYL719, INC280, LDK378 and MEK162	PK parameters including but not limited to AUC0-t, Cmax, Tmax, T1/2, CL/F and Vz/F	Refer to Section 10.5.3
[redacted]		

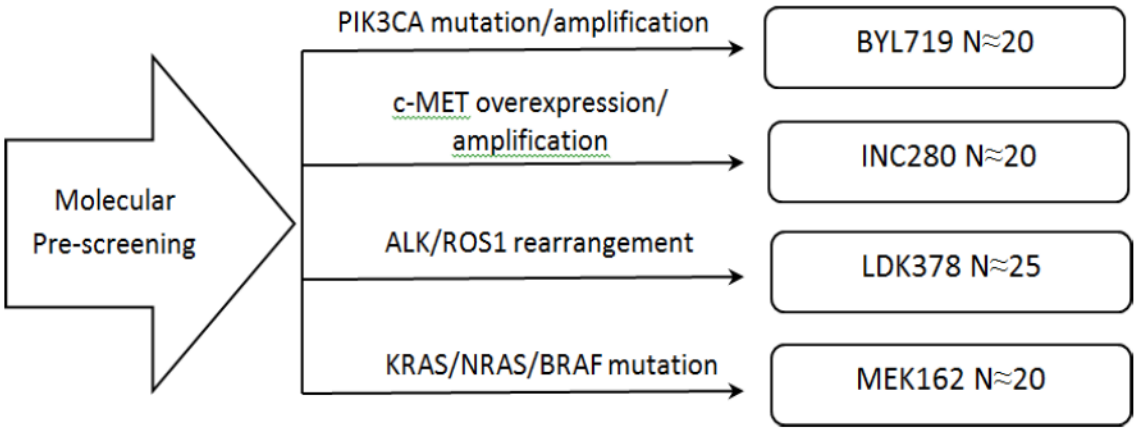
[redacted]

4 Study design

4.1 Description of study design

This is a Phase II, multiple arm, open-label study of single agent BYL719, INC280, LDK378 and MEK162. This study will enroll approximately 20-25 advanced NSCLC patients to each treatment arm according to their molecular alterations (Figure 4-1). Each treatment arm is independent from one another and will be analyzed separately.

Figure 4-1 Study Design



Molecular pre-screening

To enter the screening phase of the study, patients must have written documentation of molecular alterations as described in Figure 4-1, which should be obtained locally or centrally on either a newly obtained tumor sample (preferred) or the most recent archival tumor sample available.

A molecular pre-screening Informed Consent allowing for the collection of a newly obtained tumor sample or archival tumor sample for local or central assessment of the molecular alteration status will be signed before molecular pre-screening. For central assessment, a designated laboratory may be used.

Screening

Once the molecular alterations status is known or determined, the patient is allowed to sign the Main Study Informed Consent. Based on the molecular alterations of the tumor, patients will be allocated to one of the treatment arms. Patients with multiple molecular alterations in EGFR and the relevant pathways that are indicated in study design Figure 4-1 will generally be excluded except under the conditions described in Section 5.2. Patients will be screened against the inclusion/exclusion criteria described in Section 5. All screening evaluations are required to be performed before administration of study treatment.

[redacted]

Treatment period

The treatment period will begin on Cycle 1 Day 1 and will continue in 28-day cycles until disease progression, unacceptable toxicity, withdrawal of informed consent, death, or the patient has been transferred to another Novartis study that can continue to provide study drug. (see also Section 7.1.4.1 and Section 7.1.5).

30-day safety, disease progression, survival follow-up assessments

All patients will be followed up for safety 30 days after the last dose of the study treatment. Patients who discontinue study treatment for any reason other than disease progression will be followed up for progression of disease. All patients will be followed for survival (see details in Section 7.1.6).

For any patient has been transferred to other Novartis study, an end of treatment visit will be performed and the patient will not enter the follow-up period.

4.2 Timing of interim analyses and design adaptations

Not applicable.

4.3 Definition of end of the study

The end of study is defined as the earliest occurrence of one of the following:

- All patients have completed 30-days safety follow up and a minimum of 12 months has elapsed since last patient first treatment, or patients have been transferred to another Novartis study that they can continue to receive study drug
- Study is terminated early

The final analysis of study data will be conducted at the end of the study.

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible for an EOT visit, and the assessments for EOT as described in Section 7 should be performed for a prematurely discontinued or 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

The study will enroll patients who have histologically or cytologically confirmed advanced (stage IIIB or stage IV) lung adenocarcinoma (all treatment arms) or lung squamous cell carcinoma (BYL719 arm only), who progressed during or following at least one prior anticancer treatment regimen or patients who are deemed unsuitable for chemotherapy in the

[redacted]

investigators' opinion (including patients who refuse chemotherapy). Evidence of molecular alterations (Section 4.1) will be documented through local or central laboratory testing. Patients with silent mutations, which are DNA mutations that do not result in a change to the amino acid, should not be enrolled.

Patients enrolled in this study are not permitted to participate in additional parallel investigational drug or device studies.

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. Depending on the study treatment selected based on the molecular pre-screening result, besides the general inclusion and exclusion criteria, the inclusion and exclusion criteria specific for each arm need to be considered before the subject being enrolled.

5.2 Inclusion criteria

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

Written informed consent must be obtained prior to any screening procedures.

1. Patients must be 18 years or older and able to sign Informed Consent.
2. Histologically or cytologically confirmed, advanced (stage IIIB or stage IV) lung adenocarcinoma. For BYL719 treatment arm, the histologically or cytologically confirmed advanced (stage IIIB or stage IV) lung adenocarcinoma or lung squamous cell carcinoma.
3. Patients who have failed at least one prior anticancer treatment regimen or patients who are deemed unsuitable for chemotherapy in the investigators opinion (including patients who refuse chemotherapy).

   Note: Chemotherapy administered as adjuvant treatment more than six months prior to study enrollment is not considered a prior line of therapy for purposes of this study.
4. Measurable disease according to RECIST v.1.1 (Irradiated lesions are not considered measurable unless they have clearly progressed since radiotherapy)
5. ECOG performance status ≤ 2
6. Patients must be suitable and willing to undergo mandatory tumor biopsy according to treating institution's guidelines and requirements for such procedure if there is no archival biopsy available.

Patients eligible for each treatment arm must meet the following criteria for respective arm:

BYL719

7. Patient's tumor must have molecular alteration (mutation and/or amplification with PIK3CA gene copy number ≥ 4) of the PIK3CA gene (patients with other PI3K pathway alterations may be enrolled after agreement between sponsor and site).

INC280

8. Patient's tumor must have IHC intensity 3+ in $\geq 50\%$ of tumor cells or c-MET IHC intensity score 2+ in $\geq 50\%$ of tumor cells and concurrent have MET gene copy number $\geq$ 5 by FISH. Patients with MET gene copy number ≥ 5 (by FISH) with unknown c-MET

[redacted]

IHC results or c-MET mutation can be enrolled in the study following discussion and agreement with Novartis.

LDK378

9. Patient's tumor must have ALK or ROS1 gene rearrangement.
10. Both crizotinib pretreated and crizotinib naive patients would be eligible.
11. Patients' tumor sample must be obtained after progression on crizotinib if patient is pre-treated with crizotinib. If tumor sample is not available, patients must be suitable and willing to undergo mandatory biopsy according to treating institution's own guidelines and requirements for such procedure.

MEK162

12. Patient's tumor must have KRAS, NRAS or BRAF mutation.

Note: Patients with multiple molecular alterations which are indicated in study design Figure 4-1 can be enrolled after discussion with Novartis.

5.3 Exclusion criteria

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

1. Symptomatic CNS metastases which are neurologically unstable or require increasing doses of steroids within the 4 weeks prior to study entry to control their CNS disease
   Note: Patients with controlled CNS metastases may participate in this trial. The patient must have completed radiotherapy or surgery for CNS metastases > 4 weeks prior to study entry. Patients must be neurologically stable, having no new neurologic deficits on clinical examination.
2. Radiation therapy within ≤ 4 weeks prior to study entry, with the exception of limited field palliative radiotherapy for bone pain relief. Any persistent side effect of prior radiotherapy must be resolved to ≤ CTCAE grade 1 prior to the first dose of study treatment.
3. Any other malignancies within the last 5 years before study start, except for adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer
4. Patients known to be HIV positive. HIV testing is not required in the absence of clinical signs and symptoms suggesting HIV infection.
5. Major surgery ≤ 2 weeks prior to study entry or who have not recovered from side effects of such therapy
6. Any disease (including psychotic disorders, drug abuse, active infection, uncontrolled hypertension, clinically significant cardiovascular disease for example cerebrovascular accident (CVA) (≤ 6 months before study entry), myocardial infarction (≤ 6 months before study entry), unstable angina, New York heart association(NYHA) ≥ grade 2 chronic heart failure (CHF), history or presence of clinically significant ventricular arrhythmias or atrial fibrillation, hepatic, renal or metabolic disease, metabolic dysfunction), physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contra-indicates the use of an investigational drug or puts the patient at high risk for treatment-related complications
7. Patients must not have received previous anti-cancer therapies ≤ 4 weeks prior to the first dose of study treatment except:

[redacted]

- ≤6 weeks for nitrosoureas and mitomycin
- ≤5 half-life of continuous or intermittent small molecule therapeutics (or ≤ 4 weeks when half-life is unknown),
  and have not recovered from the side effects of such treatment (CTCAE grade ≤ 1) prior to the first dose of study treatment, except for alopecia.

8. Currently receiving any prohibited medications including vitamins supplements, and herbal preparations medications/supplements. Refer to Section 6.3 and Section 14.4 for excluded medications.
9. Any of the following laboratory values at baseline:
   - Hemoglobin < 9 g/dL (SI Units: 90 g/L)
   - Platelet count <100 x 10^9/L
   - Absolute neutrophil count (ANC) < 1.5 x 10^9/L
   - Serum albumin < 2.5 g/dl
   - Total bilirubin > 1.5 x upper limit of normal (ULN)
   - AST/SGOT or ALT/SGPT > 3.0 x upper limit of normal (ULN) or > 5.0 x ULNif liver metastases are present
   - Serum creatinine > 1.5 x ULN or calculated creatinine clearance by Cockcroft-Gault formula < 50 mL/min
   - Serum calcium, potassium and magnesium < LLN (lower limit of normal)
10. Positive urine β-HCG test (female patients of childbearing potential only) within 72 hours prior to first dose
11. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
12. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 30 days after stopping of study medication. 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 total 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.

    Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.In case of use of oral contraception

[redacted]

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.

13. Sexually active males unless they use a condom during intercourse while taking drug and for 3 months after stopping study medication and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.

Patients eligible for each treatment arm must not meet any of the following criteria for respective arm:

BYL719

14. Impaired cardiac function or clinically significant cardiac disease, including any one of the following:
    - History of heart failure or left ventricular (LV) dysfunction (LVEF ≤ 50%) by MUGA or ECHO
    - ST depression or elevation of ≥ 1.5 mm in 2 or more leads
    - Mean QTcF>450 msec for males and QTcF> 460 msec for females using Fridericia's correction on screening ECG. Patients with unreadable or uninterpretable ECGs are also excluded.
    - Congenital long QT syndrome
    - History or presence of clinically significant ventricular arrhythmias or atrial fibrillation
    - Clinically significant resting bradycardia (< 50 beats / min)
    - Complete left bundle branch block (LBBB)
    - Right bundle branch block (RBBB) + left anterior hemiblock (LAHB - bifascicular block)
    - Unstable angina pectoris ≤ 3 months prior to study entry
    - Acute Myocardial Infarction (AMI) ≤ 3 months prior to study entry
15. Fasting plasma glucose (FPG) > 140 mg/dL / 7.7 mmol/L or Glycosylated Hemoglobin (HbA1c) ≥6.5% (both criteria have to be checked)

    * For patients with FPG ≥ 100 mg/dL and/or HbA1c ≥5.7% (i.e. threshold for pre-diabetes) at screening, -recommend lifestyle changes according to ADA guidelines, i.e. dietary advice (e.g. small frequent meals, low carbohydrate content, high fiber, balancing carbohydrate intake over the course of the day, three small meals and 2 small snacks rather than one large meal) and exercise. A consultation with a diabetologist is also highly recommended.

[redacted]

16. Impaired gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral BYL719 (e.g. total gastrectomy, ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection) or patients unable to take oral medication.
17. Patients who are currently receiving treatment with medication that has the potential to prolong the QT interval or inducing Torsades de Pointes, and the treatment cannot either be discontinued or switched to a different medication prior to starting study treatment.
18. Treatment with therapeutic doses of coumarin-based anticoagulants (e.g., warfarin sodium, Coumadin®). Low doses of courmarin-based anticoagulants (e.g. ≤ 2mg/day for line patency) are permitted.
19. Patients receiving chronic or high dose corticosteroids therapy (inhaled steroids and short courses of oral steroids for anti-emesis or as an appetite stimulant, or single i.v. doses, i.e., for prophylaxis of contrast media allergy are allowed)
20. A history of acute or chronic pancreatitis, surgery of the pancreas, or any risk factors that may increase the risk of pancreatitis
21. Prior treatment with PI3K inhibitor

INC280

22. Any of the following laboratory values at baseline:
    - Asymptomatic serum amylase > grade 2
    - Patients with grade 1 or grade 2 serum amylase at the beginning of study must be confirmed to have no signs and/or symptoms pancreatitis or pancreatic injury (e.g. elevated P-amylase, abnormal imaging findings of pancreas, etc.)
    - Serum lipase > ULN
    - Fasting serum triglyceride level > 500 mg/dL
23. A history of acute or chronic pancreatitis, surgery of the pancreas, or any risk factors that may increase the risk of pancreatitis
24. A history of cystic fibrosis.
25. Patients with highly suspicious pulmonary fibrosis or interstitial lung disease.
26. Prior treatment with a c-MET inhibitor or HGF-targeting therapy

LDK378

27. Serum potassium, magnesium, phosphorus and total calcium (corrected for serum albumin) which is out of normal limits or could not be corrected to within normal limits with supplements before the first dose of LDK378
28. Alkaline phosphatase (ALP) >5.0 x ULN
29. Serum amylase >2 x ULN
30. Serum lipase >ULN
31. Fasting plasma glucose >175 mg/dL (>9.8 mmol/L)
32. Impaired cardiac function or clinically significant cardiac disease, including any one of the following:
    - Supraventricular and nodal arrhythmias not controlled with medication
    - Other cardiac arrhythmia not controlled with medication

[redacted]

- Corrected QTcF interval ≥450 msec (male patients), ≥ 470 msec (female patients) using Fridericia's correction on screening 12-lead ECG (as mean of triplicate)
- Resting heart rate which is out of 50-90 bpm on screening 12-lead ECG (as mean of triplicate)
- History of myocardial infarction, angina pectoris, coronary artery bypass graft (CABG) within 6 months prior to starting study treatment
- Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block)

33. Congenital long QT syndrome or family history of idiopathic sudden death , or any of the following:
    - Risk factors for Torsades de Pointe (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia
    - Concomitant medication(s) with a known risk to prolong the QT interval and/or known to cause Torsades de Pointe that cannot be discontinued or replaced by safe alternative medication (e.g. within 5 half-lives or 7 days prior to starting study drug)
    - Inability to determine the QTcF interval
34. History or current diagnosis of cardiac disease indicating significant risk of safety for patients participating in the study such as uncontrolled or significant cardiac disease, including any of the following:
    - Unstable angina within 6 months prior to screening.
    - Recent myocardial infarction within 6 months prior to screening.
    - Uncontrolled congestive heart failure
    - Clinically significant (symptomatic) cardiac arrhythmias (e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker
35. Prior treatment with any other ALK inhibitor except crizotinib
36. Patient is currently receiving treatment with warfarin sodium (Coumadin®) or any other coumarin-derivative anticoagulants.
37. Patient is receiving treatment with any enzyme-inducing anticonvulsant that cannot be discontinued at least 1 week before first dose of study treatment, and for the duration of the study. Patient on non enzyme-inducing anticonvulsants is eligible.
38. Patient has history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention).
39. Patient has other severe, acute, or chronic medical conditions including uncontrolled diabetes mellitus or psychiatric conditions or laboratory abnormalities that, in the opinion of the investigator, may increase the risk associated with study participation or may interfere with the interpretation of study results.
40. Patient has a history of pancreatitis or history of increased amylase or lipase that was due to pancreatic disease.

[redacted]

MEK162

41. Impaired cardiac function or clinically significant cardiac disease, including:
    - History of heart failure or left ventricular (LV) dysfunction (LVEF ≤ 50%) by MUGA or ECHO
    - Uncontrolled arterial hypertension, defined as blood pressure > 140/100 mmHg
    - History of acute coronary syndromes (including myocardial infarction, unstable angina, CABG, coronary angioplasty, or stenting) ≤6 months prior to study entry
    - Symptomatic chronic heart failure, history or current evidence of clinically significant cardiac arrhythmia and/or conduction abnormality ≤6 months prior to study entry
42. 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)
43. Patients who have neuromuscular disorders that are associated with elevated CK (e.g. Inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy);
44. History of Gilbert's syndrome
45. Prior therapy with a MEK inhibitor

6 Treatment

6.1 Study treatment

Investigational treatment: BYL719, INC280, LDK378 and MEK162 are the investigational treatment or the "study treatment" for this study.

6.1.1 Dosing regimen

Table 6-1 Dose and treatment schedule

Study treatment	Pharmaceutical form and route of administration	Dose	Frequency
BYL719	Tablets for oral use	350 mg	Once daily
INC280	Capsules/tablets for oral use	600 mg capsule/400 mg tablet	Twice daily
LDK378	Capsules for oral use	750 mg	Once daily
MEK162	Tablets for oral use	45 mg	Twice daily

Instructions for administration of BYL719/INC280/LDK378/MEK162

- Patients will be instructed to self-administer the study treatment with at least a glass (approximately 250 mL) of water at approximately the same time each day (24 ± 4 hours apart for morning dose of QD regimen and 12 ± 2 hours apart for morning and evening doses of BID regimen). Patients in INC280 treatment arm are recommended to consume another glass of water (about 250 mL) at 2 hours after each INC280 administration. For the BYL719 arm, if the patient forgets to take BYL719 during the daytime it should be taken in the evening at the latest within 1 hour after a meal, but not later than 6 pm. If not taken by this time, the dose should be withheld that day.

[redacted]

- For INC280 arm, the newly enrolled patients will initiate treatment with INC280 tablets at 400 mg BID in compliance with the local regulation. The ongoing patients may be switched to the tablet after discussion with Novartis and in compliance with local regulation.
- BYL719 must be taken within 1 hour after a meal or snack (preferably in the morning after breakfast). If, for any reason, a breakfast (or other meal) was not consumed, then the patient should take study treatment with a glass of water within 1 hour after a snack at any later point in time. If this happens on days of PK sampling, it should be documented in the CRF.
- INC280/LDK378 should be administered in the fasted state, at least 1 hour before or 2 hours after a meal.
- For all treatment arms, patients are free to drink water during the fasting period.
- Patients should be instructed to swallow the capsules/tablets whole and not to chew or crush them.
- Patients should be instructed not to make up missed doses or partial doses (i.e. when the entire dose is not taken as instructed). If the patient forgets to take BYL719 during the daytime it should be taken in the evening at the latest within 1 hour after a meal, but not later than 6 pm. If not taken by this time, the dose should be withheld that day. For other QD regimen, a missed or partial dose will be defined as a case when the full dose is not taken within 8 hours after the approximate time of the usually daily dosing. That day's dose (or part remaining dose) should be omitted and the patient should continue treatment with the next scheduled dose on the following day. For a BID regimen, a missed or partial dose is defined as the full dose is not taken within 4 hours after the approximate time of the usual morning or evening dosing schedule. That morning or evening dose should be omitted and the patient will continue treatment with the next scheduled dose.
- 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 increased stool frequency) must be noted in the AEs section of the eCRF. In addition, on the days of PK sampling, the onset time of any episodes of vomiting within the first 4 hours post-dosing on that day must be noted in the corresponding Dose Administration Record PK eCRF.
- Patients who are assigned to LDK378 or INC280 treatment arms must avoid consumption of grapefruit, pomegranates, star fruits, Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study medications, due to potential effect on the exposures of the study medications. Normal orange juice is allowed.
- On days when PK blood samples are to be collected, patients will be instructed to hold their dose until arrival at the study center and take the dose at any later point of time after PK blood collection. The same dietary restrictions for dosing will be in place on days with PK blood sampling days.
- The investigator or responsible site personnel should instruct the patient to take the study treatments 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

[redacted]

the Dosage Administration Record eCRF. Drug accountability must be performed on a regular basis.

Instructions for administration of INC280

- During the entire duration of treatment with INC280, the patient is recommended to use precautionary measures against ultraviolet exposure (e.g., use of sunscreen, protective clothing, avoid sunbathing or using a sunlamp or tanning bed).

6.1.2 Treatment duration

Patients may continue treatment with single agent BYL719, INC280, LDK378 and MEK162 until the patient experiences disease progression, death, unacceptable toxicity and/or treatment is discontinued at the discretion of the investigator or the patient or consent withdrawal as described in Section 7.1.4.1 and Section 7.1.5. Patients who have disease progression and have evidence of clinical benefit, such as disease shrinkage at other sites or symptomatic improvement, may continue treatment with BYL719, INC280, LDK378 and MEK162. In addition, BYL719, INC280, LDK378 and MEK162 treatment may be temporarily interrupted to permit local therapy for symptomatic metastases after disease progression has been documented. Patients who continue on treatment after disease progression should discontinue study treatment once they are no longer deriving benefit as assessed by the investigator.

6.2 Dose modifications

6.2.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. The following guidelines need to be applied.

These changes must be recorded on the Dosage Administration Record CRF.

All dose modifications should be based on the worst preceding toxicity. In general, each patient is only allowed one dose reduction. In addition, a patient should discontinue treatment with study treatment if, after treatment is resumed at a lower dose, the Grade 3/4 toxicity recurs with the same or worse severity. Second dose reductions may only be allowed after discussion with Novartis.

For each patient, once a dose level reduction has occurred, the dose level may not be re-escalated during subsequent treatment cycles with the study treatments.

Dose reduction levels for study treatment are listed in Table 6-2. Recommendations of criteria for interruption and re-initiation of study treatment can be found in Section 14.2.

If a patient requires a dose interruption of > 21 days from the intended day of the next scheduled dose, then the patient must be discontinued from the study. However, if the patient is clearly benefiting from the study treatment (i.e. stable disease, partial response, complete response), and the AEs are resolved to grade ≤ 1, and, after discussion and agreement with the Novartis clinical team, the patient may remain on the study treatment at a dose level adjusted based on safety.

[redacted]

Table 6-2 Dose reduction steps for BYL719, INC280, LDK378 and MEK162

Study treatment	Starting dose level - 0	Dose level - 1	Dose level -2*
BYL719	350 mg qd	300 mg qd	250 mg qd
INC280(capsule/tablet)	600 mg capsule bid/ 400mg tablet bid	450 mg capsule bid/ 300mg tablet bid	350mg capsule bid/ 200mg tablet bid
LDK378	750 mg qd	600 mg qd	450 mg qd
MEK162	45 mg bid	30 mg bid	Not allowed
* may only be allowed after discussion and agreement with Novartis			

6.2.2 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts such as ophthalmologist, endocrinologist, dermatologist, psychiatrists etc. should be consulted as deemed necessary. Recommended guidelines for follow up of selected toxicities of each study treatment are provided in Section 14.3.

6.2.3 Anticipated risks and safety concerns of the study treatment

Appropriate eligibility criteria and specific dose modification and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced adverse events, i.e., hyperglycemia, skin toxicity and diarrhea are provided in Section 14.3. The risks to patients in this trial may be minimized by compliance with eligibility criteria and study procedures, as well as, close clinical monitoring. There may be unforeseen risks with LDK378, BYL719, MEK162 and INC280 which may be serious. Refer to preclinical toxicity and/or clinical data in the [Investigator's Brochure].

6.3 Concomitant medications

6.3.1 Permitted concomitant therapy

Patients are permitted to use the following medications while taking the study drugs, except when specifically prohibited (see Section 6.3.3):

- Oral or topical antibiotics
- Medications to prevent or treat nausea or vomiting
- Anti-diarrheal medications (e.g., loperamide) for subjects who develop diarrhea.

BYL719

The use of bisphosphonates/denosumab regardless of indication is allowed provided patients have been on stable doses for at least 2 weeks prior to randomization. Stable dose should be maintained during the treatment period. Patients requiring initiation of bisphosphonates/denosumab during the course of the study should be discontinued due to progressive disease unless disease progression can be completely ruled out and this is clearly documented in the patients' source documentation.

[redacted]

Patients who develop diabetes mellitus during the study should be treated according to the ADA (American Diabetes Association) guidance. It is recommended to start treatment with metformin. Patients receiving oral antidiabetics which are predominantly metabolized by CYP2C9 and CYP2C8, including but not limited to, repaglinide, rosiglitazone, glipizide and tolbutamide, should be monitored for hypoglycemia as BYL719 was found to be weak reversible inhibitor of these enzymes *in vitro*.

Hematopoietic growth factors may be used according to American Society of Clinical Oncology (ASCO) guidelines.

BYL719 is characterized by a pH-dependent solubility. Therefore acid reducing agents (ARAs, e.g. proton-pump inhibitors, H2-antagonists and antacids) may alter the solubility of BYL719 and hence its bioavailability. A drug-drug interaction study in human healthy volunteers confirmed that co-administration of BYL719 with the H2-antagonist ranitidine after a meal lead to a decrease in exposure by only ~20%, considered to be not clinically relevant. Hence BYL719 can be co-administered with any ARAs.

Chronic dosing of high levels of corticosteroids such as dexamethasone and prednisone may prolong or aggravate hyperglycemia (steroid-induced diabetes). Hyperglycemia is a common adverse event for PI3K inhibitors like BYL719 and should therefore be used with caution and patients closely monitored.

INC280 arm

The use of PPIs and other acid reducing agents (gastric acid modulators and H2 receptor antagonists) is allowed.

LDK378 arm

The use of bisphosphonates is allowed regardless of indication provided patients have been on stable doses optimally for at least 4 weeks prior to the start of treatment. Patients requiring initiation of bisphosphonate treatment during the course of the study should be evaluated for progressive disease and the result of the evaluation should be clearly documented in the patients' source documentation. No drug-drug interaction is expected between LDK378 and bisphosphonates as the two drugs are eliminated through different elimination pathways. Bisphosphonates are not inhibitors of human CYP450 enzymes involved in the metabolism of LDK378 and do not undergo metabolism *in vivo*. The same guidelines apply to the use of denosumab for the treatment of bone metastatic disease.

Non-enzyme inducing anti-epileptic medication (Non-EIAED) is allowed.

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

6.3.2 Permitted concomitant therapy requiring caution and/or action

Refer to Section 14.4, Table 14-13 for a list of the medications that require caution when

[redacted]

concomitantly used with BYL719, INC280, LDK378 or MEK162. If a patient requires the concomitant use of any medication with a possible or conditional risk for QT prolongation and/or torsade de points (Refer to Section 14.4, Table 14-15) as per discretion of investigators, these medications may be allowed however must be monitored.

Herbal preparations/medications are not encouraged throughout the study, as a potential drug-drug interaction is always possible.

BYL719 arm

BYL719 is a potent and time dependent CYP3A4/5 inhibitor and moderate inhibitor of CYP2C8 and CYP2C9 *in vitro*. Concomitant medications that are sensitive substrates of these enzymes (except those are prohibited as stated in Section 6.3.3) shall be used with caution. *In vitro* studies showed that CYP3A4 is the major enzyme involved (92%) in the primary oxidative metabolism of BYL719 in human liver microsomes. Sensitive substrates for CYP3A4, CYP2C8 or CYP2C9 and/or which have a narrow therapeutic index shall then be used with caution.

BYL719 was identified as a substrate for the human BCRP. Co-administration of BYL719 with BCRP inhibitors may increase systemic exposure and/or alter tissue uptake of oral BYL719 and should therefore be used with caution.

Therapeutic doses of warfarin sodium (Coumadin®) or any other coumarin-derivative anticoagulants should be used with caution and fully avoided whenever possible because of its known interaction with many commonly used medications and certain foods. Alternatively, therapeutic anticoagulation may be accomplished using low-molecular weight heparin or Direct Thrombin inhibitors (DTIs) and Factor Xa inhibitors.

Local radiotherapy for analgesic purposes or for lytic lesions at risk of fracture may be carried out if required. Whenever possible, these patients should have a tumor assessment of the lesion(s) before they actually receive the radiotherapy in order to rule out progression of disease. In case of Progressive Disease, patients should discontinue treatment. No dose modification of study treatment is needed during radiotherapy.

INC280 arm

Medications that are moderate inducers or inhibitors of CYP3A4 are not prohibited but should be administered with caution. Sensitive substrates for CYP3A4, CYP1A2, CYP2C8, CYP2C9 and CYP2C19, except those with narrow therapeutic window which are prohibited, should be administered with caution. Sensitive substrates for P-gp, BCRP, MATE and OATP transporters should also be administered with caution.

LDK378 arm

LDK378 is a time-dependent CYP3A4/5 inhibitor and is also a potent reversible inhibitor of CYP2A6, CYP2E1, CYP2C9 and CYP3A4/5. Concomitant medications that are sensitive substrates of these enzymes (except those are prohibited as stated in Section 6.3.3) shall be used with caution. Metabolism of LDK378 is primarily mediated by

[redacted]

CYP3A4/5 *in vitro*. Concomitant treatment of LDK378 with weak inhibitors or weak inducers of CYP3A4/5 is permitted. Caution should be used when LDK378 is co-administered with moderate inhibitors or inducers. Duration of these concomitant treatments should be kept as short as possible (e.g., less than 1 week) or avoided whenever possible.

Chronic dosing of corticosteroids such as dexamethasone and prednisone is known to induce CYP3A enzymes, thereby increasing the risk of reducing LDK378 drug exposure to sub-therapeutic levels. If possible, systemic corticosteroid treatment should not be given during the study, except for:

- Topical applications (e.g., rash), inhaled sprays (e.g., obstructive airways diseases), eye drops or local injections (e.g., intra-articular);
- Stable doses of corticosteroid therapy such as dexamethasone and prednisone (e.g., for tumor associated symptoms) are permitted during the course of the study. The corticosteroid dose must have been stabilized (or decreasing) for at least 5 days before initiation of study therapy.

Local radiotherapy for analgesic purposes or for lytic lesions at risk of fracture may be carried out if required. If palliative radiotherapy is initiated after start of study treatment, the reason for its use must be clearly documented and progression as per RECIST 1.1 must be assessed and documented. Patients who develop progressive disease but are still deriving clinical benefit from LDK378 therapy, as determined by the Investigator may undergo radiotherapy and/or surgical resection as palliative localized therapy to treat metastatic lesions. LDK378 should be held for at least 4 days prior to radiotherapy and at least 1 day prior to any surgery. LDK378 may be resumed ≥3 days after completing radiotherapy or minor surgery, and ≥2 weeks after major surgery.

The use of gastric protection agents including antacids, H2-antagonists, and PPIs is allowed. However, PPIs should be used with caution due to the theoretical effects of long-acting pH elevating agents (i.e., prolonged acid suppression) on reducing LDK378 absorption. When the concurrent use of a H2-antagonist or an antacid with LDK378 is necessary, the H2 blocker must be administered 10 hours before or 2 hours after the LDK378 dose, and the antacid must be administered 2 hours before or 2 hours after the LDK378 dose. Time restrictions for the concurrent use of PPIs and LDK378 are not applicable due to the long-acting effects of PPIs on gastric pH (i.e., separation of doses will not likely impact this interaction).

MEK162 arm

MEK162 is a potent inhibitor of CYP2B6 (Ki of 1.67 µM) *in vitro*. Concomitant medications that are sensitive substrates of CYP2B6 shall be used with caution. MEK162 is a potential inducer of CYP3A4 mRNA and activity *in vitro*. Caution should be used in patients receiving concomitant medications that are sensitive substrates of CYP3A4 as the efficacy of these drugs could be reduced when administered with MEK162.

MEK162 has been identified to be primarily metabolized by UGT1A1 in vitro. It is advised that inhibitors and inducers of UGT1A1 should be taken with caution when co-administered with MEK162. Patients should be closely monitored for the occurrence of adverse events.

[redacted]

The solubility of MEK162 is pH dependent and a 10-fold decrease in solubility is observed between pH 1 and 2. Short acting gastric acid modulators can be taken, at least 3 hours before or 3 hours after MEK162 administration. H2 receptor antagonists should be avoided.

If H2 receptor antagonists are used during the course of this study, MEK162 shall be taken at least 2 hours before or 8 hours after H2 receptor antagonists. *In vitro* data showed that MEK162 is a substrate of P-gp and BCRP with moderate to high permeability and thus the use of drugs that are potent inhibitors of these transporters may be used with caution. Please refer to Section 14.4, Table 14-13 for a list of these drugs.

6.3.3 Prohibited concomitant therapy

Drugs with known risk of causing TdP are prohibited (refer to Section 14.4, Table 14-15). Study treatment must be interrupted as long as the patient requires therapy with QT prolonging agent.

Other investigational therapies must not be used while the patient is on the study.

Anticancer therapy (chemotherapy, targeted therapy, biologic therapy, radiation therapy or anti-cancer surgery [except palliative radiotherapy and palliative surgical as described in Section 6.3.2]), other than the study treatment, must not be given to patients while they are enrolled in the treatment portion of the trial. If such agents are required then the patient must be permanently discontinued from the treatment portion of the study.

Herbal preparations/medications for disease treatment are not allowed throughout the study. Patients should stop using herbal medications at least 7 days prior to first dose of study treatment.

Other prohibited concomitant therapy is listed in Section 14.4, Table 14-14 and specified below for each treatment arm.

BYL719 arm

BYL719 is a potent and time dependent CYP3A4/5 inhibitor and moderate inhibitor of CYP2C8 and CYP2C9 *in vitro*. Concomitant medications that are sensitive substrates of these enzymes and have narrow therapeutic index are prohibited. *In vitro* studies showed that CYP3A4 is the major enzyme involved (92%) in the primary oxidative metabolism of BYL719 in human liver microsomes. Strong inhibitors and inducers of CYP3A4/5 are prohibited.

INC280 arm

INC280 is moderately metabolized by CYP3A4 *in vitro*. Strong inhibitors or inducers of CYP3A4/5 are prohibited during the course of the study. INC280 is an irreversible inhibitor of CYP1A2and CYP3A4. All agents that are metabolized mainly by CYP1A2 or CYP3A4/5 and have a narrow therapeutic index are prohibited during this study.

LDK378 arm

In vitro metabolism studies suggest that oxidative metabolism of LDK378 is predominantly mediated by CYP3A4/5. Strong inhibitors or inducers of CYP3A4/5 are prohibited. Patients

[redacted]

receiving concomitant medications known to strongly inhibit and/or induce CYP3A4/5 that are deemed medically necessary should be excluded from the study.

LDK378 is a potent inhibitor of drugs metabolized by the cytochromes CYP2C9 and CYP3A4/5 *in vitro*. Concomitant medications known to be mainly metabolized by these enzymes and having a low therapeutic index are prohibited in the study. Therapeutic doses of warfarin sodium or any other coumarin-derivative anticoagulants are not permitted. LDK378 is an inhibitor of CYP2C9, the major metabolizing enzyme of warfarin. A clinically relevant increase in warfarin exposure is possible.

Use of EIAEDs is not permitted. If a patient is currently taking an EIAED, he/she must have discontinued the EIAED therapy for at least 1 week prior to starting study drug. If a patient was previously on a non-EIAED and needs to permanently change anticonvulsant agent but cannot change to another non-EIAED, the patient will be taken off LDK378.

MEK162 arm

The solubility of MEK162 is pH dependent. Long-acting proton pump inhibitors are prohibited and must be discontinued at least 3 days prior to the first dose of study treatment.

6.4 Patient numbering, treatment assignment or randomization

6.4.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for pre-screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the pre-screening Informed Consent, the patient is assigned to the next sequential Subject No. available to the investigator through the Oracle clinical RDC interface.

6.4.2 Treatment assignment or randomization

Approximately 20-25 patients will be assigned to each treatment arm according to their characterized molecular alteration.

6.4.3 Treatment blinding

Not applicable.

[redacted]

6.5 Study treatment preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study treatments as per protocol. Study treatment(s) will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

BYL719/INC280/LDK378/MEK162 arm

Study treatment including instructions for administration are dispensed by study personnel on day 1 of each cycle. Patients will be provided with adequate supply of study treatments.

6.5.1 Study treatment packaging and labeling

The study medication packaging has a 2-part label for BYL719, INC280, LDK378 and MEK162. Site personnel will add the patient number on the label.

Immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug.

6.5.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the study treatment should be stored according to the instructions specified on the drug labels and in the [Investigator's Brochure].

Table 6-3 Supply and storage of study treatments

Study treatments	Doses to be supplied	Storage requirement
BYL719	200mg, 50mg Tablets	Refer to the label of the clinical supplies for expiration date and proper storage conditions
INC280	50mg Capsules / 200 mg, 100 mg*, 150 mg*, 50 mg Tablets	Do not store above 25°C
LDK378	150mg Capsules	Do not store above 25 °C
MEK162	15mg Tablets	Do not store above 25°C Protect from light
*The INC280 100mg tablet and 150 mg tablet usage will depend on the availability of drug supplies and follow by regulatory requirement.		

[redacted]

6.5.3 Study treatment compliance and accountability

6.5.3.1 Study treatment compliance

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.

6.5.3.2 Study treatment 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 Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.5.3.3 Handling of other study treatment

Not applicable.

6.5.4 Disposal and destruction

The study treatment supply can be destroyed at the local Novartis facility, drug supply group or third party, as appropriate.

Study treatment destruction at the investigational site will only be permitted if authorized by Novartis in a prior agreement and if permitted by local regulations.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 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. The tables indicate which assessments produce data to be entered into database (D) or remain in source documents only (S) ("Category" column).

No CRF will be used as a source document.

[redacted]

Visits and schedule windows

Screening/baseline evaluations (including baseline radiological assessment/s) must be performed ≤ 28 days of cycle 1 day 1. Laboratory assessments including hematology, chemistry, coagulation, urinalysis, insulin/glucose monitoring (BYL719 only) and cardiac enzymes (BYL719, LDK378 and MEK162) performed as part of the screening evaluations and within 72 hours of the first dose of study treatment, are not required to be repeated on the first dosing day.

During the course of the study visits, test and/or procedures should occur on schedule whenever possible. A visit window of +/- 3 days is allowed. On days that PK is collected the window is only +/- 1 day. PK sample of C1D1 must be collected at the same day of first dose.

Radiological assessments must be performed +/-7 days of the scheduled date of the assessment.

[redacted]

Table 7-1 Visit evaluation schedule

	Category	Protocol Section	Molecular Pre-screening	Screening	Cycle 1				Cycle 2				Cycle 3 and Subsequent cycles				EOT	30-day safety FU	Disease progression FU	Survival FU
Visit Name			1	2	3	4	5	6	7	8	9	10	11	12 BYL719	13	14 BYL719	Within 14 days of the last dose	30 days after the last dose	Every 8 weeks after the last dose	Every 3 months after the last dose
Day of cycle				-28 to -1	1	8	15	22	1	8	15	22	1	8	15	22	N/A	N/A	N/A	N/A
Obtain Informed Consent																				
Obtain molecular pre-screening Informed Consent	D	7.1.1	X																	
Obtain Informed Consent	D	7.1.2		X																
Patient history																				
Archival or newly obtained tumor sample for assessment	D	7.1.1	X																	
Demography	D	7.1.2.2		X																
Inclusion/exclusion criteria	D	5		X																

[redacted]

	Category	Protocol Section	Molecular Pre-screening	Screening	Cycle 1				Cycle 2				Cycle 3 and Subsequent cycles				EOT	30-day safety FU	Disease progression FU	Survival FU
Visit Name			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12 BYL719**	**13**	**14 BYL719**	**Within 14 days of the last dose**	**30 days after the last dose**	**Every 8 weeks after the last dose**	**Every 3 months after the last dose**
Day of cycle				**-28 to -1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**N/A**	**N/A**	**N/A**	**N/A**
Relevant medical history	D	7.1.2.2		X																
Diagnosis and extent of cancer	D	7.1.2.2		X																
Prior antineoplastic therapy	D	7.1.2.2		X																
Prior/concomitant medications	D	7.1.2.2		X																
Physical examinations																				
Physical examination	S	7.2.2.1		X	X				X				X				X			
Vital signs	D	7.2.2.2		X	X	X	X	X	X		X		X				X			
Height	D	7.2.2.3		X																
Weight	D	7.2.2.3		X	X				X				X				X			
Performance status	D	7.2.2.4		X	X				X				X				X			

[redacted]

	Category	Protocol Section	Molecular Pre-screening	Screening	Cycle 1				Cycle 2				Cycle 3 and Subsequent cycles				EOT	30-day safety FU	Disease progression FU	Survival FU
Visit Name			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12 BYL719**	**13**	**14 BYL719**	**Within 14 days of the last dose**	**30 days after the last dose**	**Every 8 weeks after the last dose**	**Every 3 months after the last dose**
Day of cycle				**-28 to -1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**N/A**	**N/A**	**N/A**	**N/A**
Laboratory assessments																				
Hematology	D	7.2.2.5.1		X	X[1]				X				X				X			
Chemistry	D	7.2.2.5.2		X	X[1]				X				X				X			
Coagulation	D	7.2.2.5.3		X[2]	X[1]												X[2]			
Urinalysis	D	7.2.2.5.4		X	X[1]												X			
Pregnancy test	D	7.2.2.5.5			X												X			
Fasting plasma glucose, insulin, c-peptide, (BYL719)	D	7.2.2.5.6		X	X[1]	X	X	X	X	X	X	X	X	X	X	X	X			
Hemoglobin A1c (BYL719)	D	7.2.2.5.6		X	X[1]								Day1 every three cycles				X			
Cardiac enzymes (BYL719/ LDK378)	D	7.2.2.6.3		X	X[1]												X			

[redacted]

	Category	Protocol Section	Molecular Pre-screening	Screening	Cycle 1				Cycle 2				Cycle 3 and Subsequent cycles				EOT	30-day safety FU	Disease progression FU	Survival FU
Visit Name			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12** **BYL719**	**13**	**14** **BYL719**	**Within 14 days of the last dose**	**30 days after the last dose**	**Every 8 weeks after the last dose**	**Every 3 months after the last dose**
Day of cycle				**-28 to -1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**N/A**	**N/A**	**N/A**	**N/A**
Cardiac enzymes (MEK162)	D	7.2.2.6.3		X	X[1]		X		X		X		X		X		X			
Imaging and other assessment																				
Tumor evaluation	D	7.2.1		X									Every 8 weeks beginning at the start of cycle 3 and as needed to confirm previous response				X (if not conducted within 30 days prior to EOT)		X	
ECG (BYL719/LDK378/MEK162)[3]	D	7.2.2.6.1		X	X		X		X		X		X				X			
ECG (INC280)[3]	D	7.2.2.6.1		X	X				X				X				X			
Cardiac imaging (BYL719)	D	7.2.2.6.2		X													X			
Cardiac imaging (MEK162)	D	7.2.2.6.2		X				X				X	Every 8 weeks following start from C2D22				X			

[redacted]

	Category	Protocol Section	Molecular Pre-screening	Screening	Cycle 1				Cycle 2				Cycle 3 and Subsequent cycles				EOT	30-day safety FU	Disease progression FU	Survival FU
Visit Name			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12 BYL719**	**13**	**14 BYL719**	**Within 14 days of the last dose**	**30 days after the last dose**	**Every 8 weeks after the last dose**	**Every 3 months after the last dose**
Day of cycle				**-28 to -1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**N/A**	**N/A**	**N/A**	**N/A**
Ophthalmology exams (MEK162)	D	7.2.2.7		X			X		X				X				X			
Safety																				
Adverse events	D	8.1	X (procedure related SAEs only)	X	Continuous monitoring during treatment												X	X		
Concomitant medication	D			X	Continuous monitoring during treatment												X	X		

[redacted]

[redacted]

	Category	Protocol Section	Molecular Pre-screening	Screening	Cycle 1				Cycle 2				Cycle 3 and Subsequent cycles				EOT	30-day safety FU	Disease progression FU	Survival FU
Visit Name			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12 BYL719**	**13**	**14 BYL719**	**Within 14 days of the last dose**	**30 days after the last dose**	**Every 8 weeks after the last dose**	**Every 3 months after the last dose**
Day of cycle				**-28 to -1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**N/A**	**N/A**	**N/A**	**N/A**
PK sampling	D	7.2.3			Refer to Table 7-5 to Table 7-12 for PK sampling schedules															
Antineoplastic therapies since discontinuation of study treatment	D	7.1.6																X	X	X
Survival status Follow-up	D	7.1.6																		X

[1] Laboratory assessments including hematology, chemistry, coagulation, urinalysis, insulin/glucose monitoring (BYL719 only) and cardiac enzymes (BYL719, LDK378 and MEK162) performed as part of the screening evaluations and within 72 hours of the first dose of study treatment, are not required to be repeated at C1D1.
[2] Coagulation during screening and EOT will only be performed if a newly obtained tumor sample is collected.
[3] Three sequential 12-lead ECGs, separated by around 2 minutes, must be performed during screening

[redacted]

7.1.1 Molecular pre-screening

Evidence of molecular alterations is required in order to begin clinical screening activities. Written documentation of molecular alterations should be obtained from:

- Local assessment on either a newly obtained tumor sample (preferred) or the most recent archival tumor sample available; central assessment may be applied in the future.
- For the LDK378 arm, patients' tumor sample must be obtained after progression on crizotinib if patient is pre-treated with crizotinib. If tumor sample is not available, patients must be suitable and willing to undergo mandatory biopsy according to treating institution's own guidelines and requirements for such procedure.

Patients must sign the molecular pre-screening consent to allow for the collection and shipment of archival and/or a newly obtained tumor samples to the local laboratory or Novartis designed central laboratory for molecular prescreening purposes. The molecular prescreening purposes could be used for analysis of gene amplification and mutation.

Molecular pre-screening data confirming patient eligibility will be documented in the eCRF if the patient becomes eligible and treated as planned.

In addition and wherever possible the archival and/or newly obtained tumor samples may be used to profile gene alterations and expression of candidate genes related to drug/subject responses, development of resistance mechanisms, or hypothesis generating approaches to delineate responder/non responder populations.

7.1.2 Screening

Patients with NCSLC who have available institutional data demonstrating molecular alterations may begin clinical screening after the main study Informed Consent Form has been signed.

The clinical screening period starts once a patient has provided written informed consent to participate in the study. Screening assessments have to be done within 28 days prior to the first dose of study medication with the exception of pregnancy test, which must be performed within 72 hours before the first dose. Clinical and radiological tumor assessment by RECIST 1.1 (Section 14.1) should be conducted preferably within 1 week (7 days) prior to the first dose of the study treatment; however tumor assessments up to 4 weeks (28 days) prior to the first dose will be acceptable. During screening the disease must be staged. The tumor assessment made during the screening phase will provide the baseline tumor measurements, which will be used to determine future responses and/or progression. A complete list of screening evaluations is provided in the visit of assessments table (Table 7-1). Assessments which are part of the patient's clinical standard of care may be performed before obtaining the ICF, if within the acceptable screening window.

7.1.2.1 Information to be collected on screening failures

Patients who signed a molecular pre-screening ICF but are considered ineligible after molecular pre-screening, as well as patients who are found not eligible after signing the main

study consent will be considered as screening failures, and data will be handled in the same manner.

The reason for molecular pre-screening failure or screening failure will be entered on the Screening Phase Disposition Page. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen Failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the subject experienced a Serious Adverse Event during the Screening Phase (see Section 8 for SAE reporting details). For molecular pre-screening failures, only SAEs possibly related to a study procedure will be reported.

7.1.2.2 Patient demographics and other baseline characteristics

Data will be collected on patient characteristics including demographic information (age, gender, race) and other background or relevant medical history, including history of disease and current disease status, staging, sites of disease, prior anticancer therapies, prior medication/ significant non-drug therapies and any other assessments that are done for the purposes of determining eligibility for inclusion in the study (i.e, ECOG performance status, complete physical examination including neurological assessment, tumor assessment by RECIST, vital signs, hematology, chemistry, 12-lead ECG, and urine pregnancy test).

7.1.3 Treatment period

A treatment cycle is defined as 28 days (4 calendar weeks) for the purposes of scheduling procedures and evaluations. Please refer to Table 7-1 for details of the timing of required assessments and Section 7.1 for visit windows.

Patients will be treated until one of the criteria described in Section 7.1.4.1 is met.

7.1.4 End of treatment visit including study completion and premature withdrawal

At the time patients discontinue study treatment, a visit should be scheduled as soon as possible and within 14 days of the last dose of study treatment or within 14 days of the decision to permanently discontinue study treatment, at which time all of the assessments listed for the End of Treatment (EOT) visit will be performed. If the decision to withdraw the patient occurs at a regularly scheduled visit, that visit may become the EOT visit rather than having the patient return for an additional visit.

An End of Treatment Phase Disposition Page should be completed, giving the date and reason for stopping the study treatment. If a withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the EOT eCRF page.

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 discontinue from the study treatment for any reason at any time. If a patient decides to discontinue from the study treatment, the investigator must make every

[redacted]

effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information in the patient's chart and on the appropriate CRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

The investigator should discontinue study treatment for a given patient if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

Study treatment may be discontinued under the following circumstances:

- Adverse event
- Death
- Progressive Disease
- Pregnancy
- Protocol deviation
- Study terminated by sponsor
- Technical problems
- Lost to follow-up
- Physician decision
- Subject/ guardian decision

Patients who discontinue study treatment should undergo an end of treatment visit and then enter the follow-up period.

7.1.4.2 Replacement policy

No replacement will be needed.

7.1.5 Withdrawal of Consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact.

Novartis will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date (or as required by local regulations).

If a patient withdraws consent, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information. Study treatment must be discontinued and no further assessments conducted.

Further attempts to contact the patient are not allowed unless safety findings require communication or follow up.

[redacted]

7.1.6 Follow up period

30-day safety follow-up

All patients must have safety evaluations for 30 days. AEs will be assessed (contact by telephone is permitted) until 30 days following the last dose of study treatment or start of new anticancer therapy. All concomitant medications given to a patient as a result of an AE experience during this period will be recorded on the concomitant medication eCRF page. All cancer medications/therapies given to a patient ≤ 30 days after the last dose of study treatment must be recorded on the antineoplastic therapies since discontinuation of study treatment eCRF.

Disease progression follow-up

Any patient who discontinues from study treatment for any reason (except for death, disease progression, lost to follow-up, or study termination) will continue to have tumor assessments performed every 8 weeks in the follow-up period until disease progression or start of new anticancer therapy.

Survival follow-up

Patients will be contacted (telephone is permitted) for survival status every 3 months from last dose until death, lost to follow-up, withdrawal of consent or study end (See Section 4.3 for details). All cancer medications/therapies given to a patient during follow-up period will be collected.

Patients lost to follow up should be recorded as such on the CRF. 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.

7.1.7 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow up should be recorded as such on the appropriate Disposition CRF.

[redacted]

7.2 Assessment types

7.2.1 Efficacy assessments

Table 7-2 Imaging collection plan

Procedure	Screening/Baseline	During Treatment/Follow-up
CT or MRI with contrast enhancement (Chest, Abdomen, Pelvis)	Mandated	Mandated, every 8 weeks (±7 days)
Whole bone scintigraphy	If clinically indicated	Not applicable
Brain CT or MRI	Mandated	If clinically indicated
Bone X-ray or CT / MRI (bone lesions only)	If hot spots on bone scintigraphy	If bone lesions at screening every 8 weeks (±7 days)
Skin color Photography (skin lesions only)	Mandated if skin lesions at screening	If skin lesions at screening

Tumor response will be determined locally according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Section 14.1). The local investigator's assessment will be used for the primary endpoint analysis and for treatment decision making.

CT/MRI scans will be performed at baseline within 28 days (preferably 7 days) before start of treatment and subsequently every 8 weeks from start of cycle 3 until progression of disease. See Table 7-1 and Table 7-2 for details. CT/MRI scan will be performed at EOT if not conducted within 30 days prior to EOT. Disease progression follow-up should be performed as described in Section 7.1.6.

After baseline, all assessments should be performed within ±7 days of the scheduled day of assessment. Imaging evaluations subsequent to an off-schedule confirmatory scan, should be performed according to the original assessment schedule. The same method of assessment and the same technique should be used to characterize each individual and reported lesion at baseline and during follow up.

All patients will undergo CT/MRI scan of the chest, abdomen and pelvis at screening/baseline and every 8 weeks thereafter. If at baseline a patient has a medical contraindication to CT i.v. contrast or develops a contraindication during the trial, a non-contrast CT of chest plus contrast-enhanced MRI of abdomen and pelvis is acceptable.

Patients with clinical evidence of bone metastases must have a whole body bone scan at baseline per local institutional practice. Hot spots identified on the whole body scintigraphy at baseline, which are not visible on the chest, abdomen and pelvis CT (or MRI) scan should be imaged at baseline and followed at subsequent scheduled visits using localized CT, MRI or X-ray. After baseline, whole body scintigraphy need not be repeated, unless clinically indicated.

Skin lesions present at baseline should be documented using color photography, including a ruler, so that the size of the lesion(s) can be determined from the photograph. Skin photographs should be continued at subsequent tumor assessments for any lesions that were photographed at screening.

[redacted]

Baseline Brain CT or MRI will be mandated for all patients prior to study treatment. Subsequent brain scans should only be conducted in patients that develop symptoms indicative of brain metastases.

All CRs and PRs must be confirmed by a second assessment not earlier than 4 weeks later and ideally no later than 5 weeks after the criteria for response are first met.

PET/CT may be used only if the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of oral and intravenous contrast media.

7.2.2 Safety and tolerability assessments

7.2.2.1 Physical examination

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

A short physical exam will include the examination of general appearance and vital signs (blood pressure [BP] and pulse). A short physical exam will be at all visits starting from Visit 3 except when it is clinically indicated.

7.2.2.2 Vital signs

Vital signs including blood pressure and pulse measurements will be collected before dosing at the clinic. After the patient has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

7.2.2.3 Height and weight

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

7.2.2.4 Performance status

ECOG performance status will be assessed.

Table 7-3 ECOG performance status

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

[redacted]

7.2.2.5 Laboratory evaluations

Table 7-4 Local Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, WBC Morphology with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)
Chemistry	Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Calcium, Magnesium, phosphorous, Potassium, Chloride, Creatinine, Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Serum amylase, Serum lipase , fasting plasma glucose, GGT
Urinalysis	Dipstick measurements for specific gravity, pH, protein, glucose, bilirubin, ketones, leukocytes, and blood will be performed. Any clinically significant findings on dipstick will be followed up with a microscopic evaluation.
Coagulation	Prothrombin time (PT) or International normalized ratio [INR]), Activated partial thromboplastin time (APTT)
Glucose and insulin monitoring (only for BYL719)	Fasting plasma glucose, insulin, c-peptide, Hemoglobin A1c
Tests for hepatotoxicity follow-up (if clinically indicated for INC280)	LFTs: albumin, ALT, AST, GGT, total bilirubin, direct and indirect bilirubin, ALP ALP fractionated (quantification of isoforms) Creatine kinase, prothrombin time (PT)/INR Testing for acute hepatitis A, B, C or E infection, other hepatotropic viral infection and autoimmune hepatitis as clinically indicated (refer to Section 14.3.2)

A local laboratory will be used for analysis of all specimens collected.

7.2.2.5.1 Hematology

Hematology panel outlined in Table 7-4 will be performed as per the assessment schedule in Table 7-1.

7.2.2.5.2 Clinical chemistry

Chemistry panel outlined in Table 7-4 will be performed as per the assessment schedule in Table 7-1.

7.2.2.5.3 Coagulation

Coagulation panel outlined in Table 7-4 will be performed as per the assessment schedule in Table 7-1. A coagulation profile must be performed within 72 hours prior to tumor biopsies. Coagulation during screening and EOT will only be performed if a newly obtained tumor sample will be collected.

7.2.2.5.4 Urinalysis

Urinalysis panel outlined in Table 7-4 will be performed as per the assessment schedule in Table 7-1.

7.2.2.5.5 Pregnancy and assessments of fertility

Pregnancy tests will be performed as per the assessment schedule in Table 7-1.

[redacted]

All women of childbearing potential must complete a urine pregnancy test at the screening visit, within 72 hours prior to first administration of the study treatment (Cycle 1 Day 1) and at EOT.

Women who are not of childbearing potential do not require a pregnancy test, but must fulfill the conditions for the non-childbearing status given in Section 5.3, point 12. In case of pregnancy, the patient must permanently stop study treatment immediately, withdraw from the trial, and the pregnancy must be reported on the Clinical Trial Pregnancy Form.

7.2.2.5.6 Glucose/insulin monitoring (BYL719)

Fasting serum insulin, fasting serum C-peptide and fasting plasma glucose (FPG) for insulin and glucose safety monitoring will be assessed pre-dose prior to the light breakfast at least once weekly. Patients must be fasting overnight for at least 8 hours. Additional measurements may be performed as clinically indicated. Hemoglobin A1c testing for hyperglycemia will be assessed at the schedule in Table 7-1.

7.2.2.6 Cardiac assessments

7.2.2.6.1 Electrocardiogram (ECG)

Standard 12 lead ECG will be performed as per the assessment schedule in Table 7-1. The unscheduled ECG will be performed in case of any signs and/ or symptoms as judged by the investigator. For all patients, 3 sequential 12-lead ECGs, separated by approximately 2 minutes, must be performed during screening. This is necessary to get an accurate baseline QTcF calculation. One single ECG will be performed for the other time-points during the trial and QTcF is used to correct the QT intervals.

Interpretation of the tracing must be made by a qualified physician and documented on the ECG CRF page. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept in the source documents at the study site. ECGs may be sent to a Novartis designated laboratory for retrospective central review in additional to the local review in case it is needed to further confirm the cardiac safety of the study treatment(s). All eligibility and patient management decisions should be made based on the local reading of the ECG.

7.2.2.6.2 Cardiac imaging - MUGA (multiple gated acquisition) scan or echocardiogram (BYL719/MEK162)

For BYL179 arm:

A MUGA or ECHO scan should be performed during screening and at EOT to assess the left ventricular ejection fraction (LVEF). These cardiac imaging assessments may be repeated during treatment only if clinically indicated.

For MEK162 arm:

A MUGA or ECHO scan should be performed during screening, C1D22, C2D22, following with every 8 weeks at the beginning of C2D22 and at EOT to assess the left ventricular

[redacted]

ejection fraction (LVEF). These cardiac imaging assessments may be repeated during treatment only if clinically indicated.

7.2.2.6.3 Cardiac enzymes (BYL719/LDK378/MEK162)

BYL719 and LDK378

Cardiac enzymes troponin-I or troponin-T will be collected per the assessment schedule in Table 7-1. These parameters should be assessed during treatment only if clinically indicated.

MEK162

CK and troponin (troponin-I or troponin-T) will be assessed per the assessment schedule in Table 7-1. If CK ≥3x ULN, a weekly follow up of isoenzymes, and myoglobin in blood and urine will be done, and troponin as applicable.

7.2.2.7 Ophthalmology exams (MEK162)

MEK162

Full ophthalmic examination including slit lamp examination, visual acuity testing, visual field testing, intraocular pressure (IOP) and indirect fundoscopy with attention to retinal abnormalities, especially central serous retinopathy and RVO, will be performed per the assessment schedule in Table 7-1.

For patients with clinical suspicion of central serous retinopathy or RVO, additional assessments of fluorescein angiography and/or optical coherence tomography and Electroretinogram (ERG) are recommended.

7.2.3 Pharmacokinetics

PK parameters will be estimated from each individual plasma concentration-time profile using non-compartmental analysis (Phoenix software version 6.2 and above). PK parameters to be evaluated are included in the statistical and data analysis section of this protocol (Section 10.5.3).

[redacted]

7.2.3.1 Pharmacokinetic blood collection and handling

Serial intensive PK blood samples will be collected from at least 12 patients from BYL719 arm, at least 6 patients treated with INC280 tablet, and at least 6 patients from other treatment arms for the analysis of the plasma concentration of each drug. Sparse PK blood samples will be collected in the rest of the patients from each treatment arm. 3ml blood sample will be collected on each time point.

If patients experience a serious adverse event or an adverse event leading to the discontinuation of the study treatment as per definition in Section 7.1.4.1, an unscheduled PK blood sample should be obtained whenever possible and the date and time of the last dose

[redacted]

should be recorded. In addition, the unscheduled PK sample should also be collected in case the patient performs the unscheduled ECG as per the Section 7.2.2.6.1.

On the day of PK sampling, if vomiting occurs within 4 hours following oral drug administration of BYL719, INC280, LDK378 and MEK162, the occurrence of vomiting and time will be recorded on the PK sampling page of eCRF.

Please refer to Table 7-5 to Table 7-8 for intensive blood collection schedule, and Table 7-9 to Table 7-12 for sparse PK blood collection schedule for each treatment arm.

Complete instructions for blood collection, handling and shipment of PK samples for each compound will be provided in the [Laboratory Manual].

Table 7-5 Intensive pharmacokinetic blood collection log for BYL719

Treatment Cycle	Day	Scheduled Time Point	Dose Reference ID BYL719	PK Sample No BYL719	Description
1	1	Pre-dose	201	201	Before dose on Cycle 1, Day 1
1	1	0.5 hours ± 10 minutes	201	202	
1	1	1 hours ± 10minutes	201	203	
1	1	2 hours ± 10 minutes	201	204	
1	1	4 hours ± 30 minutes	201	205	
1	1	6 hours ± 1 hour	201	206	
1	1	8 hours ± 1 hour	201	207	
1	2	24 hours ± 2 hours [c]	201 [a] / 2001 [b]	208	Before dose on Cycle 1, Day 2
1	15	Pre-dose [c]	202 [b] / 2002 [a]	209	Before dose on Cycle 1, Day 15
1	15	0.5 hours ± 10 minutes	202	210	
1	15	1 hours ± 10 minutes	202	211	
1	15	2 hours ± 30 minutes	202	212	
1	15	4 hours ± 30 minutes	202	213	
1	15	6 hours ± 1 hour	202	214	
1	15	8 hours ± 1 hour	202	215	
1	16	24 hours ± 2 hours [c]	202 [a] / 2003 [b]	216	Before dose on Cycle 1, Day 16
2	1	Pre-dose [c]	203 [a] / 2004 [b]	217	Before dose on Cycle 2, Day 1
3	1	Pre-dose [c]	204 [a] / 2005 [b]	218	Before dose on Cycle 3, Day 1
		Unscheduled		2101+[d]	

Intensive PK blood collection will be performed in at least 12 patients from BYL719 treatment arm
[a] dose administration record before PK sampling;
[b] dose administration record after PK sampling;
[c] PK sample should be collected before next dose schedule
[d] Unscheduled PK sample number starts from 2101

[redacted]

Table 7-6 Intensive pharmacokinetic blood collection log for INC280

Treatment Cycle	Day	Scheduled Time Point	Dose Reference ID INC280	PK Sample No INC280	Description
1	15	Pre-dose [c]	301[b]/ 3001[a]	301	Before morning dose on Cycle 1, Day 15
1	15	0.5 hour ± 10 minutes	301	302	
1	15	1 hour ± 10 minutes	301	303	
1	15	2 hours ± 10 minutes	301	304	
1	15	4 hours ± 30 minutes	301	305	
1	15	6 hours ± 1 hour	301	306	
1	15	8 hours ± 1 hour	301	307	
2	1	Pre-dose [c]	302 [a] / 3002 [b]	308	Before morning dose on Cycle 2, Day 1
3	1	Pre-dose [c]	303 [a] / 3003 [b]	309	Before morning dose on Cycle 3, Day 1
		Unscheduled		3101+[d]	

Intensive PK blood collection will be performed in at least 6 patients from INC280 treatment arm
[a] dose administration record before PK sampling;
[b] dose administration record after PK sampling;
[c] PK sample should be collected before next dose schedule
[d] Unscheduled PK sample number starts from 3101

Table 7-7 Intensive pharmacokinetic blood collection log for LDK378

Treatment Cycle	Day	Scheduled Time Point	Dose Reference ID LDK378	PK Sample No LDK378	Description
1	15	Pre-dose [c]	401[b]/ 4001[a]	401	Before dose on Cycle 1, Day 15
1	15	0.5 hour ± 10 minutes	401	402	
1	15	1 hour ± 10 minutes	401	403	
1	15	2 hour ± 10 minutes	401	404	
1	15	4 hours ± 30 minutes	401	405	
1	15	6 hours ± 1 hour	401	406	
1	15	8 hours ± 1 hour	401	407	
1	16	24 hours ± 2 hours	401 [a] / 4002 [b]	408	Before dose on Cycle 1, Day 16
2	1	Pre-dose [c]	402 [a] / 4003 [b]	409	Before dose on Cycle 2, Day 1
3	1	Pre-dose [c]	403 [a] / 4004 [b]	410	Before dose on Cycle 3, Day 1
		Unscheduled		4101+[d]	

Intensive PK blood collection will be performed in at least 6 patients from LDK378 treatment arm
[a] dose administration record before PK sampling;
[b] dose administration record after PK sampling;
[c] PK sample should be collected before next dose schedule
[d] Unscheduled PK sample number starts from 4101

[redacted]

Table 7-8 Intensive pharmacokinetic blood collection log for MEK162

Treatment Cycle	Day	Scheduled Time Point	Dose Reference ID MEK162	PK Sample No MEK162	Description
1	15	Pre-dose [c]	501[b]/ 5001[a]	501	Before morning dose on Cycle 1, Day 15
1	15	0.5 hour ± 10 minutes	501	502	
1	15	1 hour ± 10 minutes	501	503	
1	15	2 hours ± 10 minutes	501	504	
1	15	4 hours ± 30 minutes	501	505	
1	15	6 hours ± 1 hour	501	506	
1	15	8 hours ± 1 hour	501	507	
2	1	Pre-dose [c]	502 [a] / 5002 [b]	508	Before morning dose on Cycle 2, Day 1
3	1	Pre-dose [c]	503 [a] / 5003 [b]	509	Before morning dose on Cycle 3, Day 1
		Unscheduled		5101+[d]	

Intensive PK blood collection will be performed in at least 6 patients from MEK162 treatment arm
[a] dose administration record before PK sampling;
[b] dose administration record after PK sampling;
[c] PK sample should be collected before next dose schedule
[d] Unscheduled PK sample number starts from 5101

Table 7-9 Sparse pharmacokinetic blood collection log for BYL719

Treatment Cycle	Day	Scheduled Time Point	Dose Reference No BYL719	PK Sample No BYL719	Description
1	15	Pre-dose [c]	251[b]/ 2051[a]	251	Before dose on Cycle 1, Day 15
	15	2 hours ± 30 minutes	251	252	
	15	6 hours ± 1 hour	251	253	
	16	24 hours ± 2 hours [c]	251 [a] / 2052 [b]	254	Before dose of Cycle 1, Day 16
2	1	Pre-dose [c]	252 [a] / 2053 [b]	255	Before dose of Cycle 2, Day 1
3	1	Pre-dose [c]	253 [a] / 2054 [b]	256	Before dose of Cycle 3, Day 1
		Unscheduled		2501+[d]	

[a] dose administration record before PK sampling;
[b] dose administration record after PK sampling;
[c] PK sample should be collected before next dose schedule
[d] Unscheduled PK sample number starts from 2501

Table 7-10 Sparse pharmacokinetic blood collection log for INC280

Treatment Cycle	Day	Scheduled Time Point	Dose Reference No INC280	PK Sample No INC280	Description
1	15	Pre-dose [c]	351[b]/ 3051[a]	351	Before morning dose on Cycle 1, Day 15
1	15	2 hour ± 30 minutes	351	352	
1	15	6 hours ± 1 hour	351	353	

[redacted]

Treatment Cycle	Day	Scheduled Time Point	Dose Reference No INC280	PK Sample No INC280	Description
2	1	Pre-dose [c]	352 [a] / 3052 [b]	354	Before morning dose on Cycle 2, Day 1
3	1	Pre-dose [c]	353 [a] / 3053 [b]	355	Before morning dose on Cycle 3, Day 1
		Unscheduled		3501+[d]	

[a] dose administration record before PK sampling;
[b] dose administration record after PK sampling;
[c] PK sample should be collected before next dose schedule
[d] Unscheduled PK sample number starts from 3501

Table 7-11 Sparse pharmacokinetic blood collection log for LDK378

Treatment Cycle	Day	Scheduled Time Point	Dose Reference No LDK378	PK Sample No LDK378	Description
1	15	Pre-dose [c]	451[b]/ 4051[a]	451	Before dose on Cycle 1, Day 15
1	15	2 hours ± 30 minutes	451	452	
1	15	6 hours ± 1 hour	451	453	
2	1	Pre-dose [c]	452 [a] / 4052 [b]	454	Before dose on Cycle 2, Day 1
3	1	Pre-dose [c]	453 [a] / 4053 [b]	455	Before dose on Cycle 3, Day 1
		Unscheduled		4501+[d]	

[a] dose administration record before PK sampling;
[b] dose administration record after PK sampling;
[c] PK sample should be collected before next dose schedule
[d] Unscheduled PK sample number starts from 4501

Table 7-12 Sparse pharmacokinetic blood collection log for MEK162

Treatment Cycle	Day	Scheduled Time Point	Dose Reference No MEK162	PK Sample No MEK162	Description
1	15	Pre-dose [c]	551[b]/5051[a]	551	Before morning dose on Cycle 1, Day 15
1	15	2 hours ± 30 minutes	551	552	
1	15	6 hours ± 1 hour	551	553	
2	1	Pre-dose [c]	552 [a] / 5052 [b]	554	Before morning dose on Cycle 2, Day 1
3	1	Pre-dose [c]	553 [a] / 5053 [b]	555	Before morning dose on Cycle 3, Day 1
		Unscheduled		5501+[d]	

[a] dose administration record before PK sampling;
[b] dose administration record after PK sampling;
[c] PK sample should be collected before next dose schedule
[d] Unscheduled PK sample number starts from 5501

[redacted]

7.2.3.2 Analytical method

Concentrations of BYL719, LDK378, INC280 and MEK162 will be measured in plasma with valid liquid chromatography-tandem mass spectrometry (LC-MS/MS) assays. LLOQs are 1 ng/mL for BYL719, LDK378, INC280 and MEK162. Any results below the LLOQ and missing samples will be labeled accordingly.

[redacted]

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

[redacted]

AEs which occur after signature of molecular pre-screening ICF will only be captured if they meet the definition of serious as outlined in Section 8.2 and are reported to be causally related with study procedures (e.g. an invasive procedure such as biopsy). Once the main study ICF is signed, all AEs per the descriptions below will be captured in the Adverse Event CRF.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

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

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to grades 1 - 4, will be used. CTCAE grade 5 (death) will not be used in this study but is collected as a seriousness criteria ; rather, information about deaths will be collected though a Death form.

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

1. The severity grade (CTCAE Grade 1-4)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown)
7. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1, and which seriousness criteria have been met.

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

[redacted]

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors or as per Cheson's guidelines for hematological malignancies), 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.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. 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. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. 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 in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

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,

[redacted]

- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - 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
  - 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
- Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors or as per Cheson's guidelines for hematological malignancies), 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.

8.2.2 Reporting

SAE collection will start upon signing the molecular pre-screening ICF. SAEs will only be reported if the event is suspected to be causally related to a study procedure as assessed by the investigator (e.g. an invasive procedure such as biopsy). SAEs will be followed until resolution or until clinically relevant improvement or stabilization. If the main ICF is not signed (molecular screen failure), SAE collection ends 30 days after the last study related procedure.

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided main informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. 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 is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and submit the completed form within 24 hours Novartis. Detailed

[redacted]

instructions regarding the submission process and requirements for signatures are to be found in the investigator folder provided to each site.

Follow-up information is submitted in the same way as the original SAE Report. 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. The follow-up information 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.

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 Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis 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 Emergency unblinding of treatment assignment

Not applicable.

8.4 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis 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 oncology Novartis Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

8.5 Warnings and precautions

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

[redacted]

8.6 Data Monitoring Committee

Due to the exploratory nature of this phase II study, an independent data monitoring committee will not be constituted. Individual patient safety data and aggregate safety data will be reviewed on an ongoing basis. Meanwhile, the efficacy data (ORR and the other efficacy endpoints) will be monitored by the study team across the duration of the trial. The safety and efficacy data review will be based on the available investigator reported data in the clinical database at the respective times. The data will be discussed with investigators in teleconferences. In case of having sufficient evidence of lack of efficacy for a study drug, Novartis and the investigator parties must reach a consensus on whether to terminate further patient enrolment in the treatment group.

9 Data collection and management

9.1 Data confidentiality

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

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

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject 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 (Subject 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 Subject Initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the subject satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

[redacted]

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis 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. Novartis 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

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

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

PK [redacted] samples drawn during the course of the study will be collected from the investigator sites and analyzed by designated Novartis Laboratories. The site staff designated by the investigator will enter the information required by the protocol onto the PK [redacted] Sample Collection eCRFs, respectively, as well as the designated CRO's requisition forms. The field monitor will review the relevant eCRFs for accuracy and completeness and will work with the site staff to adjust any discrepancies as required. The field monitor will also review the requisition forms for completeness.

9.4 Database management and quality control

Novartis 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

[redacted]

investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments 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 for PK sampling [redacted] will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO). ECGs may be reviewed retrospectively by a Novartis designated ECG laboratory and the results will be sent to Novartis. At the conclusion of the study, the occurrence of any protocol violations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked and made available for data analysis. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Global Head of Biostatistics and Data Management and the Global Head of Clinical Development.

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

Data will be summarized with respect to demographic and baseline characteristics, efficacy and safety observations and measurements and all relevant PK and PD measurements using descriptive statistics (quantitative data) and contingency tables (qualitative data).

The five treatment arms will be analyzed separately. For each treatment arm the primary analysis will be conducted on all patient data at the time when all patients of the respective treatment arm have potentially completed at least six cycles of treatment or discontinued the study. The results of the primary analyses of the four treatment arms will be reported in a single primary CSR. Any additional data for patients continuing to receive study treatment past the data cut-off date for the respective primary analysis, as allowed by the protocol, will be reported on end of study (12 months after LPLV) in a single final CSR.

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 as described in Section 7.1.2.2, will not be included in any analysis, but will be reported in a separate listing.

[redacted]

10.1 Analysis sets

10.1.1 Full Analysis Set

For each treatment arm the Full Analysis Set (FAS) comprises all patients who received at least one dose of the respective study treatment. 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

For each treatment arm the Safety Set includes all patients who received at least one dose of the respective study medication and had at least one valid post-baseline safety assessment. Please note: A **"no"** to indicate that the 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
- If the assigned treatment was never received, then the first treatment received when starting therapy with study treatment will be used for classification

The safety set will be used for the safety summary of the study.

10.1.3 Per-Protocol Set

For each treatment arm the Per-Protocol Set (PPS) consists of a subset of the patients in the respective FAS who are compliant with requirements of the clinical study protocol (CSP).

Protocol deviations potentially leading to exclusion from the PPS are:

- type of indication different from those required in Section 5 (e.g., incorrect histology/cytology, incorrect molecular alteration etc.)
- prior therapy does not match with requirements in Section 5 in terms of number and types of previous therapy regimens
- missing or incomplete documentation of stage of disease
- ECOG>2
- another anti-neoplastic therapy administered after start of study treatment and prior to first tumor assessment
- study treatment received different from treatment assigned
- patient without measurable lesions

Any other protocol deviations leading to exclusion from the PPS will be described in the RAP prior to clinical database lock.

10.1.4 Pharmacokinetic analysis set

For each treatment arm the pharmacokinetic analysis set (PAS) consists of all patients who have at least one sample providing evaluable PK.

[redacted]

The PAS will be used for summaries of PK data (tables and figures) as well as for listings of derived parameters.

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 analysis along with the reason for their removal.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data, including age, gender, height, weight, medical condition, disease characteristics etc., will be summarized descriptively by treatment arm.

10.3 Treatments (study treatment, concomitant therapies, compliance)

10.3.1 Study treatment

For each treatment arm the actual dose and duration in days of study 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 actual dose intensity and planned dose intensity) will be listed and summarized by means of descriptive statistics in the CSR. Categories for relative dose intensity 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.

10.3.2 Concomitant therapies

For each treatment arm concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed by patient and summarized by ATC (anatomical therapeutic chemical classification system) term.

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 arm. Compliance to each of the study treatments will be assessed by the number of dose reductions and dose interruptions, see Section 10.5.

10.4 Primary objective

The primary objective is to investigate the anti-tumor activity of single agent BYL719, INC280, LDK378 and MEK162 in Chinese patients with advanced NSCLC carrying specific molecular alterations.

10.4.1 Variable

The primary endpoint is ORR per RECIST v1.1 (Section 14.1).

For each treatment arm, individual lesion measurements and overall response at each assessment will be listed by patient, from which the best overall response (BOR) will be derived for all patients according to RECIST v1.1. The ORR is the proportion of patients with BOR of either CR or PR among all patients in the respective FAS.

[redacted]

Patients with symptoms of rapidly progressing disease without radiologic evidence will be classified as progression only when clear evidence of clinical deterioration is documented and/or patient discontinued due to 'Disease progression' or death due to study indication.

10.4.2 Statistical hypothesis, model, and method of analysis

A Bayesian approach will be used to estimate ORR and to provide inferential statements in each arm.

For INC280, BYL719 and MEK162, a minimally informative unimodal Beta prior distribution for each arm i with parameters a_i and b_i (Neuenschwander et al. 2010) that reflects the degree of uncertainty around ORR before starting the current trial was elicited. Based on prior clinical assumption, the prior median of ORR of each treatment arm is obtained. If the prior median ORR is smaller than 50%, b_i=1 and a_i=ln(0.5)/ln(median$_i$); otherwise a_i=1 and b_i=ln(0.5)/ln(1-median$_i$). The values of prior median$_i$, a_i and b_i for the three treatment arms are listed in Table 10-1.

For BYL719 arm, based on the assumption that similar response is expected in adenocarcinoma and squamous cell carcinoma patients, primary analyses will be done using the pooled data from these two subgroups of patients.

For the LDK378 treatment arms, a mixture of prior distributions with this component (also listed in Table 10-1) will be used:

- [CLDK378X2101], [CLDK378X1101] and [CLDK378X2201] for the LDK378 treatment am); In order to reflect potential variability of the heterogeneity between trials, the heterogeneity parameter τ was given a half-normal distribution with scale 0.5. This distribution is right skewed with median 0. 34 and 95% probability interval (0.016-1.12). It allows the heterogeneity to vary from small to large but at the same time gives small probability to very large values of tau (tau > 1) .This component receives a prior weight of 80%.
- The second minimally informative component is derived as described above for INC280, BYL719 and MEK162 treatment arms, and receives a prior weight of 20%.

At time of analysis for each treatment arm the respective prior distribution will be updated with all available data from patients in the respective FAS. Once updated, the posterior risks that the true ORR lies in the following efficacy intervals will be provided:

- [0, L_i) unacceptable efficacy
- [L_i, M_i) limited efficacy
- [M_i, 100%] clinically relevant efficacy

The values of thresholds L_i and M_i for the five treatment arms are listed in Table 10-1. If the estimated ORR in arm i is equal to or greater than M_i and the posterior risk of being in the unacceptable efficacy category is lower than 5%, then preliminary activity of the respective study treatment will be declared. Otherwise, the inferential summaries for the 3 categories above will be assessed for further characterization of the efficacy. For each treatment arm, the estimated ORR will be taken from the median value of the respective posterior distribution.

[redacted]

Table 10-1 Parameters of prior distributions and thresholds for posterior distributions of ORR

Arm		Prior distribution				Threshold	
i	Component	a	b	Median	90% Credible interval	L_i	M_i
1. LDK378	1** (80%)	6.9374	5.2562	57%	(34%, 79%)	40%	55%
	2 (20%)	1	0.7565	60%	(7%, 98%)		
	Mixture			58%	(26%, 87%)		
2. INC280	1	0.3654	1	15%	(0.03%, 87%)	7.5%	17.5%
3. MEK162	1	0.3654	1	15%	(0.03%, 87%)	7.5%	17.5%
4. BYL719	1	0.3654	1	15%	(0.03%, 87%)	7.5%	17.5%

** Component derived from MAP approach. Based on [CLDK378X1101] data with 2 responders in 5 patients at 750 mg QD, with cut-off date of 29-Apr-2013, and [CLDK378X2101] data with 47 responders in 78 patients at 750 mg QD, with cut-off date of 28-Feb-2013. This component received 80% weight and will be updated with additional data prior to the final analysis.

In addition, for each treatment arm the mean, median, and two-sided 90% credible interval for ORR from the posterior distribution will be presented.

10.4.3 Handling of missing values/censoring/discontinuations

Missing data will simply be noted as missing on appropriate tables/listings. Patients with missing best overall response will be considered as non- responders for the primary ORR analysis.

10.4.4 Supportive analyses

- For each treatment arm the Bayesian posterior estimate of median and two-sided 90% credible interval of ORR will be presented using PPS, if PPS is different from FAS.
- For each treatment arm, individual tumor lesion assessments will be listed along with the overall response by assessment. BOR will be listed by patient and summarized with frequency and percentage, together with the observed ORR and frequentist exact two-sided 90% confidence interval.
- For BYL719 arm, BOR summaries may also be provided by subtypes of cancer (e.g. lung adenocarcinoma and lung squamous cell carcinoma)

10.5 Secondary objectives

10.5.1 Secondary efficacy objectives

The secondary efficacy objective of this study is to further estimate clinical activity of single agent BYL719, INC280, LDK378 and MEK162 in Chinese patients with advanced NSCLC carrying specific molecular alterations. Tumor response will be evaluated based on RECIST v1.1 (Section 14.1). Disease control rate (DCR), duration of response, PFS and OS will be assessed and analyzed as follows:

- DCR is defined as the proportion of patients with a BOR of CR, PR or SD at any time on study. For each treatment arm the observed DCR with exact two-sided 90% confidence interval will be presented.

[redacted]

- Duration of overall response is defined as the time from the first documented CR or PR (confirmed by the subsequent assessment) to the date of the first documented progression or death due to underlying cancer. 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. If a patient has not experienced a documented progression or death due to underlying cancer, duration of overall response is censored at the date of the last adequate tumor assessment. If a patient discontinued trial treatment and received a new anti-neoplastic therapy prior to disease progression, duration of overall response is censored at the start date of the new therapy. The Kaplan-Meier curve, median and quartile will be presented if a sufficient number of responses is observed. For each treatment arm the subset of patients with documented CR or PR in FAS will be used.
- PFS is defined as the time from start of study treatment to the date of the first documented progression or death due to any cause. 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. If a patient has not experienced a documented progression or death, PFS is censored at the date of the last adequate tumor assessment. If a patient discontinued trial treatment and received a new anti-neoplastic therapy prior to disease progression, PFS is censored at the start date of the new therapy. The Kaplan-Meier estimate of PFS distribution function will be presented graphically using FAS. The resulting median and quartile estimates will be provided along with two-sided 90% confidence intervals.
- OS is defined as the time from start of study treatment to date of death due to any cause. If a patient is not known to have died, OS will be censored at the date of the last contact. The Kaplan-Meier estimate of OS distribution function will be presented graphically using FAS. The resulting median and quartile estimates will be provided along with two-sided 90% confidence intervals.

For BYL719 arm, based on the assumption that similar response is expected in adenocarcinoma and squamous cell carcinoma patients, analyses for the secondary endpoints will be done using the pooled data from these two subgroups of patients. However, separate analyses by these two subgroups may also be performed.

10.5.2 Safety objectives

The safety objective of this study is to characterize the safety and tolerability of single agent BYL719, INC280, LDK378 and MEK162 in Chinese patients with advanced NSCLC carrying specific molecular alterations.

10.5.2.1 Analysis set and grouping for the analyses

Listings of AEs will be provided based on the FAS. For all safety analyses, the safety set will be used unless otherwise specified. All listings and tables will be presented for each treatment arm separately.

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

[redacted]

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 or upon disease progression or initiating a new antineoplastic therapy, whichever occurs first.
3. post-treatment period: starting at day 31 after last dose of study medication, or at date of disease progression or initiating a new antineoplastic therapy.

10.5.2.2 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, using safety set.

However, all safety data (including those from the pre and post-treatment periods) will be listed using FAS and those collected during the pre-treatment and post-treatment period are to be flagged.

For each treatment arm the incidence of treatment-emergent AEs (new or worsening from baseline) will be summarized by system organ class and/or preferred term, severity (based on CTCAE grades), type of AE, relation to study treatment.

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

Specific safety event categories (SEC) might be considered. Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment(s).

For each specified SEC, number and percentage of patients with at least one event part of the SEC might be reported.

10.5.2.3 Laboratory abnormalities

For laboratory tests covered by the 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.

For each treatment arm the following summaries will be generated separately for hematology, biochemistry, urinary and coagulation laboratory tests:

- frequency table for newly occurring on-treatment grades 3 or 4 using the safety set
- shift tables using CTCAE grades to compare baseline to the worst on-treatment value using the safety set
- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high) using the safety set
- listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges using the FAS.

[redacted]

In addition to the above mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the RAP.

10.5.2.4 Other safety data

ECG

If available, central ECG data will be used for all ECG summary tables and analyses.

The following reports will be produced:

- 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

Definitions of notably abnormal results will be given in the RAP. The following reports will be produced:

- 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.
  - Both local and central (if collected) ECG data will be listed.

Additional glucose/insulin monitoring for BYL719 treatment arm

Additional safety assessments include fasting serum insulin, fasting serum C-peptide, fasting plasma glucose and hemoglobin A1c (Section 7.2.2.5.6). The data will be listed with notable values being flagged. Summary tables with descriptive statistics will be presented for raw assessments and for changes from baseline at each time points.

Additional safety assessments for BYL719/LDK378/MEK162 treatment arms

Additional safety assessments include cardiac imaging (Section 7.2.2.6.2), cardiac enzymes (Section 7.2.2.6.3) and ophthalmology exams (Section 7.2.2.7). For each treatment arm, the data will be listed with notable values being flagged. Summary tables will be presented for assessments and changes from baseline at each time point.

Further safety data will be collected as appropriate and listed with notable values being flagged.

10.5.2.5 Supportive analyses for secondary objectives

Any supportive analyses that are considered appropriate for secondary variables will be described in the RAP prior to DBL.

10.5.2.6 Tolerability

For each treatment arm the tolerability of study treatment will be assessed by summarizing the number of dose interruptions and dose reductions. Reasons for dose interruption and dose reductions will be listed by patient.

[redacted]

10.5.3 Pharmacokinetics

PAS will be used in all pharmacokinetic data analysis and PK summary statistics.

For each treatment arm all concentration data will be listed and summarized by time. Descriptive statistics will include arithmetic and geometric mean, median, standard deviation, and coefficient of variation (CV), geometric CV, minimum and maximum. Missing concentration values will be reported as is in data listings. Concentration values below Lower Limit of Quantitation (LLOQ) will be handled as zero in summary statistics, and reported as is in data listings. Individual concentration-time profile as well as mean concentration-time profile will be plotted.

Pharmacokinetic parameters as listed in Table 10-2 will be analyzed and summarized. Missing data will not be imputed. Descriptive statistics of all pharmacokinetic parameters will include arithmetic and geometric mean, median, standard deviation, and CV, geometric CV, minimum and maximum. Only median values and ranges will be given for Tmax. Zero concentrations will not be included in the geometric mean calculation.

Table 10-2 Noncompartmental pharmacokinetic parameters

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume-1)
AUCinf	The AUC from time zero to infinity (mass x time x volume-1)
AUCtau	The AUC calculated to the end of a dosing interval (tau) (amount x time x volume-1)
AUC0-t	The AUC calculated from time zero (0) to t hours (amount x time x volume-1)
Cmax	The maximum (peak) observed plasma concentration (mass x volume-1)
Tmax	The time to reach maximum (peak) plasma concentration (time)
Lambda_z	Smallest (slowest) disposition (hybrid) rate constant (time-1) may also be used for terminal elimination rate constant (time-1)
T1/2	The elimination half-life associated with the terminal slope (Lambda z) of a semi logarithmic concentration-time curve (time). Use qualifier for other half-lives
CL/F	The apparent total body clearance of drug from the plasma (volume x time-1) for oral administration
Vz/F	The apparent volume of distribution during terminal phase (associated with Lambda z) (volume)
CL	The total body clearance of drug from the plasma (volume x time-1) for intravenous administration
Vz	The volume of distribution during terminal phase (associated with Lambda z) (volume) for intravenous administration

[redacted]

[redacted]

10.7 Interim analysis

No interim analyses will be performed. However, safety and efficacy data will be reviewed on an ongoing basis by the study team across the duration of the trial (refer to Section 8.6). The safety monitoring will be done according to Section 7.2.2.

10.8 Sample size calculation

For each treatment arm a Bayesian single-stage single-arm design is used. Given the prior distribution and decision rules described in (Section 10.4.2), the likelihood to wrongly/correctly declare preliminary activity under various scenarios of efficacy was derived.

Given the prior, the posterior distribution and posterior probabilities can be derived using simulated data (i.e. assuming number of patients and number of responders). Therefore, for a particular sample size i.e. number of patients, the minimum number of patients required to satisfy the two criteria mentioned in Section 10.4.2 and declare clinically relevant efficacy can then be derived. Thus, whether the double criteria to declare preliminary activity can be satisfied or not is then translated into the single criterion with observed number of responders (R_i). The operating characteristics shown in the Table 10-3 and Table 10-4 below are calculated based on this R_i.

Table 10-3 below lists for each arm i the sample size, maximum ORR for the unacceptable efficacy category (L_i), minimum ORR for the clinically relevant efficacy category (M_i), minimum number of responses for the clinically relevant efficacy category (R_i), and probability to wrongly declare preliminary activity when ORR=L_i. The chosen sample sizes all have <7.8% probability of wrong conclusion when the true ORR is within the unacceptable efficacy interval.

Table 10-4 presents the probability of correctly declaring preliminary activity under 3 scenarios of true ORR. The proposed design achieves high power (>=88.9%) when the true ORR is >=71.0% and 29.8% in LDK378 and the other arms, respectively.

Table 10-3 Bayesian design parameters and sample size

Armi	Sample size	Maximum ORR for unacceptable efficacy L_i	Minimum ORR for clinically relevant efficacy M_i	Minimum # of responses for clinically relevant efficacy R_i	Probability to wrongly declare preliminary activity when true ORR=L_i
1. LDK378	25	40%	55%	14	7.8%
2. INC280	20	7.5%	17.5%	4	5.8%
3. MEK162	20	7.5%	17.5%	4	5.8%
4. BYL719	20	7.5%	17.5%	4	5.8%

Table 10-4 Probabilities of correctly declaring preliminary activity (A_i) under 3 scenarios of true overall response rates (P_i)

Arm	Scenario 1		Scenario 2		Scenario 3	
i	P_i (=M_i)	A_i	P_i (=U_{i1}^*)	A_i	P_i (=U_{i2}^{**})	A_i
1. LDK378	55.0%	54.3%	64.7%	86.8%	71.0%	96.6%
2. INC280	17.5%	47.4%	24.1%	74.6%	29.8%	88.9%
3. MEK162	17.5%	47.4%	24.1%	74.6%	29.8%	88.9%
4. BYL719	17.5%	47.4%	24.1%	74.6%	29.8%	88.9%

* defined so that odds(U_{i1})/odds(M_i)=1.5
** defined so that odds(U_{i2})/odds(M_i)=2.0

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. 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 Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

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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.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their CRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis 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

Novartis 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

Novartis is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. Novartis assures that the key design elements of this protocol will be posted on the publicly accessible database, e.g. such as www.clinicaltrials.gov, before study start. In addition, results of interventional clinical trials in adult patients are posted on www.novartisclinicaltrials.com, a publicly accessible database of clinical study results within 1 year of upon study completion (i.e., LPLV), and finalization of the study report the results of this study will be either submitted for publication and/or posted in those for interventional clinical trials involving pediatric patients within 6 months of study completion

Novartis follows the ICMJE authorship guidelines (www.icmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted

Authors will not receive remuneration for their writing of a publication, either directly from Novartis or through the professional medical writing agency. Author(s) may be requested to present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

As part of its commitment to full transparency in publications, Novartis supports the full disclosure of all funding sources for the study and publications, as well as any actual and

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potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

For the Novartis Guidelines for the Publication of Results from Novartis-sponsored Research, please refer to www.novartis.com.

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 subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

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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 Novartis. 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 Novartis 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.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis 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 Novartis 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 Novartis, 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, Novartis 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.

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14 Appendix

14.1 Guidelines for Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1

Harmonization of efficacy analysis of solid tumor studies

Authors (Version 3): [redacted]
Authors (Version 2): [redacted]
Authors (Version 1): [redacted]
Document type: TA Specific Guideline
Document status: Version 3: Final,October 19, 2009
Version 2: January 18, 2007
Version 1: December 13, 2002

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Glossary

CR	Complete response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed tomography
DFS	Disease-free survival
eCRF	Electronic Case Report Form
FPFV	First patient first visit
GBM	Glioblastoma multiforme
LPLV	Last patient last visit
MRI	Magnetic resonance imaging
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
RAP	Report Analysis Preparation
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Stable disease
SOD	Sum of Diameter
TTF	Time to treatment failure
TTP	Time to progression
UNK	Unknown

[redacted]

14.1.1 Introduction

The purpose of this document is to provide the working definitions and rules necessary for a consistent and efficient analysis of efficacy for oncology studies in solid tumors. This document is based on the RECIST criteria for tumor responses (Therasse et al 2000) and the revised RECIST 1.1 guidelines (Eisenhauer et al 2009).

This document will not address the use of RECIST 1.1 for glioblastoma multiforme (GBM).

The efficacy assessments described in Section 14.1.2 and the definition of best response in Section 14.1.17 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 14.1.18 is summarizing the "time to event" variables and rules which are mainly derived from internal discussions and regulatory consultations, as the RECIST criteria do not define these variables in detail. Section 14.1.28 of this guideline describes data handling and programming rules. This section is to be referred to in the analysis plan(s) to provide further details needed for programming.

As for a usual Novartis template, comments are written in italic font. The protocol authors must take these comments into consideration and provide project or study specific details in the protocol. Specifically, definitions highlighted in red must be discussed, defined and then documented in the study protocol. Any deviations to the guideline must be clearly specified in the protocol with justification.

14.1.2 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.

14.1.3 Definitions

14.1.4 Disease measurability

In order to evaluate tumors throughout a study definitions of measurability are required in order to classify lesions appropriately at baseline. In defining measurability a distinction also needs to be made between nodal lesions (pathological lymph nodes) and non-nodal lesions.

- **Measurable disease** - the presence of at least one measurable nodal or non-nodal lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

For patients without measurable disease see Section 14.1.26

Measurable lesions (both nodal and non-nodal)

- Measurable non-nodal - As a rule of thumb, the minimum size of a measurable non-nodal target lesion at baseline should be no less than double the slice thickness or 10mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.

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- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components, that can be evaluated by CT/MRI, can be considered as measurable lesions.
- Measurable nodal lesions (i.e. lymph nodes) - Lymph nodes ≥15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring ≥10mm and <15mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at baseline, regardless of the slice thickness, are normal and not considered indicative of disease.
- Non-measurable lesions - all other lesions are considered non-measurable, including small lesions (longest diameter <10 mm with CT scan or pathological lymph nodes with ≥ 10 to < 15 mm short axis), e.g., blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions.

14.1.5 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations (e.g. in Phase III studies where PFS is the primary endpoint). However, it is recommended that patients be excluded from trials where the main focus is on the 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 14.1.26.

14.1.6 Methods of tumor measurement - general guidelines

The following considerations are to be made when evaluating the tumor:

- All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.
- For optimal evaluation of patients the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm.If at baseline a patient is known to be allergic to CT contrast or develops allergy during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.
- A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a change in technique (eg. 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 Novartis calculated UNK response may be accepted from

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the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information."

If head and neck tumors and those of extremities are evaluated in the study, please specify the methods in detail in the protocol.

- **FDG-PET**: can complement CT scans in assessing progression (particularly possible for 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PT 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-PT 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.
- **Tumor markers**: Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g. CA-125 for ovarian cancer, PSA for prostate cancer, alfa-FP, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- **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

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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.

14.1.7 Baseline documentation of target and non-target lesions

For the evaluation of lesions at baseline and throughout the study, the lesions are classified at baseline as either target or non-target lesions:

- **Target lesions**: All measurable lesions (nodal and non-nodal) up to a maximum of five lesions in total (and a maximum of two lesions per organ), representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). Each target lesion must be uniquely and sequentially numbered on the CRF (even if it resides in the same organ).

Minimum target lesion size at baseline

- **Non-nodal target**: Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination) should be at least 10mm in longest diameter. See Section 14.1.4.
- **Nodal target**: See Section 14.1.4.

A sum of diameters (long axis for non-nodal lesions, short axis for nodal) for all target lesions will be calculated and reported as the baseline sum of diameters (SOD). The baseline sum of diameters will be used as reference by which to characterize the objective tumor response. Each target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

- **Non-target lesions**: All other lesions are considered non-target lesions, i.e. lesions not fulfilling the criteria for target lesions at baseline. Presence or absence or worsening of non-target lesions should be assessed throughout the study; measurements of these lesions are not required. Multiple non-target lesions involved in the same organ can be assessed as a group and recorded as a single item (i.e. multiple liver metastasis). Each non-target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

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

To assess tumor response, the sum of diameter for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for the target (Table 14-1) and non-target lesions (Table 14-2) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 14-3) as well as the presence or absence of new lesions.

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14.1.9 Follow-up & recording of lesions

At each visit and for each lesion the actual date of the scan or procedure which was used for the evaluation of each specific lesion should be recorded. This applies to target and non-target lesions as well as new lesions that are detected. At the assessment visit all of the separate lesion evaluation data are examined by the investigator in order to derive the overall visit response. Therefore all such data applicable to a particular visit should be associated with the same assessment number.

14.1.10 Non-nodal lesions

Following treatment, lesions may have longest diameter measurements smaller than the image reconstruction interval. Lesions smaller than twice the reconstruction interval are subject to substantial "partial volume" effects (i.e., size may be underestimated because of the distance of the cut from the longest diameter; such lesions may appear to have responded or progressed on subsequent examinations, when, in fact, they remain the same size).

If the lesion has completely disappeared, the lesion size should be reported as 0 mm.

When a tumor does not disappear completely and shrinks to less than the slice thickness a default value should be assigned depending on the slice thickness. With 5 mm contiguous slice thickness, the default value will be 5 mm. Similarly, for a 7 mm slice thickness, the default value will be 7 mm. Actual measurement should be given for all lesions larger than the default value.

In other cases where the lesion cannot be reliably measured for reasons other than its size (e.g., borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

14.1.11 Nodal lesions

A nodal lesion less than 10 mm in size by short axis is considered normal. Lymph nodes are not expected to disappear completely, so a "non-zero size" will always persist.

If a nodal lesion shrinks to less than the slice thickness a default value should be assigned depending on the slice thickness. With 5 mm contiguous slice thickness, the default value will be 5 mm. Similarly, for a 7 mm slice thickness, the default value will be 7 mm. Actual measurement should be given for all lesions larger than the default value.

However, once a target nodal lesion shrinks to less than 10 mm in its short axis, it will be considered normal for response purpose determination. The lymph node measurements will continue to be recorded to allow the values to be included in the sum of diameters for target lesions, which may be required subsequently for response determination.

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14.1.12 Determination of target lesion response

Table 14-1 Response criteria for target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm [1]
Partial Response (PR):	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm[2].
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD.
Unknown (UNK)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline.[3]

[1] SOD for CR may not be zero when nodal lesions are part of target lesions
[2] Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10mm in size. In this case, the target lesion response is CR
[3] Methodology change See Section 14.1.6.

Notes on target lesion response

Reappearance of lesions: If the lesion appears at the same anatomical location where a target lesion had previously disappeared, it is advised that the time point of lesion disappearance (i.e., the "0 mm" recording) be re-evaluated to make sure that the lesion was not actually present and/or not visualized for technical reasons in this previous assessment. If it is not possible to change the 0 value, then the investigator/radiologist has to decide between the following three possibilities:

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as progressive disease
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the CRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 14-1 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline). Proper documentation should be available to support this decision.
- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.
- **Missing measurements:** In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is 100mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit is 140mm (with data for 2 other lesions missing) then a PD should be assigned. However, in other cases where a PD cannot definitely be attributed the target lesion response would be UNK.

[redacted]

- **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 b recorded for the size of one of the original lesions while a size of "0"mm should be entered for the remaining lesion numbers which have coalesced.
- The **measurements for nodal lesions**, even if less than 10mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.
    - Since lesions less than 10mm are considered normal a CR for target lesion response should be assigned when nodal target lesions shrink to less than 10mm and all non-nodal target lesions have disappeared.
    - Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
    - Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion "reappears" or if the absolute sum of the remaining nodal target lesions increases by at least 5mm **and** at least one of those remaining lesions are at least 10mm in size. i.e. if the short axis of a remaining nodal target lesion increases from 5 mm to 10 mm or from 7 mm to 12.5 mm this is called PD, but if it increases from 7 mm to 10 mm it does not qualify for PD.

When both nodal and non-nodal lesions are still present there may be rare occasions when a PD for target lesion response is primarily due to increases in size of nodal lesions but where the target lymph nodes are still all less than 10mm in size. This kind of rare anomaly is acceptable since otherwise the rules for determining target lesion response would become too complex.

[redacted]

14.1.13 Determination of non-target lesion response

Table 14-2 Response criteria for non-target lesions

Response Criteria	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions. In addition, all lymph nodes assigned a non-target lesions must be non-pathological in size (< 10 mm short axis)
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions.[1]
Incomplete Response/ Stable Disease (SD):	Neither CR nor PD
Unknown (UNK)	Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a different method than baseline.

[1] Although a clear progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the treating physician does prevail and the progression status should be confirmed later on by the review panel (or study chair).

Notes on non-target lesion response

- The response for non-target lesions is **CR** only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e. < 10mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e. ≥ 10 mm) the response can only be '**Incomplete response/Stable disease**' unless any of the lesions was not assessed (in which case response is **UNK**) or there is unequivocal progression of the non-target lesions (in which case response is **PD**).
- Unequivocal progression: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. Even in cases where there is no measurable disease at baseline, in order for a PD to be assigned on the basis of non-target lesions the increase in the extent of the disease must be substantial. In studies where the overall non-target lesion response is not recorded but instead the individual status of individual lesions (Absent, Present or Worsened) is determined, if there is unequivocal progression of non-target lesions then at least one of the non-target lesions must be assigned a status of "Worsened". Similarly, an individual non-target lesion should only be assigned a "Worsened" status if there is unequivocal progression of non-target lesions overall.
- Where possible, similar rules to those described in Section 14.1.12 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

14.1.14 New lesions

The appearance of a new lesion is always associated with Progressive Disease (PD) and has to be recorded as a new lesion in the New Lesion CRF page.

[redacted]

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion1
- If new disease is observed in a region which was **not scanned at baseline** or where the particular baseline scan is not available for some reason then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment (see Section 14.1.15).
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ≥ 10mm for the first time in the study plus 5mm absolute increase.
  FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 14.1.6.

14.1.15 Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table 14-3.

Table 14-3 Overall lesion response at each assessment

Target lesions	Non-target lesions	New Lesions	Overall lesion response
CR	CR	No	CR[1]
CR	Incomplete response/SD[3]	No	PR
CR, PR, SD	UNK	No	UNK
PR	Non-PD and not UNK	No	PR[1]
SD	Non-PD and not UNK	No	SD[1, 2]
UNK	Non-PD or UNK	No	UNK[1]
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

[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 14.1.8.

If there are no baseline scans taken at all at baseline then the overall lesion response at each assessment should be considered Unknown (UNK).

If the evaluation of any of the target or non-target lesions identified at baseline could not be made during follow-up, the overall status must be 'unknown' unless progression was seen.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

[redacted]

14.1.16 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 14.1.26 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

14.1.17 Best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

The best overall response will usually be determined from response assessments undertaken while on treatment. However, if any assessments occur after treatment withdrawal the protocol should specifically describe if these will be included in the determination of best overall response and/or whether these additional assessments will be required for sensitivity or supportive analyses. As a default, any assessments taken more than 28 days after the last dose of study therapy will not be included in the best overall response derivation. If any alternative cancer therapy is taken while on study any subsequent assessments would ordinarily be excluded from the best overall response determination. If response assessments taken after withdrawal from study treatment and/or alternative therapy are to be included in the main endpoint determination then this should be described and justified in the protocol.

Where a study requires a response PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met.

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).

If PD in a different follow-up period is considered overall response='progressive disease', this must be specified in the protocol.

The protocol should state if discontinuation due to 'Disease progression' or death due to study indication is considered PD even if this was not accompanied by documentation of PD based on tumor measurements. This depends on Phase of the study and the primary endpoint (e.g. Phase III studies in which progression-free survival is primary endpoint should consider only

[redacted]

documented PD, whereas Phase I and II studies may consider all clinical deteriorations PD). The following sentence therefore is only applicable if this is specified in the protocol:

- Patients with symptoms of rapidly progressing disease without radiologic evidence will be classified as progression only when clear evidence of clinical deterioration is documented and/or patient discontinued due to 'Disease progression' or death due to study indication.
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks)

Overall lesion responses of CR must stay the same until progression sets in, with the exception of a UNK status. A patient who had a CR cannot subsequently have a lower status other than a PD, e.g. PR or SD, as this would imply a progression based on one or more lesions reappearing, in which case the status would become a PD.

Once an overall lesion response of PR is observed (which may have to be a confirmed PR depending on the study) this assignment must stay the same or improve over time until progression sets in, with the exception of an UNK status. However, in studies where confirmation of response is required, if a patient has a single PR (≥30% reduction of tumor burden compared to baseline) at one assessment, followed by a <30% reduction from baseline at the next assessment (but not ≥20% increase from previous smallest sum), the objective status at that assessment should be SD. Once a confirmed PR was seen, the overall lesion response should be considered PR (or UNK) until progression is documented or the lesions totally disappear in which case a CR assignment is applicable. In studies where confirmation of response is not required after a single PR the overall lesion response should still be considered PR (or UNK) until progression is documented or the lesion totally disappears in which case a CR assignment is applicable.

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

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
- Novartis 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.

[redacted]

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.

14.1.18 Time to event variables

14.1.19 Progression-free survival

Progression-free survival (PFS) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of last adequate tumor assessment.

14.1.20 Overall survival

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

14.1.21 Time to progression

Time to progression (TTP) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to underlying cancer. If a patient has not had an event, time to progression is censored at the date of last adequate tumor assessment.

14.1.22 Time to treatment failure

Time to treatment failure (TTF) is the time from date of randomization/start of treatment to the earliest of date of progression, date of death due to any cause, or date of discontinuation due to reasons other than 'Protocol violation' or 'Administrative problems'. The time to treatment failure for patients who did not experience treatment failure will be censored at last adequate tumor assessment.

14.1.23 Duration of response

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.

[redacted]

Duration of stable disease (CR/PR/SD): For patients with a CR or PR (which may have to be confirmed) or an SD the start and end date as well as censoring is defined the same as that for time to progression.

14.1.24 Time to response

Time to overall response (CR or PR) is the time between date of randomization/start of treatment until first documented response (CR or PR). The response may need to be confirmed depending on the type of study and its importance. Where the response needs to be confirmed then time to response is the time to the first CR or PR observed.

Although an analysis on the full population is preferred a descriptive analysis may be performed on the "responders" subset only, in which case the results should be interpreted with caution and in the context of the overall response rates, since the same kind of selection bias may be introduced as described for duration of response in Section 14.1.23. It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a responders only descriptive analysis is presented. Where an inferential statistical comparison is required then all patients should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all patients, patients who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

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

Time to overall complete response (CR) is the time between dates of randomization/start of treatment until first documented CR. Similar analysis considerations including (if appropriate) censoring rules apply for this endpoint described for the time to overall response endpoint.

Indicate in the protocol whether a subgroup analysis of responders only will be performed in addition to the full population analysis (which should be included as default).

14.1.25 Definition of start and end dates for time to event variables

Assessment date

For each assessment (i.e. evaluation number), the **assessment date** is calculated as the latest of all measurement dates (e.g. X-ray, CT-scan) if the overall lesion response at that assessment is CR/PR/SD/UNK.

Otherwise - if overall lesion response is progression - the assessment date is calculated as the earliest date of all measurement dates at that evaluation number.

[redacted]

Start dates

State in the protocol if date of randomization or date of start of treatment is to be used for all definitions. For randomized studies specify exactly where the randomization date comes from, e.g. from IVRS, or if start of treatment is used as randomization date. For non-randomized studies please specify which treatment start date is taken if more than one treatment is to be given.

For all "time to event" variables, other than the duration of responses, the randomization/ date of treatment start will be used as the start date.

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

- Date of first documented response is the assessment date of the first overall lesion response of CR (for duration of overall complete response) or CR / PR (for duration of overall response) respectively, when this status is later confirmed.

End dates

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

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

When there is no documentation of radiologic evidence of progression, and the patient discontinued for 'Disease progression' due to documented clinical deterioration of disease, the date of discontinuation is used as date of progression.

- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of CR, PR or SD which was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate tumor assessment plus the protocol specified time interval for assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 14.1.26).

Example (if protocol defined schedule of assessments is 3 months): tumor assessments at baseline - 3 months - 6 months - missing - missing - PD. Date of next scheduled assessment would then corresponds to 9 months.

- Date of discontinuation is the date of the 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.

[redacted]

- Date of secondary anti-cancer therapy is defined as the start date of any additional (secondary) antineoplastic therapy or surgery.

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

It is possible that patients with just non-measurable disease present at baseline are entered into the study, either because of a protocol violation or by design (e.g. 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.

The protocol should state clearly whether patients with non-measurable disease only at baseline will be allowed into the study. If patients with non-measurable disease only are allowed to be enrolled then the statistical section should describe clearly how data from these patients will be incorporated into the primary analysis and main analyses of the key secondary endpoints. In studies where presence or otherwise of measurable disease is expected to have a relatively large impact on the primary endpoint, this factor can even be considered as a stratification factor in the randomization process.

It is recommended that any patients with only non-measurable disease at baseline should be included in the main (ITT) analysis of each of these endpoints.

For studies which specifically exclude patients with non-measurable disease only at baseline the pre-specified analysis plan should describe how to handle data from these types of patients if they are enrolled by error. It is recommended for these types of studies that patients with non-measurable disease identified through the local site evaluation be included in the list of protocol violations. However, decisions on exclusion from a per protocol analysis should relate to whether the patient has measurable disease according to the primary data source. For example, if the primary data source is from a central independent review then patients with non-measurable disease only according to this central review should be excluded from the relevant per protocol analyses.

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also be incorporated in an appropriate manner. The overall response for patients with measurable disease is derived slightly differently according to Table 14-4.

Table 14-4 Overall lesion response at each assessment: patients with non-target disease only

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

[1] As defined in Section 14.1.8

[redacted]

In general, the **non-CR/non-PD response** for these patients is considered equivalent to an SD response in endpoint determination. In summary tables for best overall response patients with just non-measurable disease may be highlighted in an appropriate fashion e.g. in particular by displaying the specific numbers with the non-CR/non-PD category.

In considering how to incorporate data from these patients into the analysis the importance to each endpoint of being able to identify a PR and/or to determine the occurrence and timing of progression needs to be taken into account.

For ORR it is recommended that the main (ITT) analysis includes data from patients with only non-measurable disease at baseline, handling patients with a best response of CR as "responders" with respect to ORR and all other patients as "non-responders". Study teams may also want to perform sensitivity analyses excluding patients from the analysis of ORR (e.g. possibly as part of a per-protocol type analysis). Similar considerations should be given to other endpoints which rely on a clear distinction being made between a PR and an SD response.

For PFS, it is again recommended that the main ITT analyses on these endpoints include all patients with just non-measurable disease at baseline, with possible sensitivity analyses which exclude these particular patients. Endpoints such as PFS which are reliant on the determination and/or timing of progression can incorporate data from patients

14.1.27 Sensitivity analyses

This section outlines the possible event and censoring dates for progression, as well is addressing the issues of missing tumor assessments during the study. For instance, if one or more assessment visits are missed prior to the progression event, to what date should the progression event be assigned? And should progression event be ignored if it occurred after a long period of a patient being lost to follow-up? It is important that the protocol and analysis plan specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed.

Based on definitions outlined in Section 14.1.25, and using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005) as a reference, the following analyses can be considered:

Table 14-5 Options for event dates used in PFS, TTP, duration of response

Situation		Options for end-date (progression or censoring?)[1] (1) = default unless specified differently in the protocol or analysis plan	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment[3]	Censored
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[2]	Progressed Progressed
C1	Progression or death after **exactly one** missing assessment	(1) Date of progression (or death) (2) Date of next scheduled assessment[2]	Progressed Progressed
C2	Progression or death after **two or more** missing assessments	(1) Date of last adequate assessment[2] (2) Date of next scheduled assessment[2] (3) Date of progression (or death)	Censored Progressed Progressed
D	No progression	(1) Date of last adequate assessment	Censored

[redacted]

Situation		Options for end-date (progression or censoring?)[1] (1) = default unless specified differently in the protocol or analysis plan	Outcome
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 (3) Date of secondary anti-cancer therapy (4) N/A	Censored Censored Event Ignored
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP and duration of response)

[1]=Definitions can be found in Section 14.1.25
[2]=After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 14.1.25
[3]=The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

The primary analysis and the sensitivity analyses must be specified in the protocol. Clearly define if and why options (1) are not used for situations C, E and (if applicable) F.

Situations C (C1 and C2): Progression or death after one or more missing assessments: The primary analysis is usually using options (1) for situations C1 and C2, i.e.

- (C1) taking the actual progression or death date, in the case of only one missing assessment.
- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments.

In the case of two or missing assessments (situation C2), option (3) may be considered jointly with option (1) in situation C1 as sensitivity analysis. A variant of this sensitivity analysis consists of backdating the date of event to the next scheduled assessment as proposed with option (2) in situations C1 and C2.

Situation E: Treatment discontinuation due to 'Disease progression' without documented progression: By default, option (1) is used for situation E as patients without documented PD should be followed for progression after discontinuation of treatment. However, option (2) may be used as sensitivity analysis. If progression is claimed based on clinical deterioration instead of tumor assessment by e.g. CT-scan, option (2) may be used for indications with high early progression rate or difficulties to assess the tumor due to clinical deterioration.

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1), i.e. censoring at last adequate assessment may be used as a default in this case.

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g. by assigning the dates for

[redacted]

censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 14-5 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

- **Date of previous scheduled assessment (from baseline)** is the date when a tumor assessment would have taken place, if the protocol assessment scheme was strictly followed from baseline, immediately before or on the date of the last adequate tumor assessment.

In addition, analyses could be repeated using the Investigators' assessments of response rather than the calculated response. The need for these types of sensitivity analyses will depend on the individual requirements for the specific study and disease area and have to be specified in the protocol or RAP documentation.

14.1.28 Data handling and programming rules

The following section should be used as guidance for development of the protocol, data handling procedures or programming requirements (e.g. on incomplete dates).

14.1.29 Study/project specific decisions

For each study (or project) various issues need to be addressed and specified in the protocol or RAP documentation. Any deviations from protocol must be discussed and defined at the latest in the RAP documentation.

The proposed primary analysis and potential sensitivity analyses should be discussed and agreed with the health authorities and documented in the protocol (or at the latest in the RAP documentation before database lock).

14.1.30 Treatment and study completion CRFs

If study treatment is discontinued, the **End of Treatment Page** is to be completed with a visit date reflecting the date the discontinuation decision was made, and with the 'Last known date subject took study treatment' and one of the following reasons:

- Adverse event(s)
- Abnormal laboratory value(s)
- Abnormal test procedure results(s)
- Protocol violation
- Subject withdrew consent
- Lost to follow-up
- Administrative problems
- Death
- Disease progression
- Treatment duration completed as per protocol

For reasons other than progression (and death) it should be checked if this was not in fact progression (especially reasons Adverse Events, Abnormal laboratory value (s), Abnormal test procedure result and subject withdrew consent). Also it should be checked if patient

[redacted]

withdrew consent because of safety issues, in which case reasons Adverse Events, Abnormal laboratory value (s), Abnormal test procedure result should be used. In such cases where the reason for discontinuation is Adverse Event, the adverse event CRF page must be consistent with the EOT reason provided

All patients who discontinued study treatment will be followed for post a treatment evaluation until progression or until a new anticancer therapy is initiated. Patients who discontinued study treatment for reasons other than documented progression, death or lost to follow-up will be followed for progression thereafter (patients who withdrew consent might not be followed with regular tumor assessments at the study site, but should ideally be followed until progression outside the study site). Ideally, all patients who discontinued study treatment for progression without documented progression will still be followed with regular tumor assessments (e.g. in case of central radiology review).If patient withdraws consent, it must be clearly stated if patient is also withdrawing consent from post treatment evaluations and/or post treatment follow-up assessments. During that evaluation period, usually only tumor measurements (and/or response status) and survival data are collected. In some protocols, the subsequent anti-cancer therapies may also be recorded.

14.1.31 Study evaluation completion

At the end of the study evaluation period, the **study evaluation completion page** is filled out with the following options:

- Subject withdrew consent
- Lost to follow-up
- Administrative problems
- Death
- New cancer therapy
- Disease progression

Thereafter, patients will be followed for survival using the survival follow-up pages. If information on death becomes available for patients who were lost to follow-up or withdrew consent, this may also be entered in the database. The reason for death must be documented (and will be coded using MedDRA); it must be also stated if death was due to ‘Study indication’ or ‘Other’ reason.

In comparative studies with long follow-up period and therefore extended visit schedule, it may be useful to collect the survival status at a pre-specified cut-off within a limited timeframe for all patients with no documented death. In this case, this requires a contact to be made with the patient or with any reliable source of information on the patient’s status, but not requiring a specific visit to be scheduled

Until the specified cut-off point has been reached, the goal is to collect tumor assessments until disease progression for all patients regardless of whether the patients are still receiving study treatment. If patients are not followed for progression, e.g. in a Phase I or II study mainly evaluating safety, the evaluation is completed when study treatment is completed (in this case only the first completion page is used).

[redacted]

14.1.32 Medical validation of programmed overall lesion response

As RECIST is very strict regarding measurement methods (i.e. any assessment with more or less sensitive method than the one used to assess the lesion at baseline is considered UNK) and not available evaluations (i.e. if any target or non-target lesion was not evaluated the whole overall lesion response is UNK unless remaining lesions qualified for PD), these UNK assessments may be re-evaluated by clinicians at Novartis 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 Novartis elect to invalidate an evaluation of overall lesion response upon internal or external review of the data, the calculated overall lesion response at that specific assessment is to be kept in a dataset. This must be clearly documented in the RAP documentation and agreed before database lock. This dataset should be created and stored as part of the 'raw' data.

Any discontinuation due to 'Disease progression' without documentation of progression by RECIST criteria should be carefully reviewed. Only patients with documented deterioration of symptoms indicative of progression of disease should have this reason for discontinuation of treatment or study evaluation.

14.1.33 Programming rules

The following should be used for programming of efficacy results:

14.1.34 Calculation of 'time to event' variables

Time to event = end date - start date + 1 (in days)

When no post-baseline tumor assessments are available, the date of randomization/start of treatment will be used as end date (duration = 1 day) when time is to be censored at last tumor assessment, i.e. time to event variables can never be negative.

14.1.35 Incomplete assessment dates

All investigation dates (e.g. X-ray, CT scan) must be completed with day, month and year.

If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and assessment date is calculated as outlined in Section 14.1.25). If all measurement dates have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

14.1.36 Incomplete dates for last contact or death

All dates must be completed with day, month and year. If the day is missing, the 15th of the month will be used for incomplete death dates or dates of last contact.

[redacted]

14.1.37 Non-target lesion response

If no non-target lesions are identified at baseline (and therefore not followed throughout the study), the non-target lesion response at each assessment will be considered 'not applicable (NA)'.

14.1.38 Study/project specific programming

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

14.1.39 Censoring reason

In order to summarize the various reasons for censoring, the following categories will be calculated for each time to event variable based on the treatment completion page, the study evaluation completion page and the survival page.

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

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

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see Table 14-5)
- Death due to reason other than underlying cancer
- New cancer therapy added

* Adequate assessment is defined in Section 14.1.25 This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor assessments prior to the cut-off date. The following clarifications concerning this reason should also be noted:-

- This may be when there has been a definite decision to stop evaluation (e.g. reason='Administrative problems' on study evaluation completion page), when patients are not followed for progression after treatment completion or when only UNK assessments are available just prior to data cut-off).
- The reason "Adequate assessment no longer available" also prevails in situations when another censoring reason (e.g. withdrawal of consent, loss to follow-up or alternative anti-cancer therapy) has occurred more than the specified period following the last adequate assessment.
- This reason will also be used for censor in case of no baseline assessment.

[redacted]

14.1.40 Reference (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, Vol.45: 228-47

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, Vol. 92; 205-16

[redacted]

14.2 Review of criteria for interruption and re-initiation of study treatment

Table 14-6 Criteria for interruption and re-initiation of BYL719

Recommended dose modifications for BYL719	
Worst toxicity CTCAE grade (value)	**During a cycle of therapy**
No toxicity	**Maintain dose level**
Investigations (Hematologic)	
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1500/mm^3)	Maintain dose level
Grade 2 (ANC < 1500 - 1000/mm^3)	Maintain dose level
Grade 3 (ANC < 1000 - 500/mm^3)	Omit dose until resolved to ≤ grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (ANC < 500/mm^3)	Omit dose until resolved to ≤ grade 1, then resume at ↓ 1 dose level
Febrile neutropenia (ANC < 1.0 x 10^9/L, with a single temperature of ≥ 38.3 °C or a sustained temperature of ≥ 38 °C for more than one hour)	Omit dose until resolved, then ↓ 1 dose level
Thrombocytopenia	
Grade 1 (PLT < LLN - 75,000/mm^3)	Maintain dose level
Grade 2 (PLT < 75,000 - 50,000/mm^3)	Maintain dose level
Grade 3 (PLT < 50,000 - 25,000/mm^3)	Omit dose until resolved to ≤ grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (PLT < 25,000/mm^3)	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level
Bleeding	
Any bleeding, related to BYL719 use, resulting in platelet transfusion	Omit dose until no further bleeding has been observed. Modify dose according to the thrombocytopenia recommended dose modifications.
Respiratory disorders	
Pneumonitis	
Any Grade	Omit BYL719 for any case of suspected pneumonitis. Obtain appropriate imaging (high resolution CT scan) and consider bronchoalveolar lavage and biopsy on clinical judgement. See Section 14.3.1 for details of management of pneumonitis. Treatment for pneumonitis should be initiated based on institution guidelines and generally includes high dose corticosteroid; antibiotic therapy should be administered concurrently if infectious causes have not been ruled out. BYL719 should be permanently discontinued in all patients with confirmed pneumonitis.

[redacted]

Recommended dose modifications for BYL719	
Worst toxicity CTCAE grade (value)	**During a cycle of therapy**
Investigations (Renal)	
Serum creatinine	
< 2 x ULN	Maintain dose level
2 - 3 x ULN	Omit dose until resolved to ≤ grade 1, then • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Grade ≥ 3 (> 3.0 baseline; > 3.0 x ULN)	Omit dose and discontinue patient from study treatment
Investigations (Hepatic)	
Isolated total Bilirubin elevation **(*for patients with Gilbert Syndrome these dose modifications apply to changes in direct bilirubin only)**	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level with LFTs* monitored as per protocol
Grade 2 (> 1.5 - 3.0 x ULN)	Omit dose. Monitor LFTs[a] weekly or more frequently if clinically indicated until resolved to ≤ grade 1, then: • If resolved in ≤ 14 days, then maintain dose level • If resolved in > 14 days, ↓ 1 dose level.
Grade 3 (> 3.0 - 10.0 x ULN)*	Omit dose. Monitor LFTs[a] weekly or more frequently if clinically indicated, until resolved to ≤ grade 1, then: • If resolved in ≤ 14 days, ↓ dose 1 dose level. • If resolved in > 14 days discontinue patient from study treatment The patient should be monitored weekly (including LFTs[a]), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks
Grade 4 (> 10.0 x ULN)*	Permanently discontinue patient from BYL719 The patient should be monitored weekly (including LFTs[a]), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks.
Isolated AST or ALT Elevation Confounding factors and/or alternative causes for increased transaminases like concomitant medications, infection, hepato-biliary disorders, obstruction, liver metastasis, etc. should be excluded before dose interruption/reduction	
Grade 1 (> ULN - 3.0 x ULN)	Maintain dose level with LFTs[a] monitored per protocol
Grade 2 (> 3.0 - 5.0 x ULN) • For patients with baseline value ≤ 3.0 x ULN • For patients with baseline value > 3.0 -5.0 x ULN	• Maintain dose level. Repeat LFTs[a] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs[a] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN • Maintain dose level

[redacted]

Recommended dose modifications for BYL719	
Worst toxicity CTCAE grade (value)	**During a cycle of therapy**
Grade 3 (> 5.0 - 20.0 x ULN) **> 5.0 - 10.0 x ULN**	
• For patients with baseline value ≤ 3.0 x ULN	• Omit dose. Repeat LFTs[a] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[a] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN Then If resolved in ≤ 14 days, maintain dose level If resolved in > 14 days, ↓ 1 dose level
• For patients with baseline value > 3.0 -5.0 x ULN	• Maintain dose level. Repeat LFTs[a] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs[a], weekly, or more frequently if clinically indicated, until resolved to ≤ 5.0 x ULN If resolved in ≤ 21 days, maintain dose level If resolved in > 21 days and confounding factors have been excluded, ↓ 1 dose level
> 10.0 x ULN	Omit dose. Repeat LFTs[a] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[a] weekly, or more frequently if clinically indicated, until resolved to ≤ baseline. Then ↓ 1 dose level.
Grade 4 (> 20.0 x ULN)	
• For patients deriving clinical benefit upon investigator's judgement	• Omit dose. Repeat LFTsa as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTsa weekly, or more frequently if clinically indicated, until resolved to ≤ 3 x ULN (or ≤ 5 x ULN for patients with baseline value > 3.0 -5.0 x ULN), then resume treatment at ↓ 1 dose level. Only 1 dose reduction is allowed; if reoccurs at > 5 x ULN, discontinue patient from BYL719.
• For all other patients	• Discontinue patient from BYL719.Repeat LFTsa as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[a] weekly, or more frequently if clinically indicated, until resolved to baseline or stabilization over 4 weeks
Combined[b] elevations of AST or ALT and total Bilirubin	
• For patients with normal baseline ALT and AST and total bilirubin value: AST or ALT > 3.0 x ULN and combined with total bilirubin > 2.0 x ULN	• Permanently discontinue BYL719
• For patients with elevated baseline AST or ALT or total bilirubin value [AST or ALT>2x baseline AND > 3.0 xULN] OR [AST or ALT > 8.0 xULN], combined with [total bilirubin >2x baseline AND >2.0 xULN	• Repeat as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs[a], or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks. Refer to Section14.3.1 for additional follow-up evaluations as applicable

[redacted]

Recommended dose modifications for BYL719	
Worst toxicity CTCAE grade (value)	**During a cycle of therapy**
[a]Core LFTs include albumin, ALT, AST, total bilirubin (fractionated [direct and indirect], if total bilirubin > 2.0 x ULN), alkaline phosphatase (fractionated [quantification of isoforms], if alkaline phosphatase is >grade 2) and GGT. For patients with Gilbert Syndrome: total and direct bilirubin must be monitored, intensified monitoring applies to changes in direct bilirubin only; the monitoring includes the following LFTs: albumin, ALT, AST, total bilirubin (fractionated [direct and indirect] if total bilirubin > 2.0 x ULN), alkaline phosphatase (fractionated [quantification of isoforms] if alkaline phosphatase is > grade 2) and GGT). [b] "Combined" defined as total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when omit dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment either at the same dose or at one dose lower if meeting a criterion for dose reduction * Note: If total bilirubin > 3.0 x ULN is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the investigator.	
Investigations (metabolic)	
Asymptomatic Amylase and/or Lipase elevation(see also Section 14.3.1)	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level
Grade 2 (> 1.5 - 2.0 x ULN)	Maintain dose level
Grade ≥3 (> 2.0)	Omit dose until resolved to baseline, then: • If resolved in ≤ 14 days, maintain dose level • If resolved in > 14 days, ↓ by 1 dose level Note: In cases of isolated amylase elevations only, dosing may be maintained provided amylase fractionation demonstrates that pancreatic amylase is ≤ Grade 1. Monitor total amylase (and continue to assess fractionated amylase) as specified in Section 14.3.1.
Note: Withhold study treatment for acute onset of new or progressive unexplained abdominal symptoms, such as severe pain or vomiting; and perform diagnostic procedures (e.g., abdominal CT scan or ultrasound) to exclude pancreatic pathology.	
Hyperglycemia (see also Section 14.3) Always consider consultation with a diabetologist and recommend/reinforce on lifestyle changes as per ADA, i.e. exercise and dietary advice (e.g. small frequent meals, low carb, high fiber, balancing carbs over the course of the day. Three small meals and 2 small snacks rather than one large meal).	
Grade 1 (> ULN - 160 mg/dL) [> ULN - 8.9 mmol/L] For patients with baseline values between >ULN – 140 mg/dL (ULN – 7.7 mmol/L) this apply only for values > 140 mg/dL (7.7 mmol/L)	

[redacted]

Recommended dose modifications for BYL719	
Worst toxicity CTCAE grade (value)	**During a cycle of therapy**
Grade 2 (>160 - 250 mg/dL) [> 8.9 - 13.9 mmol/L]	**Maintain dose level** and remind patient on lifestyle changes*, exclude confounding factors like e.g. urinary tract infection, consider consultation with a diabetologist and start oral-antidiabetic treatment, e.g. metformin 500 mg bid with breakfast and dinner. If no GI intolerance, increase to 500 mg with breakfast, 1000 mg with dinner. If tolerated, 1000 mg bid with breakfast and dinner. If not tolerated, reduce to prior tolerated dose. Titrate to the maximum tolerated dose over a period of 3 weeks. If FPG is still rising on maximum tolerated dose of metformin or persistently >160mg/dl (>8.9 mmol/L), add an insulin-sensitizer, e.g. pioglitazone 30 mg (max. dose). Monitor FPG as clinically indicated and at least weekly until FPG resolves to ≤ Grade 1 • If FPG does not resolve to ≤ Grade 1 within 21 days after institution of appropriate anti-diabetic treatment, reduce BYL719 by 1 dose level • Continue with anti-diabetic treatment and check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks, alert treating physician if FPG>250mg/dl
Grade 3 (> 250 - 500 mg/dL) [> 13.9 - 27.8 mmol/L]	**Omit BYL719** and confirm fasting status of the assessment. If non-fasting, re-check within 24 hours. Exclude confounding factors like e.g. urinary tract infection and consider consultation with a diabetologist. Administer intravenous hydration and intervention for electrolyte/ketoacidosis/hyperosmolar disturbances as clinically appropriate. Start metformin and titrate as outlined for Grade 2, add pioglitazone as outlined for Grade 2. Insulin may be used for 1-2 days until hyperglycemia resolves, however this may not be necessary in the majority of BYL719-induced hyperglycemia given the short half-life of BYL719. Monitor FPG as clinically indicated and at least twice weekly until FPG resolves to ≤ Grade 1. • If FPG resolves to ≤ Grade1 within 3-5 days, while off study treatment and on metformin, re-start BYL719 and reduce 1 dose level, continue with anti-diabetic treatment and check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks, alert treating physician if FPG>250mg/dl • If FPG does not resolve to Grade1 within 3-5 days while off study treatment and on metformin, consult a diabetologist for management of diabetes is strongly recommended. If FPG does not resolve to ≤ Grade 1 within 21 days after institution of appropriate anti-diabetic treatment in cooperation with diabetologist and exclusion of confounding factors e.g. urinary tract infection, permanently discontinue patient from BYL719 treatment

[redacted]

<table>
<tr><th colspan="2">Recommended dose modifications for BYL719</th></tr>
<tr><th>Worst toxicity
CTCAE grade (value)</th><th>During a cycle of therapy</th></tr>
<tr><td>Grade 4 (> 500 mg/dL) [≥ 27.8 mmol/L]</td><td>Omit BYL719, confirm fasting status of the assessment. If non-fasting, re-check within 24 hours.
Exclude confounding factors like e.g. urinary tract infection.
Consider cooperation with diabetologist, initiate or intensify medication with appropriate anti-diabetic treatment (see Grade 3), re-check within 24 hours.
• If grade improves then follow specific grade recommendations
• If FPG is confirmed at Grade 4 and confounding factors could be excluded, permanently discontinue patient from BYL719</td></tr>
<tr><td colspan="2">A diabetologist consultation should always be considered.
For all grades : instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study, e.g. .small frequent meals, low carbohydrate content, high fiber, balancing carbohydrates over the course of the day; three small meals and 2 small snacks rather than one large meal
*specific recommendations please see Section 14.3.1.</td></tr>
<tr><td colspan="2">Cardiac</td></tr>
<tr><td colspan="2">Cardiac - prolonged QTcF interval</td></tr>
<tr><td>QTcF ≥ 501 msec (≥ Grade 3) or > 60 msec change from baseline on at least two separate ECGs</td><td>First Occurrence:
1. Assess the quality of the ECG recording and the QT value and repeat if needed
2. Interrupt study treatment
3. Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities before resuming study drug treatment.
4. Review concomitant medication use for other causes for QT prolongation (refer to crediblemeds.org for known QT prolonging drugs), and for drugs with the potential to increase the risk of drug exposure related QT prolongation
5. Check study drug dosing schedule and treatment compliance
6. Consider collecting a time-matched PK sample and record time and date of last study drug intake.
After confirming ECG reading at site, if QTcF > 500 ms or > 60 ms change from baseline
• Interrupt study treatment
• Repeat ECG and confirm ECG diagnosis by a cardiologist

If QTcF confirmed > 500 ms or > 60 ms change from baseline
• Correct electrolytes, eliminate culprit concomitant treatments, and identify clinical conditions that could potentially prolong the QT
• Consult with a cardiologist (or qualified specialist)
• Increase cardiac monitoring as indicated, until the QTcF returns to ≤ 480 ms or < 60ms change from baseline.
• After resolution to ≤ 480 ms /60 ms change from baseline, consider re-introducing treatment at reduced dose, and increase ECG monitoring</td></tr>
</table>

[redacted]

Recommended dose modifications for BYL719	
Worst toxicity CTCAE grade (value)	**During a cycle of therapy**
	• If QTcF remains ≤ 500 ms/60 ms change from baseline after dose reduction, continue planned ECG monitoring during subsequent treatment If QTcF recurs > 500 ms/60 ms change from baseline after dose reduction, discontinue patient from BYL719.
Cardiac - Left Ventricular Systolic Dysfunction	
Asymptomatic, resting ejection fraction 40-50%; or 10-20% drop from baseline	• Maintain dose level, and continue BYL719 with caution • Repeat LVEF within 4 weeks or as clinically appropriate
Symptomatic, responsive to intervention, ejection fraction 20-39% or > 20% drop from baseline	• Omit BYL719 until resolved* (as defined below), then ↓ 1 dose level • LVEF measurement to be repeated, if not resolved* within 28 days permanently discontinue patient from BYL719 treatment
Refractory or poorly controlled, ejection fraction < 20%	Permanently discontinue patient from BYL719
*the event is considered resolved when the patient is asymptomatic, has a resting ejection fraction ≥ 40% and ≤20% decrease from baseline.	
Cardiac general	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level
Grade 4	Omit dose and discontinue patient from study
Nervous system disorders	
≥ 1 CTCAE grade level increase of neurotoxicity	Omit dose until resolved to ≤ grade 2, then ↓ 1 dose level
≥ Grade 3 neurotoxicity	Omit dose and discontinue patient from study
Gastrointestinal	
Pancreatitis	
Grade 2 (enzyme elevation or radiologic finding only)	Omit dose until resolved to Grade ≤ 1, then resume treatment at ↓ 1 dose level. If toxicity recurs, permanently discontinue patient from BYL719

Grade ≥ 3
• For patients deriving clinical benefit upon investigator's judgement:
• For other patients:
	• Omit dose until complete resolution of symptoms and lipase resolved to Grade ≤ 1, then resume treatment at ↓ 1 dose level. Only 1 dose reduction is allowed.
	  • If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study.
	  • If toxicity reoccurs, permanently discontinue patient from BYL719
	• Permanently discontinue patient from BYL719

Diarrhea(see also Section 14.3.1)	
Grade 1	Maintain dose level
Grade 2	Omit dose until resolved to ≤ Grade 1, then re-start at the current dose.
Grade ≥ 3	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level

[redacted]

Recommended dose modifications for BYL719	
Worst toxicity CTCAE grade (value)	**During a cycle of therapy**
Visual symptoms or signs	
≥ Grade 3 ocular/vision symptoms interfering with ADL (Activities of daily living) or requiring medical intervention	Omit dose and discontinue patient from study
Stomatitis/Oral mucositis (see also Section 14.3.1)	
Grade 1/Tolerable Grade 2	Maintain dose level. Non-alcoholic or salt water mouth wash.
Intolerable Grade 2 or Grade 3	First occurrence: hold until ≤ Grade 1 and ↓ 1 dose level (if stomatitis is readily manageable with optimal management, re-introduction at the same level might be considered at the discretion of the investigator). Second occurrence: hold until ≤ Grade 1 and ↓ 1 dose level.
Grade 4	Permanently discontinue patient from BYL719.
Skin and subcutaneous tissue disorders	
Consultation with a dermatologist is highly recommended for better assessment and management of BYL719-induced skin toxicity. (see also Section14.3.1)	
Photosensitivity	
Grade 1 (<10% BSA with active skin toxicity*)	**Maintain dose level** • Initiate topical corticosteroids 3-4 x daily, preferred compounds to use are Triamcinolone, Betamethasone as long as skin toxicity is active, during maximum 28 days For patients with symptoms like burning and/or pruritus add non-sedating anti-histamine, consider adding a sedating anti-histamine at night If active rash is not resolved within 28 days of appropriate treatment, consider adding low dose systemic corticosteroid (20-40 mg/d)
Grade 2 (10-30% BSA with active skin toxicity*)	**Maintain dose level**. • Initiate topical corticosteroids 3-4x daily, preferred compounds to use are Triamcinolone or Betamethasone as long as skin toxicity is active, during max. 28 days • Consider adding systemic corticosteroids 20-40mg/d If rash resolves to ≤ G1 within 10 days systemic corticosteroid may be discontinued For patients with symptoms like burning, stinging and/or pruritus add non-sedating anti-histamine, consider adding a sedating anti-histamine at night

[redacted]

Recommended dose modifications for BYL719	
Worst toxicity CTCAE grade (value)	**During a cycle of therapy**
Grade ≥ 3 (> 30% BSA with active skin toxicity*)	**Omit BYL719** dose until rash /skin toxicity is no longer active but fading (G1), [redacted] • Initiate topical corticosteroids 3-4x daily, preferred compounds to use are Triamcinolone or Betamethasone for at least 28 days • Add systemic corticosteroids 20-40mg/d If rash resolves to ≤ G1 within 10 days systemic corticosteroid may be discontinued For patients with symptoms like burning, stinging and/or pruritus add non-sedating anti-histamine during day time, consider adding a sedating anti-histamine at night Re-start BYL719 dose once rash /skin toxicity is no longer active but fading (G1): • at same dose in case of first occurrence, at reduced dose level in case of second occurrence • If rash/skin toxicity still active in up to 10% BSA after more than 14 days, continue oral corticosteroid for at least 48 hours upon re-challenge with BYL719; if rash and/or pruritus do not reoccur within 48 hours after re-challenge with BYL719, systemic corticosteroid may be discontinued For patients with symptoms like burning, stinging and/or pruritus antihistamine regimen should be continued for a minimum of 28 days after re-challenge with BYL719.
Grade 4 (any % BSA associated with extensive superinfection, with IV antibiotics indicated; life-threatening consequences)	• Permanently discontinue patient from BYL719 and consider a dermatology consult. • Treatment of rash should follow guidelines for Grade 3 above with the exception of rechallenge and with any additional measures needed. [redacted]
*"Active" skin toxicities: If there are no new lesions or new areas of involvement developing, and if lesion appearance is changing color from red to pale or light brown, it is likely the skin toxicity has begun to fade and is not to be considered "active" any longer. Treatment reduction can be considered for these areas. The appearance of skin toxicity may fade slowly, over 10 days or more but not requiring ongoing therapy.	
Fatigue / Asthenia (General disorders and administration site conditions)	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ grade 1, then • If resolved in ≤ 7 days, maintain dose level • If resolved in > 7 days, ↓ 1 dose level
Other adverse events	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level
Grade 4	Permanently discontinue patient from BYL719 Omit dose for ≥ grade 3 vomiting or grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetic (as per local practice)

[redacted]

Table 14-7 Criteria for interruption and re-initiation of INC280

Recommended dose modifications for INC280	
Worst toxicity CTCAE Grade (value)	**During a cycle of therapy**
No toxicity	**Maintain dose level**
Investigations (Hematologic)	
Neutropenia (ANC)	
Grade 1 (LLN - 1500/mm^3 or LLN - 1.5 x10^9/L)	Maintain dose level
Grade 2 (< 1500 - 1000/mm^3 or <1.5 - 1.0 x10^9/L)	Maintain dose level
Grade 3 (< 1000 - 500/mm^3 or < 1.0 - 0.5 x10^9/L)	Discontinue INC280: • If elevation lasts for ≤ 7 days: Resume treatment 1 same dose level • If elevation lasts for >7 days: Resume treatment at ↓ 1 dose level
Grade 4 (< 500/mm^3 or < 0.5 x10^9/L)	Discontinue INC280
Febrile neutropenia (ANC < 1.0 x 10^9/L or 1000/mm^3 and a single temperature of >38.3°C (101 °F) or a sustained temperature of ≥38 °C (100.4 ° F) for more than one hour.)	Discontinue INC280: • If ≤ 7 days in duration: Resume treatment at ↓ 1 dose level • If > 7 days in duration: Discontinue INC280
Thrombocytopenia	
Grade 1 or 2 (< LLN – 50 x10^9/L) Grade 3 (<50 – 25 x10^9/L) Grade 4 (< 25 x10^9/L)	Maintain dose level Discontinue INC280 until resolved to ≤ Grade 1 or baseline, then: • If ≤7 days in duration: Resume treatment at same dose level • If > 7 days in duration: Resume treatment at ↓ 1 dose level Discontinue dose until resolved to ≤ Grade 1 or baseline, then ↓ 1 dose level
Investigations (Renal)	
Serum creatinine	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level
Grade 2 (> 1.5 - 3 x ULN)	Discontinue INC280 until resolved to ≤ Grade 1 or baseline, then resume treatment at the same dose level. Patients will be instructed to increase their fluid intake until resolution to ≤ Grade 1 or baseline.
Grade 3 or 4 (≥ 3 x ULN)	Discontinue INC280 until resolved to ≤ Grade 1 or baseline, then resume treatment at ↓ 1 dose level. Patients will be instructed to increase their fluid intake until resolution to ≤ Grade 1 or baseline. If Grade 4 event recurs at any point during participation, discontinue INC280.
Investigations (Hepatic)	
Isolated Total Bilirubin[a]	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level of INC280 with LFTs* monitored
Grade 2 (> 1.5 - 3 x ULN)	Omit/delay dose of INC280 with weekly monitoring of LFTs*, or more frequently if clinical indicated, until resolved to ≤ grade 1, then: • If resolved in ≤ 7 days, maintain dose level of INC280 • If resolved in > 7 days, ↓ 1 dose level of INC280
Grade 3 (> 3 - 10 x ULN)	Omit/ delay dose of INC280 until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, ↓ 1 dose level of INC280 • If resolved in > 7 days, discontinue patient from study drug treatment. The patient should be monitored weekly (including LFTs*) , or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks.

[redacted]

Recommended dose modifications for INC280	
Worst toxicity CTCAE Grade (value)	**During a cycle of therapy**
Grade 4 (> 10 x ULN)	Discontinue patient from study drug treatment. The patient should be monitored weekly (including LFTs*), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks.
Isolated AST or ALT	
Grade 1 or 2 (> ULN - 5 x ULN)	Maintain dose level of INC280 with LFTs* monitored
Grade 3 (> 5 - 20 x ULN)	Omit/delay dose of INC280 until resolved to ≤ grade 1 or ≤ grade 2 if grade 2 elevation at baseline, then: • If elevation in ≤ 7 days: Resume treatment same dose level • If elevations in >7 days: Resume treatment at ↓ 1 dose level
Grade 4 (>20 x ULN)	Discontinue patient from study drug treatment.
Combined[c] elevations of AST or ALT and total bilirubin	
For patients with normal baseline ALT and AST and total bilirubin value: AST or ALT >3.0xULN combined with total bilirubin >2.0 x ULN without evidence of cholestasis[d] OR For patients with elevated baseline AST or ALT or total bilirubin value [AST or ALT>2x baseline AND > 3.0 xULN] OR [AST or ALT > 8.0 xULN], combined with [total bilirubin >2x baseline AND >2.0 xULN	Discontinue study treatment permanently Repeat LFTs as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs*, or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks.
*LFTs include albumin, ALT, AST, GGT, total bilirubin (fractionated [direct and indirect] if total bilirubin > 2.0 x ULN) and ALP (fractionated [quantification of isoforms], if alkaline phosphatase > 2.0 x ULN.	
Investigation(metabolic)	
Amylase or Lipase Increased[b]	
Asymptomatic Grade 1 or 2 (>ULN -2.0 x ULN)	Maintain dose level of INC280
Asymptomatic Grade 3 (> 2.0 - 5.0 x ULN)	Omit dose until resolved to Grade ≤ 2, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then↓ 1 dose level
Asymptomatic Grade 4 (>5.0 x ULN)	Discontinue patient from study drug treatment
Symptomatic elevations of any grade	Discontinue patient from study drug treatment

[redacted]

Recommended dose modifications for INC280	
Worst toxicity CTCAE Grade (value)	**During a cycle of therapy**
[a] If total bilirubin > 3.0 x ULN is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g. review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level of INC280, and continue treatment at the discretion of the Investigator [b] A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within 1 week of the first occurrence of any ≥ Grade 3 of amylase or lipase. [c] "Combined" defined as: total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when omit dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment either at the same dose or at one dose lower if meeting a criterion for dose reduction [d] "Cholestasis" defined as: ALP elevation (>2xULN and R value <2) in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis Note : The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R≤2), hepatocellular (R≥5), or mixed (R>2 and <5) liver injury	
Neurologic	
Any Neurological Toxicity	
Grade 2 (> 1.5 - 3 x ULN)	Discontinue INC280. Neurological assessments must be repeated at least twice a week until resolution to < grade 1. Unscheduled MRI and gadolinium enhanced T1 imaging may also be conducted to evaluate patients for intramyelinic edema like lesions, brain metastases and other unanticipated CNS occurrences. An EEG may be performed to monitor for physiological changes in brain activity.
Cardiac	
Cardiac general	
Grade 1 or 2	Maintain dose level
Grade 3	Discontinue INC280 until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4	Discontinue INC280
Other adverse events	
Grade 1 or 2	Maintain dose level
Grade 3	Discontinue INC280 until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4	Discontinue INC280

[redacted]

Table 14-8 Criteria for interruption and re-initiation of LDK378

Recommended dose modifications for LDK378	
Worst toxicity CTCAE Grade (value)	**During a cycle of therapy**
No toxicity	**Maintain dose level**
Investigations (Hematologic)	
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1.5 x 10^9/L) Grade 2 (ANC < 1.5 and ≥ 1.0 x 10^9/L) Grade 3 (ANC < 1.0 and ≥ 0.5 x 10^9/L)	Maintain dose level
Grade 4 (ANC < 0.5 x 10^9/L)	Omit dose until resolved to ≤ Grade 2, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Febrile neutropenia	
(ANC < 1.0 x 10^9/L, with a single temperature of ≥ 38.3 °C or a sustained temperature of ≥ 38 °C for more than one hour)	Omit dose until clinically resolved and neutropenia ≤ Grade 2, then ↓ 1 dose level
Thrombocytopenia	
Grade 1 (PLT < LLN - 75 x 10^9/L) Grade 2 (PLT < 75 and ≥ 50 x 10^9/L)	Maintain dose level
Grade 3 (PLT < 50 and ≥ 25 x 10^9/L)	Omit dose until resolved to ≤ Grade 2, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (PLT < 25 x 10^9/L)	Omit dose until resolved to ≤ Grade 2, then ↓ 1 dose level
Investigations (Hepatic)	
Alkaline phosphatase and/or GGT	
Isolated elevations of any grade	Maintain dose level
Total Bilirubin* (for patients with Gilbert Syndrome these dose modifications apply to changes in direct [conjugated] bilirubin only)	
Grade 1 (> ULN and ≤ 1.5 x ULN)	Maintain dose level with LFTs** monitored as per protocol
Grade 2 (> 1.5 and ≤ 3.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Omit dose until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Grade 3 (> 3.0 and ≤ 10.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Omit dose until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, ↓ 1 dose level • If resolved in > 7 days, then discontinue patient from LDK378. The patient should be monitored LFTs** per protocol section 14.3.3, or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks.
Grade 4 (> 10.0 x ULN)	Permanently discontinue patient from LDK378. The patient should be monitored LFTs** per protocol Section 14.3.3, or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks.

[redacted]

Recommended dose modifications for LDK378	
Worst toxicity CTCAE Grade (value)	**During a cycle of therapy**
AST or ALT	
Grade 1 (> ULN and ≤ 3.0 x ULN)	Maintain dose level with LFTs** monitored per protocol
Grade 2 (> 3.0 and ≤ 5.0 x ULN) without total bilirubin elevation to > 2.0 x ULN	Maintain dose level with LFTs** monitored per protocol Section 14.3.3 or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN
Grade 3 (> 5.0 and ≤ 20.0 x ULN) without total bilirubin elevation to > 2.0 x ULN	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4 (> 20.0 x ULN) without bilirubin elevation to > 2.0 x ULN	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level Monitoring LFTs** per protocol Section 14.3.3, or more frequently if clinically indicated, until resolved to baseline or stabilization over 4 weeks.
AST or ALT and concurrent Bilirubin	
AST or ALT > 3.0 x ULN and total bilirubin > 2.0 x ULN	Permanently discontinue patient from LDK378
PANCREATIC	
Amylase and/or lipase elevations (in the absence of clinical symptoms)	
Grade 1 (> ULN and ≤1.5 x ULN)	Maintain dose level
Grade 2 (>1.5 - 2.0 x ULN)	Maintain dose level
Grade 3 (> 2.0 – 5.0 x ULN)	Omit dose until resolved to ≤ Grade 2, then If resolved in ≤ 7 days, maintain dose level If resolved in > 7 days, ↓ 1 dose level
Grade 4 (> 5.0 x ULN)	Omit dose and then discontinue from study drug treatment
Investigations (Renal)	
Serum creatinine	
Grade 1 (>1 and ≤1.5 x baseline; >ULN and < 1.5 x ULN)	Maintain dose level
Grade 2 (>1.5 and ≤3.0 x baseline; ≥ 1.5 and ≤ 3 x ULN)	Omit dose until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Grade 3 (>3.0 x baseline; > 3.0 and ≤ 6.0 x ULN)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4 (> 6.0 x ULN)	Permanently discontinue patient from LDK378
Gastrointestinal	
Diarrhea	
Grade 1 (despite maximal anti-diarrheal medication)	Maintain dose level but adjust anti-diarrhea treatment
Grade 2 (despite maximal anti-diarrheal medication)	Omit dose until resolved to ≤ Grade 1, then maintain dose level. If diarrhea returns as ≥ Grade 2, then suspend dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 3 (despite maximal anti-diarrheal medication)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4 (despite maximal anti-diarrheal medication)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level

[redacted]

Recommended dose modifications for LDK378	
Worst toxicity CTCAE Grade (value)	**During a cycle of therapy**
Nausea	
Grade 1 or 2 (despite standard anti-emetics)	Maintain dose level but adjust anti-emetic treatment
Grade 3 (despite standard anti-emetics)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Vomiting	
Grade 1 (despite standard anti-emetics)	Maintain dose level but adjust anti-emetic treatment
Grade 2 (despite standard anti-emetics)	Omit dose until resolved to ≤ Grade 1, then maintain dose level. If vomiting returns as ≥ Grade 2, then suspend dose until resolved to ≤ Grade 1, then ↓ 1 dose level.
Grade 3 (despite standard anti-emetics)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4 (despite standard anti-emetics)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
METABOLIC	
Any Grade hypophosphatemia	**Treatment with phosphate supplements as clinically indicated and maintain dose level**
Persistent hyperglycemia (glucose >250 mg/dL) despite optimal anti-hyperglycemic therapy	Omit dose until hyperglycemia is adequately controlled, then resume LDK378 at ↓ 1 dose level If adequate hyperglycemic control cannot be achieved with optimal medical management, permanently discontinue patient from LDK378
Fatigue/asthenia	
Grade 1 or 2	Maintain dose level
Grade 3	• If grade 3 fatigue resolves in ≤ 7 days, maintain dose level • If grade 3 fatigue lasts > 7 days, omit dose until resolved to ≤ Grade 2 and then ↓ dose level
PULMONARY	
Notes: • Withhold LDK378 for acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnea, cough and fever and during diagnostic workup for pneumonitis/ILD. • During evaluation of potential grade 2, 3, and 4 pneumonitis, if an infectious etiology is confirmed (i.e., pneumonia) and pneumonitis is excluded, then consider resuming LDK378 at current dose level after the pneumonia resolves.	
PNEUMONITIS	
Grade 1 Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Exclude infectious etiology. Omit LDK378 dose during diagnostic workup for pneumonitis/ILD. Omit LDK378 dose until resolved, then ↓ 1 dose level. Discontinue LDK378 if does not resolve within 6 weeks. If grade 1 pneumonitis recurs after dose reduction, omit LDK378 dose until resolved, then ↓ 1 dose level (i.e., 450 mg QD). Discontinue LDK378 if does not resolve within 6 weeks. If grade 1 pneumonitis recurs after 2nd dose reduction (i.e., 450 mg QD), the patient must be discontinued.
Grade 2 Symptomatic; medical intervention indicated; limiting instrumental ADL	Exclude infectious etiology. Omit LDK378 dose during diagnostic workup for pneumonitis/ILD. Administer symptomatic therapy. Consider treatment with corticosteroids and/or antibiotics. Permanently discontinue patient from LDK378.
Grade 3 Severe symptoms; limiting self-care ADL; oxygen indicated	Exclude infectious etiology. Omit LDK378 dose during diagnostic workup for pneumonitis/ILD. Administer symptomatic therapy. Consider treatment with corticosteroids and/or antibiotics. Permanently discontinue patient from LDK378.

[redacted]

Recommended dose modifications for LDK378	
Worst toxicity CTCAE Grade (value)	**During a cycle of therapy**
Grade 4 Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Exclude infectious etiology. Omit LDK378 dose during diagnostic workup for pneumonitis/ILD. Administer symptomatic therapy. Consider treatment with corticosteroids and/or antibiotics. Permanently discontinue patient from LDK378.
CARDIAC	
Electrocardiogram QT corrected (QTc) interval prolonged	
Grade 1 (QTcF 450-480 ms) Grade 2 (QTcF 481-500 ms)	Maintain dose level
Grade 3 (QTcF ≥501 ms on at least two separate ECGs)	Omit dose until QTcF is less than < 481ms, then ↓ 1 dose level • Assess the quality of the ECG recording and the QT value and repeat if needed Repeat ECG in 24 hours, or less, as clinically indicated; continue monitoring as clinically indicated until QTcF < 481 ms In addition:-Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities before resuming study drug treatment • Review concomitant medication use for drugs with the potential to increase the risk of drug exposure related to QT prolongation • Consider collecting a time-matched PK sample and record time and date of last study drug intake After resumption of dosing: • Repeat ECGs 7 days after dose resumption for all patients who had therapy interrupted due to QTcF ≥ 501 ms.
Grade 4 (QTcF ≥501 or >60 ms change from baseline and Torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Permanently discontinue patient from LDK378
Bradycardia	
Grade 1 or 2	Omit dose until recovery to asymptomatic bradycardia or to a heart rate ≥60 bpm Evaluate concomitant medications known to cause bradycardia, and adjust the dose of LDK378.
Grade 3 Grade 4 (in patients taking a concomitant medication also known to cause bradycardia or a medication known to cause hypotension)	Omit dose until recovery to asymptomatic bradycardia or to a heart rate ≥60 bpm If the concomitant medication can be adjusted or discontinued, resume ceritinib at ↓ 1 dose level with frequent monitoring
Grade 4 (in patients who are not taking a concomitant medication also known to cause bradycardia or known to cause hypotension)	Permanently discontinue LDK378.
* If Grade 3 or 4 hyperbilirubinemia is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the investigator. **LFTs include albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 x ULN), alkaline phosphatase and GGT.	
Other adverse events	
Grade 1 or tolerable Grade 2	Patients are encouraged to continue at the current dose of study treatment.
Intolerable Grade 2	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level

[redacted]

Recommended dose modifications for LDK378	
Worst toxicity CTCAE Grade (value)	**During a cycle of therapy**
Grade ≥ 3 • For patients deriving clinical benefit and AE is not life threatening upon investigator's judgement: • For other patients:	If it is not considered by the investigator to be life-threatening, study treatment should be interrupted until resolution to ≤ Grade 1, then study treatment may continue following a dose reduction to the next dose level. Permanently discontinue study treatment

Table 14-9 Criteria for interruption and re-initiation of MEK162

Recommended dose modifications for MEK162	
Worst toxicity CTCAE Grade (value)	**During a cycle of therapy**
No toxicity	**Maintain dose level**
Eye disorder - Retinal event: The current guidance is based on grading by Table 14-10 for Retinal Detachment. Any diagnosis of retinal events must be supported by presence or absence of symptoms, or visual acuity impairment and findings in Ocular Coherence Tomography (OCT) Note: Results and images of Ocular Coherence Tomography (OCT) must be made available upon request.	
Grade 1**	Maintain dose level of MEK162 and repeat ophthalmic monitoring* including visual acuity assessment and OCT within 10 days • If patient remains asymptomatic (Grade 1) maintain dose level of MEK162 and continue the schedule of visual assessments established per protocol including visual acuity assessment and OCT at each visit. In case OCT findings denote definitive worsening, treatment should be interrupted and the case should be discussed with the investigator, including ophthalmologist and the Sponsor prior to resumingtreatment. • If patient becomes symptomatic (blurred vision, photopsia, etc) or visual acuity assessment shows grade 2, follow Grade 2 dose guidelines below
Grade 2**	Interrupt dose of MEK162 and repeat ophthalmic monitoring* including visual acuity assessment and OCT within 10 days • If resolved to baseline or Grade ≤ 1 , resume dose of MEK162 at the same dose level and continue the schedule of visual assessments established per protocol including visual acuity assessment and OCT in each visit. • If not resolved to baseline or Grade ≤ 1, resume dosing of MEK162 at a reduced dose level and continue the schedule of visual assessments established per protocol including visual acuity assessment and OCT in each visit. In case OCT findings denote definitive worsening, treatment should remain interrupted and the case should be discussed with the investigator , including ophthalmologist and the Sponsor prior to resuming treatment. Continue the schedule of visual assessments established per protocol including visual acuity assessment and OCT in each visit.
Grade 3**	Interrupt MEK162 and repeat ophthalmic monitoring* including visual acuity assessment and OCT within 10 days: • If resolved to baseline or Grade ≤ 2, resume MEK162 at a reduced dose level and continue the schedule of visual assessments established per protocol including visual acuity assessment and OCT at each visit. In case OCT findings denote definitive worsening, treatment should be interrupted and the case should be discussed with the investigator, including ophthalmologist and the Sponsor prior to resumingtreatment. • If not resolved to baseline or Grade ≤ 2, continue the interruption and repeat the ophthalmic assessment including visual acuity assessment and OCT in 10 days. • If remains Grade 3, permanently discontinue MEK162

[redacted]

Recommended dose modifications for MEK162	
Worst toxicity CTCAE Grade (value)	**During a cycle of therapy**
Grade 4	Permanently discontinue MEK162 and immediately follow up with ophthalmic monitoring*
NOTE: Any visual acuity impairment at screening should be documented and should be considered as baseline NOTE: In case that the patient improves or remains stable in terms of symptoms and visual acuity assessment but the OCT denotes definitive signs of worsening, the treatment must be interrupted. Re-initiation of treatment will be discussed between the investigator (including ophthalmologist) and the sponsor.	
Other eye disorders	
Grade 1 - 2	Maintain dose level of MEK162 and increase frequency of ophthalmic monitoring* to at least every 14 days.
Grade 3	Omit dose of MEK162 and refer patient to ophthalmologist within one week: • If resolved to Grade ≤ 1 in ≤ 21 days, then ↓ 1 dose level of MEK162 • If not resolved to Grade ≤ 1 in ≤ 21 days, then discontinue patient from study treatment and refer the patient to ophthalmologist for ophthalmic monitoring*[a].
Grade 4	Omit dose of MEK162 and discontinue patient from study treatment and refer the patient to ophthalmologist for ophthalmic monitoring*[a].
Eye disorder – RVO Note: Results of ophthalmic examinations must be made available upon request. This includes scans/images of fluorescein angiography should a patient be assessed using this technique	
RVO of any grade	**Permanently discontinue patient from MEK162.**
Investigations (Hepatic)	
AST or ALT	
Grade 1 (> ULN - 3 x ULN)	Maintain dose level
Grade 2 AST or ALT (> 3 - 5.0 x ULN or 3 X baseline value****) without bilirubin elevation > 2.0 x ULN	Omit dose until resolved to Grade ≤ 1 (or Grade ≤ 2 in case of liver metastasis), then: • If resolved in ≤ 14 days, then maintain dose level. • If resolved in > 14 days, then ↓ 1 dose level.
AST or ALT > 3.0 - 5.0 x ULN and **blood bilirubin[a] > 2.0 x ULN**	Interrupt dose of MEK162 until resolved to Grade ≤ 1, then: • If resolved in ≤ 7 days, reduce dose level** of MEK162. • If resolved in > 7 days, discontinue patient from study drug treatment.
• Grade 3 AST or ALT (> 5.0 - 8.0 x ULN) without bilirubin elevation > 2.0 x ULN AST or ALT (>8.0 x ULN) without bilirubin elevation > 2.0 x ULN	Omit dose until resolved to Grade ≤ 1 (or Grade ≤ 2 in case of liver metastasis), then: • If resolved in ≤ 14 days, then maintain dose level . • If resolved in > 14 days, then ↓ 1 dose level. Permanently discontinue MEK162
Grade 4 (> 20.0 x ULN)	Permanently discontinue patient from MEK162.
AST or ALT and Bilirubin	
AST or ALT > 3.0 - 5.0 x ULN and blood bilirubin > 2.0 x ULN	Omit dose until resolved to Grade ≤ 1, then: • If resolved in ≤ 7 days, then ↓ 1 dose level • If resolved in > 7 days, then discontinue patient from study treatment.

[redacted]

Recommended dose modifications for MEK162	
Worst toxicity CTCAE Grade (value)	**During a cycle of therapy**
AST or ALT ≥ 5.0 x ULN and blood bilirubin ≥ 2.0 x ULN	Permanently discontinue patient from MEK162.
Cardiac disorders	
Left ventricular systolic dysfunction	
Asymptomatic absolute decrease of >10% in LVEF compared to baseline and the ejection fraction is below the institution's lower limit of normal** (i.e. a decrease of 60% to 48% is an absolute decrease of 12%)	Omit dose and repeat evaluation of LVEF within 2 weeks If the LVEF recovers (defined as LVEF ≥50% or ≥ LLN and absolute decrease ≤ 10% compared to baseline) within ≤ 3 weeks, then reduce 1 dose level . Monitor LVEF 2 weeks after restarting on MEK162, then every 3 weeks for 12 weeks and then per protocol. If the LVEF recovers ≥ 3 weeks, then discontinue patient from study treatment. Close follow-up of LVEF for 16 weeks or until resolution.
Grade 3 - 4	Permanently discontinue patient from study treatment. Close follow-up of LVEF for 16 weeks or until resolution Note: Copies of ECHO and/or MUGA scans could be requested for patients with absolute decrease of >10% in LVEF compared to baseline and LVEF < LLN
CK elevation	
Grade 1-2	Continue treatment on same dose level. Ensure patient is adequately hydrated and monitor CK and creatinine (Section 7.2.2.6.3) (If total CK ≥ 3 X ULN, measure isoenzymes, serum creatinine and myoglobin in blood or urine
Grade 3 (> 5.0 - 10.0 x ULN) **without** renal impairment (i.e. serum creatinine < 1.5 X ULN or < 1.5 X baseline)	If asymptomatic, maintain dose of MEK162. Ensure patient is adequately hydrated. Monitor closely and measure isoenzymes, serum creatinine and myoglobin in blood or urine (Section 7.2.2.6.3) If symptomatic (muscle pain/spasms), interrupt dose of MEK162 until resolved to CTCAE Grade ≤ 1 and monitor closely (Section 7.2.2.6.3), then: - If resolved in ≤ 21 days, reduce 1 dose level of MEK162 - If resolved in > 21 days, discontinue patient from study drug treatment
Grade 4 **without** renal impairment (i.e. serum creatinine < 1.5 X ULN or < 1.5 X baseline) Grade 3 or 4 **with** renal impairment (i.e. serum creatinine ≥ 1.5 X ULN or ≥ 1.5 X baseline	If asymptomatic, interrupt dose of MEK162. Ensure patient is adequately hydrated and monitor closely and measure isoenzymes, serum creatinine and myoglobin in blood or urine (Section 7.2.2.6.3) - If resolved in ≤ 21 days, reduce 1 dose level of MEK162 - If resolved in > 21 days, discontinue patient from study drug treatment If symptomatic, permanently discontinue study drug treatment
QTc Prolongation	
QTcF > 500 msec (Grade 3) (confirmed by triplicate ECGs 5 minutes apart)	1st occurrence: Treatment with MEK162 should be temporarily suspended. Electrolyte abnormalities, if any, should be corrected and any concomitant medication that may potentially prolong QT should be discontinued. Patient monitoring until resolution of the adverse event should be implemented in the hospital including a consultation with a cardiologist. Once the QTcF prolongation has resolved (returned to baseline value or CTC Grade < 1), MEK162 may be restarted at a reduced dose (30 mg BID). 2nd occurrence: If a second episode occurs that is attributed to MEK162, study drug must be permanently discontinued.

[redacted]

Recommended dose modifications for MEK162	
Worst toxicity CTCAE Grade (value)	**During a cycle of therapy**
Rash	
Grade 1	Treatment with MEK162 should be maintained at the current dose Initiate prophylactic regimen if it was not already started and monitor closely
Grade 2	1st occurrence: Treatment with MEK162 should be maintained at the current dose and rash should be closely monitored. Initiate prophylactic regimen if it was not already started Reassess within a maximum of two weeks. If rash worsens or does not improve, interrupt dosing until improvement to Grade ≤ 1. Resume treatment at the same dose level. 2nd occurrence: Reassess within a maximum of 2 weeks. If rash worsens or does not improve, interrupt dosing until improvement to Grade ≤ 1. Resume treatment at a reduced dose level. Only one dose reduction is permitted.
Grade 3	1st occurrence: Treatment with MEK162 should be interrupted. Reassess the patient weekly. Consider referral to dermatologist and manage rash per dermatologist's recommendation. -Interrupt treatment until improvement to Grade ≤ 1. Resume treatment with MEK162 at the same dose level. 2nd occurrence: Interrupt treatment until improvement to Grade ≤ 1. Resume treatment with MEK162 at a reduced dose level. Consider referral to dermatologist and manage rash per dermatologist's recommendation
Grade 4	Permanently discontinue MEK162
Other adverse events	
Grade 1-2	In the event of a persistent Grade 2 other AE that is not responsive to supplemental therapy or that prevents the patient from receiving treatment at full dose, then study treatment should be reduced.
Grade 3	For other AEs, interrupt study treatment until resolution to Grade ≤1 or to worst pre-treatment/ Baseline level, whichever is more abnormal. If the event resolves within 21 days then study treatment may be restarted at a lower dose (one level below that previously received) based upon the Investigator's discretion.
Grade 4	Permanently discontinue study treatment***
* Ophthalmic monitoring recommended: further evaluation with specialized retinal imaging (e.g. Ocular coherence tomography, angiography) *a Ophthalmic monitoring mandated for retinal events, posterior uveitis, RVO: further evaluation with specialized retinal imaging (e.g. ocular coherence tomography, angiography) ** Not according to CTCAE, For retinal detachment, please follow the Table 14-10, grading for retinal detachment. ***A patient with a Grade 4 AE may resume treatment at the lower dose level if the AE recovers to Grade ≤1 within 21 days of discontinuing drug and, if in the opinion of the Investigator and Novartis Medical Monitor, the event is not life-threatening, and the patient can be managed and monitored for recurrence of AE. ****For patients enrolled with liver metastases and baseline LFT elevations.	

Table 14-10 Grading for retinal detachment

Grade	Description
1	Asymptomatic (But with findings of retinal detachment in OCT, fundoscopy or biomicroscopy)
2	Symptomatic with moderate decrease in visual acuity (20/40 or better); limiting instrumental activities of daily living
3	Symptomatic with marked decrease in visual acuity (worse than 20/40); limiting self-care activities of daily living
4	Blindness (20/200 or worse) in the affected eye

[redacted]

14.3 Anticipated risks and notification to investigators

It is in the investigators' judgment on how to treat study treatment induced adverse events. Below are recommendations of treatment guideline.

14.3.1 BYL719

Guideline for the treatment of study treatment induced hyperglycemia

BYL719, like other PI3K inhibitors, may affect glucose homeostasis which could result in increases of plasma glucose and insulin resistance (Busaidy 2012). BYL719 induced hyperglycemia is generally manageable with adequate antidiabetic treatment. BYL719 induced hyperglycemia typically occurs within the first month of treatment. Patients with pre-diabetes (i.e. FPG 100 – 125 mg/dl; 5.6 - 6.9 mmol/L) and those with an established diagnosis of type 2 diabetes mellitus should be monitored carefully, thus allowing an early detection and prompt management of increases in FPG while on BYL719 treatment. However all patients, even those with FPG within normal limits at screening, may develop BYL719 induced hyperglycemia. Patients should always be instructed to follow dietary guidelines provided by the American Diabetes Association, e.g. small frequent meals, low carbohydrate content, high fiber, balancing carbohydrates over the course of the day; three small meals and 2 small snacks rather than one large meal and exercise, as appropriate.

Detailed guidelines for management of BYL719 induced hyperglycemia is provided in Table 14-6 following discussion with an advisory board. This includes early administration of metformin. Metformin may be titrated to a daily dose of 1000 mg BID. Local protocols per standard clinical practice may be followed. Fasting plasma glucose may be performed locally for rapid availability for safety evaluation and management guidance. Special attention should be paid to the risk of hypoglycemia in patients interrupting BYL719 treatment and concomitantly receiving insulin and/or sulfonylureas.

Consultation with a diabetologist is highly recommended for better assessment and management of BYL719-induced hyperglycemia.

Guidelines for the treatment of study drug induced skin toxicity

Skin toxicity is a class-effect adverse event observed with PI3K i/mTORi agents.

Close monitoring of potential skin reactions will be performed at each planned visit and will be reported as adverse event. The most frequent skin adverse events reported are: maculopapular rash (only a minority present acneiform rash); pruritus and dry skin. The onset is typically within the first 2 months of treatment start and is reversible with adequate comedication and treatment interruption if needed. Skin reactions may fade slowly over 10 days or more and may not require ongoing concomitant therapy. If there are no new lesions or new areas of involvement developing, and if the appearance is changing color from red to pale or light brown, it is likely the eruption has begun to fade, i.e. not considered active any longer. Consultation with a dermatologist is highly recommended for better assessment and management of BYL719-induced skin toxicity. Photographs of skin rashes events as well as skin biopsy, if possible, are recommended. According to the investigator discretion, a paired skin biopsy could be obtained (from both affected and an unaffected skin area) for local

histopathology assessment to further assess rash if clinically appropriate. In case of Grade 3/4 skin toxicity, Novartis requests that a skin biopsy is performed and sent to Novartis Central laboratory for further research purpose on the pathology and mechanism of PI3K inhibitor treatment induced skin toxicity. At the Investigator's discretion, non-sedating antihistamines (e.g. cetirizine (Zyrtec©) once daily) may be used as prophylactic treatment to reduce severity of rash, especially for patients with a history of hypersensitivity reactions like seasonal allergies, hay fever, allergic asthma or drug induced exanthema.

Consultation with a dermatologist is highly recommended for better assessment and management of BYL719-induced skin toxicity.

Recommended therapies for skin toxicity events include:

- Topical steroids Triamcinolone or Betamethasone 3-4x daily for at least 28 days. Consider spray preparation for ease of application on trunk. For scalp involvement, consider a foam preparation
- In case of burning, stinging, pruritus: oral antihistamines (sedating, evening): diphenhydramine 25-50mg t.i.d.; hydroxizine 25mg t.i.d. or q.i.d
- Oral antihistamines (non-sedating, day time): fexofenadine 180mg q.d. or 60mg TID (monitor the use of this class of drugs since skin toxicity has also been reported)
- Low dose oral corticosteroids, e.g. 20-40mg q.d. prednisone or equivalent up to 10 days of treatment. If lesions are still not controlled with all of the above, consideration can be given to the use of:
  - Topical antibiotics: clindamycin 1 - 2%; erythromycin 1% -2% (gel or solution formulation can be used, ointments cannot be used); metronidazole 1%; silver sulphadiazine
  - Oral antibiotics: doxycycline 100mg b.i.d.; minocycline 100mg b.i.d.; oxytetracycline 500mg b.i.d
  - Topical antipruritics (pramoxine 1%, doxepin 5% cream) applied twice daily
  - GABA Agonists: Gabapentin 300mg every 8 hours, Pregabalin 50-75 mg every 8 hours (to adjust of renal impairment). Depending on patient's clinical condition be aware of potential and common side effects observed with GABA agonists such as: somnolence, dizziness (both drugs) and peripheral edema (Gabapentin) among others adverse events.

Dry skin has been reported. It is recommended that patients with dry skin use mild and fragrance free soaps and detergents. According to the severity and BSA extension patients may apply mild moisturizers, e.g. ammonium lactate cream 12%.

It is recommended to caution patients to avoid sun exposure during treatment with BYL719, especially when they already have experienced rash or other skin toxicities as the increased blood flow of the skin may worsen skin symptoms. Patients should be advised to take measures to protect themselves from direct exposure to sunlight, including the wearing of sunglasses as well as the regular use of sunscreen, hats, long-sleeve shirts and long pants when outdoors.

[redacted]

Management of pneumonitis

All patients will be routinely asked about and observed for the occurrence of adverse events including new or changed pulmonary symptoms (consistent with lung abnormalities). Patients who are suspected to have developed pneumonitis should stop study treatment BYL719 immediately and undergo appropriate imaging (high resolution CT scan) and bronchoalveolar lavage for biopsy should be considered if clinically appropriate. Infectious causes of interstitial lung disease should be ruled out. Investigators should follow institutional practice for management of pneumonitis which should include treatment with high dose corticosteroids; antibiotic therapy should be administered concurrently if infectious causes have not been ruled out. Consultation with a pulmonologist is highly recommended for any pneumonitis case during the study treatment. If pneumonitis is confirmed, then BYL719 should be permanently discontinued.

Follow-up on amylase or lipase elevation (≥ CTCAE Grade 3)

Patient with amylase or lipase elevation ≥ CTCAE Grade 3 must be tested weekly (or more frequently if clinically indicated) until ≤ Grade 1 (or baseline). After resumption of dosing, continue to test weekly for one additional cycle. If no reoccurrence of ≥ Grade 2 event, continue monitoring every cycle.

An exception to these follow-up guidelines will be made for cases of isolated amylase elevations in which amylase fractionation demonstrates that pancreatic amylase is ≤ Grade 1. In such cases, total amylase and fractionated amylase should be monitored weekly (or more frequently if clinically indicated) for 4 weeks. If pancreatic amylase remains ≤ Grade 1, subsequent monitoring must be performed at least every 4 weeks (or more frequently if clinically indicated).

Patients who discontinue study treatment due to pancreatic toxicity must be monitored weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 1 or stabilization occurs (no CTCAE grade change over 4 weeks).

If amylase and/or lipase elevations are accompanied by new or progressive unexplained abdominal symptoms such as severe pain or vomiting, withhold study treatment, then perform diagnostic procedures (e.g., abdominal CT scan or ultrasound) to exclude pancreatic pathology.

See also dose modification guidelines described in Table 14-6.

Follow up on potential drug-induced liver injury (DILI) cases

Refer to Section 14.3.2 (Follow up on potential drug-induced liver injury (DILI) cases)

Guidelines for the treatment of study treatment induced diarrhea

In the event diarrhea is observed in patients the below management plan should be followed. This treatment algorithm is based on publications on how to manage diarrhea caused by cytotoxic regimens (Wadler 1998, Kornblau 2000).

[redacted]

- **First report of diarrhea**

Please obtain a history of onset and duration of the diarrhea. This should include the description of number of stools from patient and stool composition (e.g. watery, presence of occult blood or mucus in stool etc.) Patients fever should be assessed and details should be obtained whether patient is also experiencing abdominal pain, cramps, bloating, distension, nausea, vomiting, dizziness and weakness in order to rule out the risk of sepsis, bowel obstruction or dehydration. Please review patient's medication profile and identify any diarrheagenic agents. Please also ask about patient's dietary profile to identify any diarrhea causing foods. Patients should be checked after starting study treatment to proactively look for start of diarrhea so that anti-diarrheal treatment can be started as soon as possible to limit severity of the diarrheal toxicity. Call patients at home, if necessary, early during the first 8 weeks of treatment start. Instruct the patient to call at the first sign of diarrhea.

- **Management of diarrhea**

General recommendations:

- Stop all lactose-containing products, alcohol
- Stop laxatives, bulk fiber (e.g. Metamucil®) and stool softeners (e.g. docusate sodium, Colace®)
- Stop high-osmolar food supplements such as Ensure Plus® and Jevity Plus® (with fiber)
- Drink 8 to 10 large glasses of clear liquids per day (e.g. water, Pedialyte®, Gatorade®, broth)
- Eat frequent small meals (e.g. bananas, rice, apple sauce, toast)

It is recommended that patients are provided with loperamide tablets at the start of each cycle. Patients should be instructed on the use of loperamide at Cycle 1 in order to manage signs or symptoms of diarrhea at home. Patients should be instructed to start oral loperamide (initial administration of 4 mg, then 2 mg every 4 hrs (maximum of 16 mg/day) at the first sign of loose stool or symptoms of abdominal pain. These instructions should be provided at each cycle and the site should ensure that the patient understands the instruction. At the beginning of each cycle, each patient should be specifically questioned regarding any experience of diarrhea or diarrhea related symptoms. If symptoms were experienced, then the site should question the patient regarding the actions taken for these symptoms.

Intensive management of diarrhea must be instituted at the first sign of abdominal cramping, loose stools or overt diarrhea. Note that all concomitant therapies used for treatment of diarrhea must be recorded on the Concomitant Medications/Non-drug Therapies eCRF.

- Loperamide is the first-line treatment of diarrhea (any Grade) in this recommended algorithm. Persistent symptoms may require the administration of high dose loperamide followed by treatment with second-line agents such as opium tincture and octreotide acetate, based on severity and duration of diarrhea and related signs/symptoms. Another first-line treatment for diarrhea is diphenoxylate hydrochloride/atropine sulfate. This medication may be used in place of loperamide however it is important to note that loperamide and diphenoxylate hydrochloride/atropine sulfate must not be used in conjunction with one another due to the risk of developing paralytic ileus. Upon treatment with any antidiarrheal agents, the patient's response to treatment should be observed and

[redacted]

appropriately documented in the source document and eCRF**Treatment of grade 1 and grade 2 diarrhea**

Grade 1 or grade 2 diarrhea will be treated with standard loperamide regimen (initial administration of 4 mg, then 2 mg every 4 hours (maximum of 16 mg/day) or after each unformed stool). Diarrhea resolved

- Continue instructions for dietary modification
- Gradually add solid foods to diet
- Discontinue loperamide after 12 hrs diarrhea-free interval

Diarrhea unresolved

Persisting diarrhea CTCAE grade 1 or 2 will be treated with addition of opium tincture or dihydrocodeine tartrate tablets/injections with monitoring of patients condition to rule out dehydration, sepsis, ileus) medical check and selected workup if patient does not need hospitalization (see section Diarrhea workup and additional test in the particular trial protocol). Observe patient for response to antidiarrheal treatment.

Persisting diarrhea CTCAE grade 3 or 4 may be treated with hospitalization, high dose loperamide (initial 4 mg, then 2 mg every 2 hrs) and addition of opium tincture (DTO) or dihydrocodeine tartrate tablets/injections, start of IV fluids and antibiotics as needed with monitoring of patients condition (to rule out dehydration, sepsis, ileus) medical check and workup (perform appropriate additional testing). Observe patient for response.

After again 12-24 hrs:

Diarrhea resolved

- Continue instructions for dietary modification
- Gradually add solid foods to diet
- Discontinue loperamide and/or other treatment after 12 hrs diarrhea-free interval

Diarrhea unresolved

- If diarrhea still persisting (CTCAE grades 1 and 2), after 2x 24 hrs with high dose loperamide and opiates then admit to hospital and employ measures as for CTCAE grade 3 and 4 until diarrhea resolved.
- If diarrhea still persisting and progressed to CTCAE grades 3 and 4, employ measures described below.
- **Treatment of grade 3 and grade 4 diarrhea**

Patients experiencing grade 3 and grade 4 diarrhea must be hospitalized. Upon hospitalization patient should be treated with high dose loperamide (initial 4 mg, then 2 mg every 2 hours with addition of opium tincturate or dihydrocodeine tartrate tablets/injections). Patient should receive i.v. fluids and antiboitics if indicated and should be monitored to rule out sepsis, dehydration or ileus. Patient should be followed per diarrhea workup plan. Continue to observe patient for response to anti-diarrheal treatment.

[redacted]

After 12-24 hrs:

- If diarrhea persisting administer s.c. Sandostatin/octreotide (100-500 µg tid)
- Continue IV fluids and antibiotics as needed
- If diarrhea CTCAE grade 3 or 4 still persists patients should receive opium tincture or dihydrocodeine tartrate injections s.c. or i.m.
- If diarrhea CTCAE grade 3 or 4 is still persisting s.c. Sandostatin/octreotide (500-1000 µg TID) should be administered.
- To control and/or resolve diarrhea, next cycle of treatment should be delayed by 1 or 2 weeks. Treatment should be continued only when diarrhea resolved.
- **Diarrhea workup**

The following appropriate tests are based on the following publication (AGA Technical Review on the Evaluation and Management of Chronic Diarrhea 1999).

- **Spot stool analysis**

Collect stool and separate it from urine, use special containers and analyze immediately. If analysis cannot be done immediately, freeze samples for later analysis. Examine the collected stool for occult blood and under the microscope examine for fecal leucocytes utilizing Wright staining. The stool should also be examined for C.difficile toxin. Lastly, examine fecal cultures for pathogens such as Shigella and pathogenic E. coli. If it is suspected that the patient might have been in contact with contaminated water, examine fecal cultures for Aeromonas and Pleisiomanas.

- **Endoscopic examinations**

Endoscopic examinations should be only considered if absolutely necessary. Patient's bowel is likely to be fragile with evidence of colitis and great care and caution must be exercised in undertaking such an invasive procedure. If endoscopy is undertaken consider gastroscopy to obtain jejunal fluid for assessment of bacterial overgrowth for cultures and biopsy of proximal jejunum to assess extent of inflammatory jejunitis. Also, consider sigmoidoscopy for reassessment of colitis.

14.3.2 INC280

Guidelines for the follow-up of laboratory liver abnormalities

In patients with any clinically relevant laboratory liver abnormality, as defined below, hepatic toxicity monitoring must include ALL of the following liver function tests (LFTs): albumin, AST, ALT, total bilirubin (fractionated if total bilirubin >2.0 x ULN), alkaline phosphatase and GGT.

In case of isolated elevations in total bilirubin, AST or ALT, additional follow-up evaluations are recommended as outlined in Table 14-12.

[redacted]

Table 14-11 Follow-up evaluations for selected toxicities*

TOXICITY	FOLLOW-UP EVALUATION
HEPATIC	
Isolated total bilirubin elevation	
CTCAE Grade 1	Monitor LFTs per protocol or more frequently if clinically indicated
CTCAE Grade 2	Weekly monitoring of LFTs, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN
CTCAE Grade 3	Weekly monitoring of LFTs, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN. If resolved in > 7 days, after discontinuing the patient from INC280 permanently, the patient should be monitored weekly (including LFTs), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks
CTCAE Grade 4	After discontinuing the patient from INC280 permanently, the patient should be monitored weekly (including LFTs), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 week
Isolated AST/ALT elevation	
CTCAE Grade 2 For patients with baseline value ≤ 3.0 x ULN	Repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN
For patients with baseline value > 3.0 - 5.0 x ULN	Monitor LFTs per protocol or more frequently if clinically indicated
CTCAE Grade 3 -For elevation > 5.0 - 10.0 x ULN: For patients with baseline value ≤ 3.0 x ULN For patients with baseline value > 3.0 - 5.0 x ULN:	Repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN Repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs, weekly, or more frequently if clinically indicated, until resolved to ≤ 5.0 x ULN
CTCAE Grade 3 For AST/ALT elevation > 10.0 - 20.0 x ULN:	Repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs weekly, or more frequently if clinically indicated, until resolved to ≤ baseline
CTCAE Grade 4	Repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs weekly, or more frequently if clinically indicated, until resolved to baseline or stabilization over 4 weeks.
*Note: this table refers only to the evaluation schedule to monitor selected toxicities. Refer to Table14-7 for dose modifications required for applicable toxicities	

Follow up on potential drug-induced liver injury (DILI) cases

Patients with transaminase increase combined with total bilirubin (TBIL) increase may be indicative of potential DILI (Drug Induced Liver Injury), and should be considered as clinically important events.

The threshold for potential DILI may depend on the patient's baseline AST/ALT and TBIL value; patients meeting any of the following criteria will require further follow-up as outlined below:

[redacted]

- For patients with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as: ALP elevation > 2.0 x ULN with R value < 2 in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis.

Note: (The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury)

In the absence of cholestasis, these patients should be immediately discontinued from study drug treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

- Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR and alkaline phosphatase.
- A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.
- Further testing for acute hepatitis A, B, C or E infection and liver imaging (eg, biliary tract) may be warranted.
- Obtain PK sample, as close as possible to last dose of study drug, if PK analysis is performed in the study.
- Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as "medically significant", thus, met the definition of SAE (Section 8.2.1) and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

14.3.3 LDK378

Guidelines for the follow-up of laboratory hematologic abnormalities

In case of any occurrence of febrile neutropenia, neutropenia ≥ grade 3, or thrombocytopenia ≥ grade 3, tests must be performed weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 2. Subsequent monitoring must be performed every 4 weeks. Please also refer to Table 14-12.

[redacted]

Guidelines for the follow-up of laboratory liver abnormalities

In patients with any clinically relevant laboratory liver abnormality, as defined below, hepatic toxicity monitoring must include ALL of the following liver function tests (LFTs): albumin, AST, ALT, total bilirubin (fractionated if total bilirubin >2.0 x ULN), alkaline phosphatase and GGT). Note: for patients with Gilbert Syndrome, total and direct bilirubin must be monitored, but intensified monitoring applies to changes in direct bilirubin only.

In case of any occurrence of AST/ALT/total bilirubin increase to grade 2, the LFTs must be monitored weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 1. Thereafter monitoring must be continued every other week (or more frequently if clinically indicated) for two additional cycles (e.g. 8 weeks). If there is no recurrence of grade 2 AST/ALT/total bilirubin elevations during this period, subsequent monitoring must be performed every 4 weeks. For patients with liver metastasis and grade 2 AST/ALT at baseline, increased monitoring is required for grade 3/4 AST/ALT; follow guidelines for grade 3 or 4 AST/ALT.

In case of any occurrence of AST/ALT/total bilirubin increase to grade 3 or 4, LFTs must be monitored weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 1 (or to baseline). Thereafter monitoring must be continued every other week (or more frequently if clinically indicated) for four additional cycles (e.g. 16 weeks). If there is no recurrence of ≥ grade 2 AST/ALT/total bilirubin elevations during this period, subsequent monitoring must be performed every 4 weeks.

Patients who discontinue study treatment due to liver toxicity must be monitored weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 1 or stabilization occurs (no CTCAE grade change over 4 weeks). Refer to Table 14-8.

Patients with transaminase increase combined with total bilirubin (TBIL) increase may be indicative of potential DILI, and should be considered as clinically important events.

Refer to Section 14.3.2 (Follow up on potential drug-induced liver injury (DILI) cases)

Guidelines for the follow-up of laboratory renal abnormalities

In case of any occurrence of serum creatinine grade 2, tests must be performed weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 1. Subsequent monitoring must be performed every 4 weeks.

In case of any occurrence of serum creatinine ≥ grade 3, tests must be performed twice weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 1. Subsequent monitoring must be performed every 4 weeks. Refer to Table 14-8.

Guidelines for monitoring pneumonitis

Monitor patients for pulmonary symptoms indicative of pneumonitis. In addition, withhold ceritinib for acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnea, cough and fever and during diagnostic workup for pneumonitis/ILD.

See also dose modification guidelines described in Table 14-8.

[redacted]

Guidelines for the treatment of study treatment induced diarrhea

Refer to Section 14.3.1 (Guideline for treatment of study induced diarrhea for BYL719)

Guidelines for the treatment of study treatment induced nausea and vomiting

Nausea and vomiting are among the most frequently reported AEs following treatment with LDK378 and patients must therefore be closely monitored for the appearance of these AEs. The investigator should consider/investigate potential concomitant medication, food or comorbidity driven causes of nausea and/or vomiting and remedy these causes if possible (e.g. discontinuation of concomitant medication, dietary modification, treatment of comorbidity).

Individualized supportive and anti-emetic treatment should be initiated, as appropriate, at the first signs and/or symptoms of these AEs. In patients with vomiting, the patient should be monitored for signs of dehydration and instructed to take preventive measures against dehydration.

Concomitant medication for the treatment of nausea and/or vomiting should follow local practice and the investigator's best judgment. For moderate emetogenic drugs, such as LDK378, International Guidelines for anti-emetic treatment recommend early treatment with 5-HT3-receptor antagonists (5-HT3RAs).

Dose adaptation of ceritinib in case of treatment related nausea and/or vomiting must follow the guidelines presented above in Table 14-12.

Guidelines for treatment of hypophosphatemia

In the phase I study [CLDK378X2101], as of 31-Oct-2013, there were 9 cases of grade 3 hypophosphatemia in all dose groups, one of which was a DLT that contributed to the MTD determination – this patient was able to continue LDK378 at the same dose. One patient in the 750 mg group had grade 3 hypophosphatemia that resolved after dose adjustment or interruption; in the remaining 8 cases, patients were able to continue therapy without dose modification. Hypophosphatemia was a commonly reported AE (6.3%), regardless of relationship to LDK378 treatment. Therefore, phosphate levels will be checked at baseline and during treatment. In cases of hypophosphatemia at baseline, phosphate supplements should be started before treatment with LDK378. For any grade of hypophosphatemia during the study, treatment with phosphate supplements should be given as clinically indicated, and the LDK378 dose can be maintained.

Guidelines for the follow-up of laboratory pancreatic abnormalities

In case of any occurrence of lipase or amylase increase to grade 3 or 4, both lipase and amylase must be monitored weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 1 (or to baseline).

After resumption of dosing, monitoring must be continued weekly (or more frequently if clinically indicated) for one additional cycle (i.e. 4 weeks). If there is no recurrence of ≥ grade 2 amylase or lipase elevations during this period, subsequent monitoring must be performed every 4 weeks.

[redacted]

Patients who discontinue study treatment due to pancreatic toxicity must be monitored weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 1 or stabilization occurs (no CTCAE grade change over 4 weeks). Refer to Table 14-8.

If amylase and/or lipase elevations are accompanied by new or progressive unexplained abdominal symptoms such as severe pain or vomiting, withhold LDK378, then perform diagnostic procedures (e.g., abdominal CT scan or ultrasound) to exclude pancreatic pathology.

See also follow-up evaluation described in Table 14-12.

Table 14-12 Follow-up evaluations for selected toxicities

Toxicity	Follow-up evaluation*
Investigations (hematologic)	**Febrile neutropenia, neutropenia or thrombocytopenia ≥ CTCAE Grade 3** Test weekly (or more frequent) until ≤ Grade 2 Subsequent monitoring must be performed every cycle (4 weeks)
Investigations (hepatic)	**Total bilirubin/AST/ALT Grade 2:** (patients with liver metastasis and grade 2 AST/ALT at baseline, increased monitoring required for grade 3 ALT/AST. Follow guidelines for grade 3 or 4 AST/ALT Test weekly (or more frequently) until ≤ Grade 1 Thereafter, continue to test every 2 weeks (or more frequently) for 2 cycles (8 weeks) If no recurrence of ≥ Grade 2 event, continue monitoring every cycle (4 weeks) **Total bilirubin/ALT/AST ≥ Grade 3:** Test weekly (or more frequent) until ≤ Grade 1 Thereafter, continue to test every 2 weeks (or more frequently) for 4 cycles (16 weeks) If no recurrence of ≥ grade 2 event, continue monitoring every cycle (4 weeks) **Discontinuation due to liver toxicity:** Test weekly (or more frequent) until ≤ Grade 1 or stabilization
Investigations (renal)	**Serum creatinine Grade 2:** Test weekly (or more frequent) until Grade 1 Thereafter, test every cycle (4 weeks) **Serum creatinine ≥ Grade 3:** Test twice weekly (or more frequent) until ≤ Grade 1 Thereafter, test every cycle (4 weeks)
Investigations (pancreatic)	**Amylase/lipase ≥ Grade 3:** Test weekly (or more frequently) until ≤ Grade 1. After resumption of dosing, continue to test weekly for one additional cycle (4 weeks). If no reoccurrence of ≥ Grade 2 event, continue monitoring every cycle (4 weeks).

*Note: this table refers to the evaluation schedule only. Refer to Table 14-8 for dose modifications required for applicable toxicities

14.3.4 MEK162

Guidelines for the management of study treatment induced diarrhea

Refer to Section 14.3.1 (Guideline for treatment of study induced diarrhea for BYL719)

Guidelines for the management of study treatment induced skin toxicity

Clinical judgment and experience of the treating physician should guide the management plan of each patient. In general, the following interventions are in addition to the dose reduction:

- Prophylaxis of skin toxicity to be initiated 24 hours prior to the first treatment with MEK162 or later as needed

[redacted]

- Application of topical agents to the most commonly affected skin areas such as face, scalp, neck, upper chest and upper back

  Topical agents include non-oily sunscreen (PABA free, SPF ≥ 30, UVA/UVB protection), topical steroids (preferably mometasone cream i.e. Elocon® and topical erythromycin evening i.e. Eryaknen® or topical pimocrolimus

  Note: Topical agents should be applied on a daily basis starting on Day 1 of study treatment or 24 hours prior to the first dose, and more often as needed.
- Possibly oral doxycycline (100 mg daily) for the first 2-3 weeks of study treatment administration.

Other effective medications are antihistamines, other topical corticosteroids, other topical antibiotics and low-dose systemic corticosteroids.

The treatment algorithm based on CTCAE grade is as follows:

Mild rash (grade 1)

- Consider prophylactic rash treatment if not already started
- Topical or other topical corticosteroid (i.e. mometasone cream) and/or topical antibiotic (i.e. erythromycin 2%) are recommended.
- The patient should be reassessed within a maximum of 2 weeks or as per investigator opinion.

Moderate rash (grade 2)

- Use of topical erythromycin or clindamycin (1%) plus topical mometasone or pimecrolimus cream (1%) plus oral antibiotics such as:, lymecycline (408 mg qd), doxycycline (100 mg bid) or minocycline (50 to 100 mg qd).
- Although there has been no evidence of phototoxicity or photosensitivity in patients being treated with MEK162, doxycycline (or minocycline as second-line) should be used with thorough UV protection (i.e., avoidance of direct exposure to sunlight, use of sunscreen and sunglasses, etc.).
- Use of acitretin is not recommended

Severe rash (grade 3-4)

Grade 3

- In addition to the interventions recommended for moderate rash, consider oral prednisolone at a dose of 0.5 mg/kg. Upon improvement, taper the dose in a stepwise manner (25 mg for 7 days, subsequently decreasing the dose by 5 mg/day every day).
- Alternatively, in addition to the interventions recommended for moderate rash, consider oral isotretinoin (low doses, i.e. 0.3 to 0.5 mg/kg) (Lacouture et al 2011)
- Use of acitretin is not recommended

Grade 4

- Immediately discontinue the patient from study treatment and treat the patient with oral and topical medications (see recommendation grade 3).

[redacted]

Symptomatic treatment:

It is strongly recommended that patients who develop rash/skin toxicities receive symptomatic treatment:

- For pruritic lesions, use cool compresses and oral antihistaminic agents
- For fissuring, use Monsel's solution, silver nitrate, or zinc oxide cream. If not sufficient use mild steroid ointments or combinations of steroids and antibiotics such as Fucicort®
- For desquamation, use emollients with mild pH 5/neutral (best containing urea 10%)
- For paronychia, antiseptic bath and local potent corticosteroids, use oral antibiotics and if no improvement is seen, refer to a dermatologist or surgion
- For infected lesions, obtain bacterial and fungal cultures and treat with topical or systemic antibiotics based on sensitivity of culture

14.3.5 References (available upon request)

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Wadler S, Benson AB, Engelking C, et al (1998) Recommended guidelines for the treatment of chemotherapy-induced diarrhea. J Clin Oncol; 16:3169-78.

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14.4 Concomitant Medications Prohibited or Permitted with Caution

If a medication is listed in both Table 14-13 and Table 14-14 for a certain treatment arm, more stringent practice shall be applied (that is, the medication shall be prohibited as in Table 14-14).

Table 14-13 Permitted concomitant medications requiring caution

Mechanism of Interaction	Drug Name
Moderate CYP3A4 inhibitor	amprenavir, aprepitant, atazanavir, casopitant, cimetidine, ciprofloxacin, crizotinib, cyclosporin, darunavir/ritonavir, diltiazem, dronedarone, erythromycin, fluconazole, fosamprenavir, imatinib, lomitapide, netupitant, nilotinib, schisandra sphenanthera(Wu Wei Zi), tofisopam, verapamil
Moderate CYP3A4 inducer	bosentan, efavirenz, etravirine, genistein, lersivirine, lopinavir, modafinil, nafcillin, ritonavir, semagacestat, talviraline, thioridazine,
Sensitive CYP1A2 substrate	alosetron, caffeine, duloxetine, melatonin, ramelteon, selegiline, tacrine, tizanidine
Sensitive CYP2C9 substrate	Celecoxib, (S)-Warfarin
CYP2C9 substrate with NTI	(S)-Warfarin, Phenytoin
Sensitive CYP2C19 substrate	clobazam, dexlansoprazole, diazepam, gliclazide, lansoprazole, (R)-mephobarbital, omeprazole, pantoprazole, (+) pantoprazole, rabeprazole, tilidine
Sensitive CYP2C8 substrate	Repaglinide
CYP2C8 substrate with NTI	paclitaxel
Sensitive CYP3A4 substrate	dronedarone, ebastine, brotizolam, midazolam, triazolam, felodipine, nisoldipine, brecanavir, capravirine, darunavir, atorvastatin, lovastatin, simvastatin, everolimus, lurasidone, perospirone, quetiapine, levomethadyl, budesonide, fluticasone, sildenafil, vardenafil, aprepitant, casopitant, alpha-dihydroergocryptine, aplaviroc, buspirone, darifenacin, eletriptan, eplerenone, lumefantrine, maraviroc, ridaforolimus, ticagrelor, tolvaptan, vicriviroc, alfentanil, almorexant, atazanavir, avanafil, bosutinib, conivaptan, danoprevir, dasatinib, elvitegravir, ibrutinib, indinavir, ivacaftor, lomitapide, lopinavir, midostaurin, neratinib, saquinavir, simeprevir, ticagrelor, terfenadine, tilidine, tipranavir, voclosporin
P-gp inhibitor	alogliptin, amiodarone, azithromycin, canaglifozin, captopril, carvedilol, clarithromycin, conivaptan, cremophor RH40, curcumin, diltiazem, dronedarone, elacridar, erythromycin, felodipine, fluvoxamine, ginko, indinavir, indinavir/ritonavir, itraconazole, ketoconazole, lapatinib, lopinavir/ritonavir, mibefradil, milk thisle, mirabegron, nelfinavir, nifedipine, nitredipine, paroxetine, propafenone, quercetin, quinidine, ranolazine, rifampin, ritonavir, sequinavir/ritonavir, schisandra chinesis extract, simepravir, St. John's wort extract, talinolol, telaprevir, telmisartan, ticagrelor, tipranavir/ritonavir, tolvaptan, valspodar, vandetanib, verapamil, voclosporin
P-gp inducer	avasimibe, carbamazepine, efavirenz, genistein, phenytoin, quercetin, rifampin, St. John's Wort extract
P-gp substrate with NTI	cyclosporine, digoxin, fentanyl, paclitaxel, phenytoin, quinidine, sirolimus, tacrolimus
H2 receptor antagonist	Cimetidine, ranitidine, famotidine, nizatidine. Take medication as instructed in Section 6.3.2.
UGT1A1 inhibitors	atazanavir, erlotinib, flunitrazepam, gemfibrozil, indinavir, ketoconazole, nilotinib, pazopanib, propofol, regorafenib, sorafenib, *silybum marianum* (herbal also known as milk thistle), *valeriana officinalis* (herbal),
UGT1A1 inducers	carbamazepine, rifampicin, testosterone propiate, cigarettesmoke

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Mechanism of Interaction	Drug Name
BCRP inhibitors	abacavir, amprenavir, atazanavir, atorvastatin, cerivastatin, cyclosporine, daunomycin, delavirdine, efavirenz, elacridar, eltrombopag, erlotinib, fluvastatin, fumitremorgin, gefitinib, lopinavir, nelfinavir, nilotinib, pitavastatin, rosuvastatin, saquinavir, simvastatin, sulfasalazine, SN-38 (irinotecan), pantoprazole4
BCRP substrate	atorvastatin daunorubicin, doxorubicin, hematoporphyrin, imatinib, methotrexate, mitoxantrone, pitavastatin, rosuvastatin, SN-38 (irinotecan), ethinylestradiol, simvastatin, sulfasalazine, sofosbuvir, topotecan, sulfasalazine
MATE substrate	metformin, tenfovir
OATP substrates	aliskiren, ambrisentan, anacetrapib, atenolol, atrasentan, atorvastatin, bosentan, bromociptine, caspofungin, cerivastatin, celiprolol, danoprevir, empagliflozin, ezetimibe, fimasartan, fexofenadine, fluvastatin, glyburide, maraviroc, SN-38, rosuvastatin, simvastatin acid, pitavastatin, pravastatin, repaglinide, rifampin, valsartan, olmesartan, telmisartan, montelukast, ticlopidine
Proton pump inhibitors	Omeprazole, pantoprazole, lansoprazole, esomeprazole, rabeprazole, dexlansoprazole
Source: Adapted from Oncology Clinical Pharmacology Drug-Drug Interaction Database (release date: Apr 2015) which was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (February 2012), and the University of Washington's Drug Interaction Database The lists provided may not be exhaustive Sensitive substrates: Drugs that exhibit an AUC ratio (AUCi/AUC) of 5-fold or more when co-administered with a known potent inhibitor.	

Table 14-14 Prohibited concomitant medications

Mechanism of Interaction	Drug Name
Strong CYP3A4 inhibitor (BYL719, INC280, LDK378)	boceprevir, clarithromycin, cobicistat, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole, troleandomycin, danoprevir/ritonavir, eltegravir/ritonavir, indinavir/ritonavir, lopinavir/ritonavir, saquinavir/ritonavir, tipranoavir/ritonavir, Jopinavir
Strong CYP3A4 inducer (BYL719, INC280, LDK378)	avasimibe, carbamazepine, enzalutamide, mitotane, phenobarbital, phenytoin, rifabutin, rifampin, St. John's wort,
CYP1A2 substrate with NTI (INC280)	theophylline, tizanidine,
CYP3A4 substrate with NTI (INC280, LDK378)	alfentanil, astemizole, cisapride, cyclosporine, diergotamine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfanadine, thioridazine,
CYP2C9 substrate with NTI (LDK378)	warfarin, phenytoin
Proton pump inhibitors (MEK162)	Omeprazole, pantoprazole, lansoprazole, esomeprazole, rabeprazole, dexlansoprazole
Enzyme-inducing anti-epileptic drugs (LDK378)	Carbamazepine, ethotoin, felbamate, fosphenytoin, phenobarbital, phenytoin, primidone, topiramate
Source: Adapted from Oncology Clinical Pharmacology Drug-Drug Interaction Database (release date: Apr 2015) which was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (February 2012), and the University of Washington's Drug Interaction	

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Mechanism of Interaction	Drug Name
Database. This lists provided may not be exhaustive.	
NTI: narrow therapeutic index	

Table 14-15 Medications with risk of TdP/QT

Medications with a known risk to prolong the QT interval and/or known to cause Torsades de Pointe	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 For a comprehensive list of drugs, refer to www.qtdrugs.org
Possible risk of TdP/QT prolongation	gatifloxacin, gemifloxacin, ofloxacin, telithromycin, clozapine, iloperidone, paliperidone, quetiapine, risperidone, sertindole, ziprasidone, dolasetron, granisertron, venlafaxine, ranolazine, voriconazole, amantadine, foscarnet, isradipine, moexipril, nicardipine, fingolimod, tacrolimus, atazanavir, felbamate, famotidine, fosphenytoin, alfuzosin, chloral hydrate, indapamide, lithium, octeoride, pasireotide, oxytocin, ranolazine, tizanidine, vardenafil
Source: Adapted from Oncology Clinical Pharmacology Drug-Drug Interaction Database (release date: April 2015) which was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (February 2012), and the University of Washington's Drug Interaction Database. The lists provided may not be exhaustive.	

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