NOVARTIS

Clinical Development

LDK378 (ceritinib)

Protocol CLDK378X2103 / NCT01742286

A Phase I, open-label, dose escalation study of LDK378 in pediatric patients with malignancies that have a genetic alteration in anaplastic lymphoma kinase (ALK)

Authors	[redacted]
Document type	Amended Protocol Version
EUDRACT number	2012-002074-31
Version number	08 (Clean)
Development phase	I
Document status	Final
Release date	18-May-2018

[redacted]

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List of abbreviations

AE	Adverse event
ALCL	Anaplastic large cell lymphoma
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
ATC	Anatomic therapeutic chemical
AUC	Area under the plasma (serum, or blood) concentration versus time curve
AUClast	Area under the concentration-time curve from time zero to the last measureable concentration time
AUCtau	Area under the plasma (serum, or blood) concentration versus time curve from time zero to end of dosing period
BCRP	Breast cancer resistance protein
BLRM	Bayesian logistic regression model
BOR	Best overall response
BSA	Body surface area
BUN	Blood urea nitrogen
CDP	Clinical development plan
CI	Confidence interval
CL	Clearance
Cmax	Maximum (peak) concentration of drug
Cmin	Minimum (trough) concentration of drug
CMV	Cytomegalovirus
CNS	Central nervous system
CR	Complete response
CRO	Contract Research Organization
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DAR	Dosage Administration Record (DAR)
DDS	Dose-determining set
DILI	Drug Induced Liver Toxicity
DLT	Dose limiting toxicity
DM	Data manager/data management
DOR	Duration of response
DS & E	Drug safety and epidemiology
EBV	Epstein-Barr virus
EC	Ethics committee
ECG	Electrocardiogram

[redacted]

eCRF	Electronic Case Report Form
EDC	Electronic data capture
EMEA	European Medicines Agency
EML4-ALK	Echinoderm microtubule associated protein like 4-anaplastic lymphoma kinase
EOT	End of treatment
EWOC	Escalation with overdose control
F	Bioavailability
FAS	Full analysis set
FCBP	Females of childbearing potential
FDA	Food and Drug Administration
FISH	Fluorescent in situ hybridization
FSH	Follicle-stimulating hormone
G	Gastric
GCP	Good Clinical Practice
GI	Gastrointestinal
HA	Health Authorities
HED	Human equivalent dose
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HSV	Herpes simplex virus
IC_{50}	Half maximal (50%) inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
ILD	Interstitial Lung Disease
IMT	Inflammatory myofibroblastic tumor
IRB	Institutional Review Board
IV	Intravenous(ly)
Ki	Inhibition constant
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MIBG	Metaiodobenzylguanidine
MRI	Magnetic resonance imaging
MRP2	Multidrug resistance protein 2
MTD	Maximum tolerated dose
N/A	Not applicable
NCI	National Cancer Institutes
NG	Naso-gastric
NPM	Nucleophosmin
NPM-ALK	Nucleophosmin-anaplastic lymphoma kinase
NSCLC	Non-small cell lung cancer
ORR	Overall response rate

[redacted]

PAS	Pharmacokinetic Analysis Set
PD	Progressive disease
PFS	Progression-free survival
PHI	Protected health information
PI	Principal investigator
PK	Pharmacokinetics
PR	Partial response
PRBC	Packed red blood cells
qd	quaque diem/once daily
QTc	Corrected QT interval
QTcF	Corrected QT interval using Fridericia formula
R Value	ALT/ALP in X ULN
Racc	Accumulation ratio
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analysis
RDE	Recommended dose for expansion
REB	Research Ethics Board
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended phase two dose
SAE	Serious adverse event
SD	Stable disease
SEC	Study evaluation completion
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
STAT3	Signal transducer and activator of transcription 3
SUSARs	Suspected unexpected serious adverse reactions
T1/2	Half-life
T1/2,acc	Effective half-life calculated from Racc
TBIL	Total bilirubin
TI	Therapeutic index
TKD	Tyrosine kinase domain
Tmax	The time to reach maximum plasma concentration
ULN	Upper limit of normal
USPI	United States Package Insert
Vss	Steady state volume of distribution
WBC	White blood count

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biological Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. obtained from a study subject or study patient
Cohort	A group of patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., 21 days)
Enrollment	Point/time of patient entry into the study; the point at which molecular pre-screening or main informed consent must be obtained (i.e., before starting any of the study procedures described in the protocol)
Patient number	A unique identifier number (consisting of the center number and a patient-specific number) assigned to each patient who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Personal Data	Patient information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
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
LDK378 discontinuation	Point/time when patient permanently stops taking LDK378 for any reason;
Variable	A quantity subject to variation of values 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 from the study occurs only when a patient does not want to participate in the study any longer, and does not allow any further collection of personal data

[redacted]

Amendment 8 (18-May-2018)

Amendment rationale

Interim safety, efficacy and pharmacokinetics data for this study have been presented previously for both the fasted (n=22 patients) and fed (n=22 patients) cohorts, and no particular safety concerns have been identified (Geoerger et al, 2015, Fischer et al, 2016). Recruitment of all planned patients was completed in October 31, 2017; eighty-three patients have been enrolled in total and treated in both escalation and expansion phases. As of release of this amendment (18-May-2018), the study has been ongoing for approximately 5 years and 3 months and twelve patients are still on treatment and currently ongoing.

The main purpose of this global amendment is to allow patients who are still deriving clinical benefit from study treatment as per the investigator to be transitioned to a separate rollover study or another option for continued treatment with LDK378 (i.e. managed access program), as soon as they become available. The end of study will occur once:

- All patients have discontinued study treatment and completed the required Study Evaluation Completion (SEC) follow-up visit, or
- All patients have died, been lost to follow-up, have withdrawn consent, or the last patient has been enrolled into a separate rollover study (or other option for continued study treatment), whichever comes first

As per original protocol, a primary analysis and clinical study report (CSR) were to prepared after all patients have completed at least 6 cycles of treatment or discontinued the study. Given interim data have been presented previously, and at the time of this amendment all patients already have completed at least 6 cycles of treatment and will be allowed to be transitioned into a separate rollover study (or other options for continued study treatment access), a single final analysis/CSR will be conducted once the end of study criteria are met.

In addition, format and grammatical corrections are made throughout the protocol to improve flow and consistency.

Changes to the protocol

- Glossary of terms has been updated to align with the new Withdrawal of Consent language
- Section 4.3: Text has been updated to allow patients' transition to the rollover study or other options for continued treatment. It has been clarified that a CSR will be prepared at the end of the study.
- Table 6-4: Text has been updated to remove the PK sample collection in case of QTc prolongation Grade 3
- Section 6.3.2.2: Text has been updated to remove the PK sample collection in case of liver laboratory abnormalities
- Section 7.1.3.2: Text has been updated to align with the new Withdrawal of Consent language

[redacted]

- Section 10: Text has been clarified that analysis and CSR will be prepared at the end of the study.

IRB/IEC/REB Approval

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

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

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

[redacted]

Amendment 7 (24-Jan-2017)

As of release of this amendment (4-Jan-2017), the recruitment is still ongoing. In total, sixty-six patients have been enrolled and treated in both escalation and expansion phases. The escalation phase is now closed to enrollment and the expansion phase is currently recruiting. Eighteen patients are currently ongoing.

The primary purpose of this amendment is to address [redacted] concerns regarding the cardiac safety monitoring conducted until Cycle 6 only and not afterwards for patient who remain on treatment, and the recent changes at Cycle 1 Day 1 (ECG monitoring at 4 and 6 hours post first dose of study drug) for the patients to be treated in the expansion phase of the study. Novartis decided to strengthen the cardiac safety monitoring: all patients will be monitored with an ECG at Cycle 1 Day 1 (4-h post dose and 6-h post dose), and at each first day of every cycle of treatment. The ECG collection is expanded throughout the entire treatment duration. This is done in alignment with the ceritinib cardiovascular safety monitoring recommendations.

In addition, guidelines for dose modification in case of Grade 3 transaminases elevation are clarified, allowing patients to stay in the study in case of a re-occurrence of Grade 3 ALT or AST elevation after a dose reduction as allowed across the ceritinib development program in adults patients. This is to avoid unnecessary withdrawal of patients who may continue to derive clinical benefit from ceritinib.

The guidelines in relation to concomitant medications use are also clarified to optimize the patient's safety.

Moreover, ALK status inclusion criterion is clarified and it is specified that 15% threshold for rearrangement is applicable only when assessed by FISH. Furthermore the ALK tyrosine kinase domain (TKD) mutation inclusion criterion is simplified.

At last, editorial changes and text corrections were made for clarification, where required.

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

The following sections were updated:

- List of abbreviations: updated.
- Amendment 6 IRB/IEC/REB Approval: the wording was revised.
- Section 5.2: updated to clarify ALK status inclusion criteria in case of rearrangement and simplify description of ALK TKD mutation accepted for inclusion.
- Section 6.1.3: wording revised to bring more clarity.
- Table 6-4 Criteria for interruption and re-initiation of LDK378 treatment: revised to delete the criteria of permanent discontinuation of the patients from LDK378 in case a Grade 3 AST/ALT reoccurs after dose reduction.
- Section 6.4.1.5: Permitted concomitant medication-Palliative radiotherapy and surgery: modified to align with other ceritinib protocols.
- Table 7-1: ECG collection schedule modified to include assessments at each on-site visit.

[redacted]

- Table 7-4: revised to capture collection of ECG at all visits (including 4h and 6h post dose at C1D1 in the expansion phase) up to Cycle 16, then at each on-site visit (even number cycles post cycle 18) and up to End Of Treatment included.
- Appendix 2: Aligned Lists of prohibited concomitant medications (Table 14-8), concomitant medications requiring caution with LDK378 (Table 14-9) and prohibited enzyme-inducing anti-epileptic drugs (Table 14-10) to align with the ceritinib protocol language.

IRB/IEC/REB Approval

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

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

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

[redacted]

Amendment 6

The dose escalation phase of this study has been completed and 40 patients have been enrolled and treated (25 fasted and 15 fed). Similar recommended LDK378 doses (RDE) were established for both fasted state (510 mg/m2 once daily, declared on 4 Dec 2014), and fed state (500 mg/m2 once daily, declared on 12 April 2016). As fed state is more convenient for pediatric patients, it has been decided to complete the recruitment of the expansion phase using this preferred regimen only. The expansion phase, to confirm the dose, is currently recruiting and as of 22 September 16, 20 patients have been enrolled (7 fasted and 13 fed). Overall, 19 patients are currently ongoing in total (6 recruited in escalation phase and 13 in the expansion phase).

The primary purpose of this amendment is to revise the dose reduction steps for LDK378. Considering the recommended doses established for fed and fasted state are similar, the dose reduction schedule has been revised to be applicable for both states.

In addition, the schedule of assessments has been revised to reduce frequency of on-site visits after cycle 16: on-site visits on day 1 of odd numbered cycles are replaced by phone calls and local laboratory tests for safety assessments.

Moreover, the pre-dose PK sample and the post-dose ECGs collection at Cycle 1 Day 1 have been removed in the expansion phase as they were no longer required at this time point as no correlation is planned in the expansion.

At last, editorial changes and text corrections were made for clarification, where required.

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

The following sections were updated:

- Section 6.3.1: Table 6-3 dose reduction steps for LDK378 was revised based on the recommended dose for expansion
- Table 7-1: revised to include telephone call and local laboratory tests instead of on-site visits on day 1 of odd numbered cycles from Cycle 17
- Section 7.2.2: revised to include information about monitoring of patients' safety by phone call
- Section 7.2.2.5.4, Table 7-4: Cycle 1 Day1 4-hour and 6-hour post-dose ECG collections have been specified as not needed in the expansion phase as no longer required
- Section 7.3.1, Table 7-6: Expansion Cycle 1 Day1 pre-dose PK sample has been removed as no longer required
- Section 8.1.1: revised to capture collection of downgrading Adverse Events in the CRF

IRB/IEC/REB Approval

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

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

[redacted]

Amendment 5

Amendment rationale

The study was initiated in February 2013. The dose escalation phase of this study for the fasted state has been completed and the recommended LDK378 dose was established at 510 mg/m2 administered orally once daily. The dose escalation phase for the fed state is still ongoing. As of 17 February 2016, 40 patients were treated in the dose escalation phase of the study (fed and fasted) and 5 in the expansion phase (fasted). Of the 45 patients who entered the treatment phase, 34 patients discontinued treatment.

The primary purpose of this amendment is to clarify the LDK378 dose modification recommendations, the guidelines for follow up of toxicities to LDK378 (including follow up evaluations for hepatic toxicities and work up guidelines for potential DILI cases) and the use of concomitant medications in order to optimize the patient safety. Furthermore, this amendment provides updated parameters for study visits for patients who are on study drug for more than 14 cycles. This was done in an effort to decrease the burden on the patient after a set number of cycles on study drug. [redacted]

In addition, the definition of highly effective contraception and the time period for using it have been updated, as well as the reporting period for pregnancy that has been revised to 3 months.

At last, editorial changes and text corrections were made for clarification, where required.

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

The following sections were updated:

- List of abbreviations: updated
- Glossary of terms: updated
- Protocol Summary: updated to match exclusion criteria list from section5.3
- Section 1.2.1: Inclusion of FDA approval of LDK378 (ceritinib) under trade name of Zykadia
- Section 1.2.1.2: Clinical experience updated from data available from ongoing clinical studies [redacted]
- Figure 4-1: number of patients for fed escalation corrected
- Section 5.3 Exclusion criteria: time period for using highly effective contraception and highly effective contraception methods have been revised
- Section 6.1.3 Treatment duration: Modified to allow patients who have disease progression, but who have evidence of continued clinical benefit from LDK378, to

[redacted]

continue receiving the study treatment. General rules for dose interruption and discontinuation were clarified.

- Section 6.2.4 : dose modification recommendations related to Dose Limiting Toxicities (DLTs) were moved from section 6.3 to this section
- Table 6-2: Reference to table 6-5 for additional follow up of toxicities was added
- Section 6.3.1: Dose modification and dose delay were aligned to match with other LDK378 protocols. In particular, addition of dose reduction steps for LDK378 fasted state (Table 6-3) and criteria for the interruption and re-initiation of LDK378 treatment based on updated safety information (Table 6-4), including addition of follow up guidance for AST or ALT and concurrent total bilirubin elevation, and for Electrocardiogram QT corrected (QTc) interval prolonged.
- Section 6.3.2- Follow-up for toxicities: modified to align with other LDK378 protocols. Table 6-3 replaced by the following sections:
  - Section 6.3.2.1: Guidelines for the follow-up of laboratory hematologic abnormalities, including addition of guidance for concomitant use of hematopoietic growth factors
  - Section 6.3.2.2: Guidelines for the follow-up of liver laboratory abnormalities, including guidelines for potential drug-induced liver injury
  - Section 6.3.2.3: Guidelines for the follow-up of renal laboratory abnormalities
  - Section 6.3.2.4: Guidelines for monitoring pneumonitis
  - Section 6.3.2.5: Guidelines for the treatment of study treatment-induced diarrhea
  - Section 6.3.2.6: Guidelines for the treatment of study treatment -induced nausea and vomiting
  - Section 6.3.2.7: Guidelines for the treatment of hypophosphatemia
  - Section 6.3.2.8: Guidelines for the follow up of laboratory pancreatic abnormalities
  - Table 6-5 Follow up evaluations for selected toxicities
- Section 6.4: Concomitant medications was updated with permitted and prohibited therapies
- Table 7-1 Reduction of radiological tumor evaluation and MIBG imaging schedule post cycle 14. Clarification about collection of Bone marrow bilateral aspirate and biopsy after screening evaluation. Clarification of screening ALK testing process and collection of tumor sample at screening and end of treatment visits. Addition of meal record (already collected in the CRF but not mentioned in Table 7-1).
- Section 7.1.1.1.2: Clarification of screening ALK testing process
- Section 7.1.3 Clarification for MIBG and bone marrow aspirate protocol requirements; End of treatment visit: Modified to allow patients who have disease progression, but who have evidence of continued clinical benefit from LDK378, to continue receiving the study treatment.
- Section 7.1.3.2: Withdrawal consent section added
- Section 7.1.5: Lost to follow up section added
- Section 7.2.1: the frequency of tumor assessment was reduced post Cycle 14. Clarification about collection of Bone marrow bilateral aspirate and biopsy after screening evaluation.

[redacted]

Addition of the option to stop collecting MIBG scans after screening if it becomes negative on 2 consecutive assessments and the concomitant tumor assessments demonstrate a complete or partial response.

- Section 7.3.1: Updated with capture of meal records
- Section 7.4.1: Clarification about sample collection date
- Table 7-7: Updated with more precise information about collection timepoint of tumor biopsy at End Of Treatement
- Section 8.1.3: section created for AEs of special interest
- Section 8.2.1: Clarification about the pregnancy which should be followed up from the estimated date of delivery plus 3 months
- Section 10.1.5: Clarification about the pharmacokinetic analysis set
- Section 10.7.2: Clarification about PK analyses
- Table 10-1: Alignment with section 10.7.2
- Section 11.3: Added the use of highly effective methods of contraception must be carried on during dosing and 3 months after stopping dosing to match exclusion criteria.
- Appendix 2: Aligned Lists of prohibited concomitant medications (Table 14-1), concomitant medications requiring caution with LDK378 (Table 14-2) and prohibited enzyme-inducing anti-epileptic drugs (Table 14-3) to match with other LDK378 protocols.
- Editorial changes and text corrections have been made in the following sections: Amendment 1 rationale, 1.1, 4.3, 6.2.4, Table 6-2, 7.1.3, 9.2, 10.7.3, Appendix 5.

IRB/IEC/REB Approval

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[redacted]

Summary of previous amendments

Amendment 4

Amendment rationale

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. The protocol has therefore been amended:

- 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.

Changes to the protocol

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

Protocol Summary

- Updated exclusion criteria to reflect new pancreatic and hepatic safety parameters

Section 1.2.1.2 Clinical Experience

- Updated to delineate overall Adverse Event occurrence and to denote adverse events of interest

Section 5.3 Exclusion criteria

- Updated exclusionary point 3 with further labs for safety
- Added exclusionary point 21 to exclude patients with significant pancreatic history

Section 6.2.4 Definition of Dose Limiting Toxicities

- Added clarity around DTLs and how to apply the follow up criteria

[redacted]

Table 6-2 Dose limiting toxicities

- Updated safety language for Hematology, hepatic, and pancreatic events

Section 6.3 Dose modifications

- Provided additional clarity and parameters for study drug dose modifications, discontinuation, with special focus on pneumonitis, hepatic, renal and pancreatic toxicities

Table 6-3 Follow up toxicity guidelines

- Updated follow up parameters for Hematology, hepatic, pancreatic and renal events

Section 8.1.1 Safety monitoring and reporting for adverse events, definitions and reporting

- Updated with additional information on adverse events of interest

Table 7-3 Local clinical laboratory parameters collection plan

- Updated with serum amylase, serum lipase and ALP

IRB/IEC/REB Approval

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[redacted]

Amendment 3

Amendment rationale

Gastrointestinal symptoms are the most common adverse events seen with LDK378, and dosing with food has been shown to improve the GI tolerability of other kinase inhibitors. However, a healthy volunteer study has shown that food increases LDK378 exposure. In order to evaluate the effect of dosing LDK378 with food in pediatric cancer patients, the protocol has been modified to include a fed state (low-fat light snack) dose escalation part following the determination of the fasted MTD/RDE. Further expansion at the fed MTD/RDE will be allowed if the safety, PK or efficacy suggest that administering LDK378 with food is preferred. The age range in the inclusion criteria has been changed to 'up to 18' to make it clear that patients are eligible until they turn18 years of age.

Changes to the protocol

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

Protocol Summary

- Updated purpose and rationale, objectives, and study design to reflect planned determination of the MTD of LDK378 in both fed and fasted states.
- Clarified the nomenclature for inclusion of patients up to their 18th birthday.

Section 1.2.1.2.1 Clinical safety and tolerability

- Updated to reflect most recent cardiac safety information

Section 1.2.1.2.3 Clinical pharmacokinetics

- Updated to reflect most recent clinical pharmacokinetics data

Section 2.1 Study rational and purpose

- Rationale added for a dose escalation arm in the fed state (low-fat snack).

Section 2.2 Rationale for the study design

- Clarified the nomenclature for inclusion of patients up to their 18th birthday.

Section 2.3 Rationale for dose and regimen section

- Added language describing planned rationale for the starting dose for fed dose escalation part.

Table 3-1 Objectives and related endpoints

- Clarification added that the primary and secondary objectives and related endpoints will be evaluated in both the fed and fasted states.

Section 4.1 Description of study design

- Updated to reflect addition of the fed dose escalation part and the addition of fed patients enrolled during expansion part.

[redacted]

Figure 4-1: Overview of study design

- Updated to reflect addition of the fed dose escalation part and the addition of fed patients enrolled during expansion part.

Section 6.1.2 LDK378 administration

- Clarification of administration guidance for LDK378 in both the fasted and the fed states for patients who are able and unable to swallow capsules.

Section 6.2.2 Provisional dose levels

- Language added to describe the plan for initiating a fed-state dose escalation part and opening the expansion part.

Section 6.2.3 Guideline for dose escalation and determination of MTD/RDE

- Language added to allow for a fed-state dose escalation

Section 6.2.3.3 Change from Fasted to Fed Dosing

- Language added to clarify the required parameters prior to allowing a patient enrolled on a fasted cohort to change to dosing with a low-fat snack.

Section 6.2.4. Definition of dose limiting toxicities

- Clarification that DLTs are attributed during cycle 1

Section 6.4.2. Permitted concomitant therapy requiring caution

- Update of medications that should be used with caution if needed during the study because of potential drug-drug interactions from LDK378 Investigator's Brochure edition 7

Table 7-6 Pharmacokinetic blood collection log-dose expansion

- Modification of sample collection for patients during dose expansion part

Section 10.4.2 Statistical hypothesis, mode, and method of analysis

- Updated to reflect BRLM plan for the fed and fasted states. It will be used to estimate the dose-DLT relationships separately for fasted and fed patients.

Section 10.10.1 Dose Escalation

- Updated to reflect plan for sample size calculation in the fed and fasted states

IRB/IEC/REB Approval

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[redacted]

Amendment 2

Amendment rationale

The following changes were requested [redacted]:

- To address the management of QTc prolongation separately from the broader array of DLTs a specific approach including a detailed monitoring plan, need for physician evaluation, and recommendations for dose reduction or permanent discontinuation have been added to Section 6.3.1. and Table 6-3.
- Cases of pneumonitis/interstitial lung disease (ILD) have been reported with LDK378 in patients treated at the 750 mg dose level. Most cases improved or resolved with interruption of LDK378 and treatment with antibiotics and/or steroids. Fatal outcome of treatment-related pneumonitis has been reported. Exclusion criteria, the definition of dose limiting toxicity, and the guidance for dose modification have been amended to address this newly observed risk.

Background safety, efficacy and clinical pharmacology information was updated for consistency with the current LDK378 Investigator's Brochure.

Due to the possibility that a dose level reduction in patients with a low BSA may not actually result in a calculated dose reduction due to rounding, the protocol has been modified to require a minimum dose reduction of 50mg.

Changes to the protocol

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Protocol Summary

- Added exclusion of patients with history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention).

Section 1.2.1.1.4 Safety pharmacology and toxicology

- Omitted line "suggesting that there is no clinical risk for QTc prolongation" describing pre-clinical data. There is now clinical evidence for risk of QTc prolongation.

Section 1.2.1.2 Clinical Experience

- Updated to reflect the most recent safety, efficacy and clinical pharmacology information from LDK378 Investigator's Brochure edition 4
- Language added that cases of pneumonitis/ILD have been reported with LDK378 in patients treated at the 750 mg dose level. Most cases improved or resolved with interruption of LDK378 and treatment with antibiotics and/or steroids. Fatal outcome of treatment-related pneumonitis has been reported.

[redacted]

Section 5.3 Exclusion Criteria

- Exclusion criteria added "history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention).
- Exclusion criteria added "Radiotherapy to lungs ≤ 4 weeks prior to starting the study treatment or patients who have not recovered from radiotherapy-related toxicities. For all other anatomic sites, radiotherapy ≤ 2 weeks prior to starting the study treatment"

Table 6-2

- Language added that dose limiting pulmonary toxicity includes pneumonitis or ILD of any grade without infectious etiology

Section 6.3.1 Dose modification and dose delay

- Clarification that a minimum dose reduction of 50 mg is required following a DLT to account for patients with low BSA.
- Language added that if pneumonitis/ILD is suspected, LDK378 should be held during the evaluation. If pneumonitis/ILD of grade 2 or worse is confirmed, study drug should be permanently discontinued. If Grade 1 pneumonitis resolves within 6 weeks LDK378 may be resumed reduced by 1 dose level, otherwise it must be discontinued.
- Clarification that in the case of a DLT of QTc prolongation (QTc >500 ms) LDK378 should be held until resolution to grade 1 or less. If LDK378 is resumed, the dose must be reduced by at least 1 dose level.
- Clarification that in the case of grade 4 QTc prolongation (QTc >500 ms complicated by Torsades de pointes, polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia; or >60 ms change from baseline complicated by Torsades de pointes, polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia) LDK378 should be permanently discontinued.

Table 6-3

- Language added that in the case of QTc >500 ms blood electrolytes, including calcium, magnesium, phosphorus and potassium, should be measured and abnormalities corrected and concomitant medications should be reviewed for other potential causes of QTc prolongation. An ECG should be repeated daily until the QTc prolongation has resolved to grade 1 or less, and the patient should be evaluated by a qualified physician before leaving the clinic or treatment facility.

Section 6.4.1 Permitted concomitant therapy

- Clarification added that palliative radiotherapy to sites of pre-existing disease that do not represent progressive disease is permitted. (Previously only stated in Section 6.4.3.)

7.2.2.5.4 Electrocardiogram (ECG)

- Language added that in the event of QTc >500 ms ECGs should be repeated daily until resolved to grade 1 or less.

[redacted]

IRB/IEC/REB Approval

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

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

[redacted]

Amendment 1

Amendment rationale

The following changes were requested [redacted]:

- In order to clarify the eligibility criteria in the protocol, a detailed definition of "a genetic alteration of ALK" has been added to the inclusion criteria.
- Due to the observation that LDK378 use is sometimes associated with hypophosphatemia, patients with abnormalities of phosphate as well as potassium, calcium or magnesium > CTCAE grade 1 are excluded from the study.
- The table defining dose-limiting toxicities (Table 6-2) has been reorganized to clarify that any adverse event of CTCAE grade 3 or higher is a DLT, except as noted in the table.
- Due to the possibility that taking LDK378 mixed with a small amount of food may affect its bioavailability, the protocol has been modified to require that all patients take LDK378 with a small amount of food. If patients can swallow intact capsules, they must eat 1-2 tablespoons (15-30 mL) of food, such as apple sauce or non-fat yogurt at the time that they take LDK378. If patients open the capsules, the contents are mixed with a food carrier, such as apple sauce or non-fat yogurt (or other carriers as defined in the separate instructions for patients who cannot swallow capsules). This will prevent unexpected differences in bioavailability between those patients who swallow intact capsules and those who open the capsules.

The amendment summarizes the results of preliminary ECG data from approximately 150 patients treated at LDK378 doses of 50-750 mg qd. Review of the data indicated that LDK378 may have an effect on the QT interval; therefore the inclusion/exclusion criteria were also updated to exclude patients taking concomitant medications with a known risk of prolonging the QT interval or inducing Torsades de Pointes. The list of excluded concomitant medications in Section 6.4.3 and in Table 14-8 has been modified accordingly.

Table 7-4 has been clarified to indicate that when an ECG and a PK sample are scheduled simultaneously, the ECG should be performed just prior to drawing the PK sample. This is to prevent any anxiety associated with PK sampling from affecting the ECG.

The protocol has been updated with additional clinical pharmacokinetic data now available for LDK378, both from the ongoing phase 1 study in adults (CLDK378X2101), and the single-dose food effect study performed in healthy volunteers (CLDK378A2101).

References have been reformatted for consistency throughout the document, and with the list of references (Section 13).

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.

List of abbreviations

- Addition of CSF (Cerebrospinal fluid)

[redacted]

Protocol Summary

- Addition of exclusion of patients with potassium, magnesium, calcium or phosphate abnormalities > CTCAE grade 1
- Patients receiving medications that are a known risk of prolonging the QT interval or inducing Torsades de Pointes

Section 1.1 Overview of disease pathogenesis, epidemiology and current treatment

- Corrected some references to proper format

Section 1.2.1.2.1 Clinical safety and tolerability

- Addition of results from preliminary analysis of ongoing data regarding LDK378 and its possible effect on the QT interval.

Section 1.2.1.2.2 Clinical efficacy

- Corrected some references to proper format

Section 1.2.1.2.4 Clinical Pharmacology

- Additional data was added regarding the CLDK378X2101 first in human study and CLDK378A2101 food effect study

Section 2.1 Study rationale and purpose

- Corrected some references to proper format

Section 2.2 Rationale for the study design

- Corrected some references to proper format

Section 5.2 Inclusion Criteria

- Clarified the requirements of various genetic alterations of ALK tumors

Section 5.3 Exclusion Criteria

- Addition of exclusion of patients with potassium, magnesium, calcium or phosphate abnormalities > CTCAE grade 1
- Addition of exclusion of patients taking medications with a known risk of prolonging the QT interval or inducing Torsades de Pointes

Section 6.1.2 LDK378 Administration

- Addition of instructions for patients able to swallow capsules to take 1-2 tablespoons of an appropriate food, such as apple sauce or non-fat yogurt with each dose
- Addition of instructions for patients not able to swallow capsules to mix with contents of capsules with an appropriate food such as apple sauce or non-fat yogurt and consume the mixture within 2 hours
- Language added that as additional foods and/or liquids become available (through further testing) to mix with capsule contents for consumption, sites will be informed

Table 6-2 Criteria for defining dose-limiting toxicities

- Table was changed to outline any adverse event of CTCAE grade 3 or higher is a DLT except for those events outlined in the new table

Section 6.4.3 Prohibited concomitant therapy

[redacted]

- Language added prohibiting the use of drugs known to have a high risk of increasing the QTc interval, and drugs known to increase the QTc interval that are also primarily metabolized by CYP3A4/5

Table 7-1 Visit evaluation schedule

Corrected table format Table 7-4 Central ECG collection plan

- Clarification that ECG does not need to be done within 30 minutes before PK sample but should be done any time prior to PK sample

Section 7.3 Pharmacokinetics

- Corrected hyperlink

Section 7.3.1 Pharmacokinetic blood sample collection and handling

- Corrected hyperlink

Section 13 References

- Corrected some references to proper format

Section 14.2 Appendix 2: Guidance on concomitant therapies with CYP3A4/5, CYP2C9 interactions and/or QTc prolongation potential

- Language added prohibiting the use of drugs known to have a high risk of increasing the QTc interval, and drugs known to increase the QTc interval that are also primarily metabolized by CYP3A4/5

Table14-8 Prohibited medications that are strong CYP3A4/5 inhibitors or inducers or sensitive CYP3A4/5 substrates with narrow therapeutic index or sensitive CYP2C9 substrates with narrow TI or causing QTc prolongation or sensitive CYP2C9 substrates with narrow TI

- Updated table to expand list of drugs known to have a high risk of QTc prolongation

IRB/IEC/REB Approval

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

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

[redacted]

Protocol summary

Protocol number	LDK378X2103
Title	A Phase I, open-label, dose escalation study of LDK378 in pediatric patients with malignancies that have a genetic alteration in anaplastic lymphoma kinase (ALK)
Brief title	Study of safety and efficacy in pediatric patients with ALK-activated tumors
Sponsor and Clinical Phase	Novartis; Phase 1
Investigation type	Drug
Study type	Interventional
Purpose and rationale	LDK378 is a novel inhibitor of ALK that is active in a broad range of ALK-activated tumor models, including models driven by mutated versions of ALK known to be resistant to crizotinib, and by ALK gene amplification. The primary purpose of this study is to determine the maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE) in both fed and fasted pediatric patients, and to delineate a clinical dose to be used in any future pediatric studies. This study will also assess the safety, tolerability, PK and preliminary evidence of antitumor activity of LDK378 in pediatric patients with neuroblastoma, and other ALK-activated tumors.
Primary Objective	Estimate the MTD and/or RDE of LDK378 as a single agent when administered orally to pediatric patients with ALK-activated tumors in the fasted and fed state
Secondary Objectives	**Objective 1:** Characterize the safety and tolerability of LDK378 in pediatric patients in the fasted and fed state **Objective 2:** Characterize single and multiple-dose PK of LDK378 in pediatric patients in the fasted and fed state **Objective 3:** Assess the anti-tumor activity of LDK378 in the fasted and fed state
Study design	This is a two-part, phase 1 study, with a dose escalation part in both the fasted and fed states, followed by an expansion part. The expansion part will start after the fasted MTD/RDE has been determined. The expansion part will include 2 diagnostic groups of patients, one restricted to patients with ALK-activated neuroblastoma and the second including patients with all other ALK-activated tumors. Enrollment will proceed in parallel. LDK378 will be administered orally, once daily, continuously.
Population	Patients, aged 12 months to <18 years, with malignancies carrying a genetic alteration of ALK.

[redacted]

Inclusion criteria	● Patients must be diagnosed with a locally advanced or metastatic malignancy that has progressed despite standard therapy, or for which no effective standard therapy exists ● Age ≥ 12 months and <18 years ● The tumor must carry a genetic alteration of ALK, such as a mutation, translocation or amplification ● Patients must have evaluable or measurable disease as defined by one of the following criteria: RECIST v1.1 for patients with non-hematologic malignancies; MIBG scan for patients with neuroblastoma; International Working Group (IWG) criteria for patients with lymphoma ● Performance status: ● Karnofsky performance status score ≥ 60% for patients >12 years of age ● Lansky score ≥ 50% for patients ≤ 12 years of age
Exclusion criteria	● Patients with symptomatic central nervous system (CNS) metastases who are neurologically unstable or require increasing doses of steroids or local CNS-directed therapy (such as radiotherapy, surgery or intrathecal chemotherapy) to control their CNS disease. ● Patients with clinically significant, uncontrolled heart disease or corrected QT (QTc) interval > 480 milliseconds, using the Fridericia correction (QTcF). ● Patients with the following laboratory values during screening: ● Creatinine > 1.5 x ULN for age. ● Total bilirubin > 1.5 x ULN for age, except for patients with Gilbert's syndrome, who may be included if total bilirubin is ≤ 3.0 x ULN and direct bilirubin is ≤ 1.5 x ULN. ● Alanine aminotransferase (ALT) > 3 x ULN for age, except for patients that have tumor involvement of the liver, who must have a value ≤ 5 x ULN. ● Serum aspartate aminotransferase (AST) > 3 x ULN for age, except for patients that have tumor involvement of the liver, who must have a value ≤ 5 x ULN. ● Absolute neutrophil count (ANC) < 0.75 x 10^9/L without use of granulocyte growth factor for ≥ 14 days. ● Platelet count < 50 x 10^9/L. ● Hemoglobin (Hgb) < 8 g/dL. ● Alkaline phosphatase (ALP) > 5.0 x ULN ● Serum amylase > 2 x ULN ● Serum lipase > ULN ● Fasting plasma glucose ≥175 mg/dL (≥9.8 mmol/L) ● Potassium, magnesium, calcium or phosphate abnormality > CTCAE grade 1. ● Body surface area (BSA) < 0.35 m2. ● Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of LDK378 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, or malabsorption syndrome). ● Evidence of active viral hepatitis, including Hepatitis A, B or C (testing for viral hepatitis is not mandatory). ● Known diagnosis of human immunodeficiency virus (HIV) infection (HIV testing is not mandatory). ● Presence of ≥ CTCAE grade 2 toxicity (except alopecia, peripheral neuropathy, ototoxicity and lymphopenia, which are not excluded if grade 3 or less) due to prior cancer therapy.

[redacted]

	● Malignant disease, other than that being treated in this study. Exceptions to this exclusion include the following: malignancies that were treated curatively and have not recurred within 3 years prior to study entry; completely resected basal cell and squamous cell skin cancers; and completely resected carcinoma in situ of any type. ● History of known interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention). ● Patients who have received systemic anticancer therapy within 3 weeks of the first dose of LDK378. Patients whose immediate prior treatment was an ALK inhibitor may start treatment with LDK378 one week after the last dose of the ALK inhibitor. ● Radiotherapy to lungs ≤ 4 weeks prior to starting the study treatment or patients who have not recovered from radiotherapy-related toxicities. For all other anatomic sites, radiotherapy ≤ 2 weeks prior to starting the study treatment. ● Major surgery within 2 weeks of the first dose of LDK378. Insertion of a gastric feeding tube (G-tube), nasogastric feeding tube (NG-tube), and central venous access are not considered major surgery. ● Patients receiving medications that are known to be strong inhibitors or inducers of CYP3A4/5 that cannot be discontinued at least 1 week prior to start of treatment with LDK378 and for the duration of the study (Appendix 2). ● Patients receiving medications that are mainly metabolized by CYP3A4/5 or CYP2C9 and have low therapeutic index that cannot be discontinued at least 1 week prior to start of treatment with LDK378 and for the duration of the study (Appendix 2). ● Medications with a known risk of prolonging the QT interval or inducing Torsades de Pointes (Appendix 2). ● Pregnant or nursing (lactating) females. ● Females of child-bearing potential, defined as all females physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 3 months after stopping dosing. Highly effective contraception methods include: ● Total abstinence (when this is in line with the preferred and usual lifestyle of the patient) 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) total hysterectomy or tubal ligation at least six weeks before taking LDK378. In case of oophorectomy alone, only when the reproductive status of the female has been confirmed by follow up hormone level assessment. ● Male sterilization (at least 6 months prior to screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient. ● 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 females should have been stable on the same pill for a minimum of 3 months before taking LDK378. ● Sexually active males, unless they use a condom during intercourse while

[redacted]

	taking LDK378 and for 3 months after stopping LDK378 treatment, and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid. ● Patient has other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may interfere with the interpretation of study results, and in the judgment of the investigator would make the patient inappropriate for the study. ● Patient has a history of pancreatitis or history of increased amylase or lipase that was due to pancreatic disease.
Investigational and reference therapy	LDK378 (ceritinib)
Efficacy assessments	Overall response rate (ORR) and duration of response (DOR), progression-free survival (PFS) as per RECIST 1.1 in patients with neuroblastoma and other solid tumors, and by International Working Group (IWG) criteria in patients with lymphoma. MIBG response in patients with neuroblastoma. Resolution of bone marrow disease in patients with neuroblastoma.
Safety assessments	Incidence rate of Dose Limiting Toxicities (DLT) during the first cycle of LDK378 treatment Adverse events and serious adverse events, changes in laboratory values, assessments of physical examinations, vital signs and electrocardiograms
Other assessments	Plasma concentration time profiles, PK parameters, including but not limited to AUCtau, Cmin, Cmax, Tmax, Racc, and T1/2,acc [redacted]
Data analysis	The primary objective of the escalation part is to estimate the MTD/RDE of the single agent LDK378 when administered orally on a once daily schedule to fed or fasted pediatric patients with ALK-activated tumors. The corresponding primary analysis method is an adaptive Bayesian logistic regression model (BLRM) guided by the escalation with overdose control (EWOC) principle. For all safety analyses, the safety set will be used. Unless otherwise specified, all listings and tables will be presented by treatment group (regimen [fasted versus fed] and dose level) in the clinical study report, with patients classified according to treatment received. Pharmacokinetic parameters will be determined using either non-compartmental method(s) or fitting of the actual values to a population PK model. Anti-tumor activity will be summarized in terms of overall response rate (ORR), duration of response (DOR), and progression-free survival (PFS). [redacted]
Key words	Phase I, pediatric, open-label, dose escalation, ALK-activated tumors

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

The ALK gene was first described in anaplastic large cell lymphoma (ALCL); it was identified as the gene on chromosome 2 fused to the NPM gene in the t(2;5)(p23;Q35) translocation, and is found in approximately half of patients with ALCL, and a majority of pediatric ALCL cases (Gascoyne 1999, McDermott 2008, Savage 2008). ALK activation by translocation, amplification, point mutations, or other genetic rearrangements has since been identified in other malignancies. About 2-8% of non-small cell lung cancers (NSCLC) carry activating translocations of ALK, most commonly an EML4-ALK translocation created by an intrachromosomal inversion in chromosome 2 (Soda 2007, Scagliotti 2012, Takeuchi 2009). ALK activation is found in approximately 10% of neuroblastomas, but in contrast to ALCL and NSCLC, ALK activation in neuroblastoma occurs by point mutation or ALK gene amplification (Chen 2008, Azarova 2011). Most pedigrees exhibiting the rare syndrome of familial neuroblastoma carry somatic mutations that result in ALK activation, indicating that ALK is an important driver in this disease (Mosse 2008). Half of inflammatory myofibroblastic tumors (IMT), a rare soft tissue sarcoma most commonly found in children, harbor genetic alterations of ALK, including translocations and changes in gene copy number (Coffin 2007, Griffin 1999). Increased ALK protein expression and increased ALK gene copy number have also been described recently in 50%-80% of rhabdomyosarcomas, more often in the alveolar subtype than the embyronal subtype. It is not yet known if ALK is an oncogenic driver in this disease (van Gaal 2012). Activating translocations of ALK, including both EML4-ALK, commonly found in NSCLC and NPM-ALK, commonly found in ALCL, act as dominant oncogenes in murine models; however, the mechanism of oncogenesis is not well understood (Chiarle 2003, Soda 2007). Overexpression and activation of ALK mediate many downstream effects that may contribute to transformation, increased proliferation, and increased survival. For example, ALK activation in ALCL is associated with activation of various signal transduction intermediates and pathways implicated in oncogenesis, including STAT3, Grb2, mTORC1, PI3K/AKT, and MEK/ERK (Tabbo 2012). Based on these findings, activation of ALK appears to be an important mechanism of oncogenesis in subsets of a variety of malignancies, several of which typically occur in pediatric patients.

The role of ALK in healthy mammals is not well understood. It is expressed throughout the nervous system during embryogenesis in the mouse, most strongly in the brain, and in the adult animal ALK expression is much reduced, but still detectable in the brain (Palmer 2009, Iwahara 1997). Despite ALK expression in the developing nervous system and in the adult mammal brain, available data suggest that inhibiting ALK in children is not a major safety concern. Mice with the ALK gene knocked out develop normally without any evident developmental abnormalities (Palmer 2009, Bilsland 2008). Behavioral testing suggests that ALK knock-out mice have an “anti-depressant” phenotype, but otherwise function and reproduce normally (Bilsland 2008). In humans, germline ALK mutations that constitutively activate the kinase domain are the likely cause of most cases of familial neuroblastoma, but the mutations are not associated with other familial abnormalities (Mosse 2008).

[redacted]

The ALK inhibitor crizotinib was approved by the US FDA in August 2011 "for the treatment of patients with locally advanced or metastatic NSCLC that is ALK-positive as detected by an FDA-approved test." Clinical experience with crizotinib indicates that ALK inhibition has potent antitumor activity in several malignancies carrying genetic alterations of ALK. The response rate to crizotinib in ALK-translocated NSCLC was 50%-60% in the phase 1 study (Kwak 2010, Kim 2012). Crizotinib is also active in several ALK-driven pediatric malignancies including neuroblastoma, ALCL, and IMT (Mosse 2012, Butrynski 2010). Crizotinib has been associated with a high frequency of visual toxicities including changes in dark-light accommodation and seeing trails of light (Kwak 2010), but these patient-reported events have not been associated with abnormalities on ophthalmology exams, or other neurological adverse events. The mechanism of these visual toxicities, and the degree that crizotinib distributes to the retina is not known; however, based on a single case report crizotinib achieves only very low concentrations in the CSF, approximately 0.26% of blood (Costa 2011).

It is anticipated that more potent and specific ALK inhibitors, such as LDK378, may be more active than crizotinib in ALK-driven diseases, and may also be active in the setting of crizotinib-resistant disease.

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

1.2.1 Overview of LDK378

LDK378 is an orally available ALK inhibitor [5-Chloro-N2-[2-isopropoxy-5-methyl-4-(4-piperidinyl)phenyl]-N4-[2(isopropylsulfonyl)phenyl]-2,4-pyrimidinediamine]. [redacted]

In addition, LDK378 shows potent antitumor activity in crizotinib-resistant models and the efficacy seen in the ongoing Phase I clinical trial in patients (with and without previous crizotinib therapy) led to the accelerated approval of LDK378 (ceritinib) by the Food and Drug Administration (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]

Submissions to other health authorities worldwide have been completed in some countries and are underway in others. In this protocol we will refer to the investigational treatment as LDK378 only.

1.2.1.1 Non-clinical experience

1.2.1.1.1 Pharmacology

LDK378 inhibits ALK and ALK-mediated signaling pathways in a dose-dependent manner. It 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 (IC_{50} of 0.15 nM for LDK378 and 3 nM for crizotinib). In a kinase panel of 35 additional enzymes, LDK378 demonstrated a high degree of selectivity for ALK inhibition since it inhibited only 2 kinases (INSR and IGF1R) but with approximately 50-fold less potency than inhibition for ALK.

Preclinical data showed inhibition of the kinase activity of the NPM-ALK fusion protein (in Karpas299 human ALCL cells) and of the EML4-ALK fusion protein (in H2228 human NSCLC cells) with LDK378 led to inhibition of cancer cell proliferation *in vitro*. The inhibition of the downstream signaling pathway by LDK378 correlated with the inhibition of proliferation. In addition, inhibition of NPM-ALK and EML4-ALK in mouse and rat xenograft models resulted in inhibition of tumor growth and tumor regression *in vivo*. LDK378 was also active in cell lines with ALK amplification or expression of activating point mutations. A single-dose pharmacodynamic study and multiple-daily dose efficacy study performed in Karpas299 and H2228 tumor models indicated that a 70% to 80% reduction in the ALK signaling pathway is required to achieve complete tumor regression in rodents.

1.2.1.1.2 Antitumor activity in xenograft models

LDK378 is highly active in mouse and rat xenograft models of lung cancer and ALCL that carry an ALK rearrangement. In murine xenograft models of H2228 NSCLC and Karpas299 ALCL cells, LDK378 dosed at 25 mg/kg daily, less than the MTD in these models, resulted in complete regression of established tumors. When dosed at 50 mg/kg daily for 14 days in the H2228 NSCLC model, LDK378 resulted in complete and prolonged (lasting for more than 4.5 months, the observation period) tumor regressions. In the same experiments, crizotinib dosed at 100 mg/kg daily for 14 days resulted in complete tumor regression, but tumors re-grew within 2 weeks after stopping treatment.

LDK378 also has potent antitumor activity against crizotinib-resistant H2228 NSCLC cell lines, including resistant variants carrying I1171T or C1156Y mutations in the ALK kinase domain. These data support that LDK378 may be clinically active in ALK-rearranged malignancies that becomes resistant to crizotinib.

1.2.1.1.3 Nonclinical pharmacokinetics (PK) and metabolism

LDK378 showed consistent PK characteristics following intravenous (IV) administration in mouse, rat, dog, and monkey. LDK378 showed low to moderate plasma clearance (CL) compared to hepatic blood flow (ranging from 9.2 to 27 mL/min/kg). The estimated plasma

[redacted]

volume of distribution at steady state (Vss) was high across all animal species (9.7 to 19.9 L/kg). The elimination T1/2 of terminal phase in plasma was long in all species (6.2 to 29 h).Good oral bioavailability (48%-100%) was observed in various animal species. LDK378 is highly bound to plasma protein (> 94%) in all species. Following oral administration of [^{14}C]LDK378 to LEH male rats, radioactivity was widely distributed. The highest tissue exposures were found in the intestine wall, uveal tract, pituitary gland, bile, adrenal cortex, harderian gland, liver, spleen, lymph node, lung, kidney, thyroid, bone marrow, adrenal medulla and pancreas (25 to 710-fold higher exposure relative to blood). Unchanged LDK378 was the major component in feces and bile of intact and bile duct-cannulated rats. In the rat, LDK378 underwent oxidation, leading to the formation of five oxygenated metabolites (designated as M23.6, M30.6, M35.8, and M33.4). In addition, LDK378 underwent sulfation, leading to M36.8, and oxidation followed by sulfation, resulting in the presence of M29.5. LDK378 also underwent glucuronidation, leading to M26.8 and M27.6. The major metabolite in feces was designated M33.4 (oxygenation) accounting for approximately 7% of the dose. All other metabolites in feces and bile were minor (< 5% of the dose). In rats dosed with [^{14}C]-LDK378, LDK378-derived radioactivity was excreted predominantly in the feces (> 99%), and renal excretion was a minor pathway for excretion (< 1%). Fecal excretion was the result of biliary excretion (69%) and gastrointestinal (GI) secretion (31%). Since parent drug was the major component in bile and feces after IV administration, enterohepatic circulation may occur.

LDK378 is a potent reversible inhibitor of cytochrome CYP3A4/5, 2B6, 2C8, 2C9 and 2A6 (half-maximal inhibitory concentration (IC_{50}) ranging from 0.162 to 0.0316 μM) and a weak inhibitor of 2C19, 2D6 and 2E1. Time-dependent inhibition of CYP3A4/5 was observed with a KI value of 1.47 μM and a Kinact of 0.0642 min^{-1}. These data suggest a potential of drug-drug interaction between LDK378 and compounds which are metabolized by these CYP isoforms if sufficiently high concentrations of LDK378 are achieved. LDK378 was likely a P-gp, not BCRP or MRP2 substrate. It did not inhibit P-gp, BCRP or MRP2 up to 1.5 μM.

In rats LDK378 crosses the intact blood brain barrier at a low level, with concentrations of LDK378 in brain tissue about 10% of that in blood.

1.2.1.1.4 Safety pharmacology and toxicology

LDK378 was evaluated for safety in 2- and 4-week studies in rats and monkeys. The principal toxicity induced by LDK378 was a systemic inflammation characterized by increased neutrophil counts in the peripheral blood and mixed cell/neutrophilic inflammation of the biliopancreatic ducts, pancreas, and/or duodenum. Gastrointestinal toxicity was observed in both species, characterized by body weight loss, decreased food consumption, emesis (monkey), diarrhea, and at high doses, by histopathologic lesions including erosion, mucosal inflammation and foamy macrophages in the duodenal crypts and ampullae of rats and monkeys, respectively. Liver (bile duct) was also affected in both species only at the highest dose levels studied (100 mg/kg/day in the 2-week studies for both species; 50 and 30 mg/kg/day in the 4-weeks studies in rat and monkey, respectively), and included increases in liver transaminases in a few animals at high doses, and mixed cell inflammation, erosion and cytoplasmic vacuolation of the bile duct epithelium. The pancreas was a target organ in the rat, but not the monkey, with acinar cell atrophy and mixed cell inflammation noted at mid- and

[redacted]

high doses. Target organ effects showed partial to complete recovery during the 4-week non-dosing period. No effects in the rat central nervous system or on the respiratory system were observed at single, high doses (100 mg/kg).

LDK378 has potent activity on the hERG channel with an IC_{50} of 0.4 µM. However, there were no LDK378-related effects *in vivo* in monkeys at doses as high as 100 mg/kg (human equivalent dose (HED) of 1950 mg).

Please refer to the current LDK378 [Investigator's Brochure] for further information.

1.2.1.2 Clinical experience

1.2.1.2.1 Clinical safety and tolerability

LDK378 is associated with a manageable safety profile (Table 1-1). For the 255 patients treated at the recommended dose (RD) of 750 mg in the ongoing study [CLDK378X2101], the median duration of exposure as of the [redacted] was 26.9 weeks (range 0.4 to 82.3 weeks). The most common adverse events (AE) regardless of study drug relationship (incidence ≥25%) were diarrhea, nausea, vomiting, alanine aminotransferase (ALT) increased, fatigue, abdominal pain, decreased appetite, aspartate aminotransferase (AST) increased, and constipation.

The incidence of grade 3-4 AEs, regardless of study drug relationship was <10% for all AEs except ALT increased (26.7%) (Table 1-1). The incidence of grade 3-4 AEs, regardless of study drug relationship was <5% for all AEs except AST increased (8.2%), diarrhea (5.9%), hyperglycemia (5.5%), lipase increased (5.1%), and blood alkaline phosphatase (ALP) increased (5.1%).

Table 1-1 All grades (at least 10%) and associated grade 3-4 adverse events, regardless of study drug relationship, by preferred term in patients treated in the 750 mg dose group (Data cut-off date: [redacted])

	LDK378 750 mg N=255	
Preferred term	**All Grades n (%)**	**Grade 3/4 n (%)**
Total	**255 (100.0)**	**184 (72.2)**
Diarrhea	219 (85.9)	15 (5.9)
Nausea	205 (80.4)	11 (4.3)
Vomiting	153 (60.0)	10 (3.9)
Alanine Aminotransferase Increased	110 (43.1)	68 (26.7)
Fatigue	102 (40.0)	10 (3.9)
Abdominal Pain	91 (35.7)	3 (1.2)
Decreased Appetite	87 (34.1)	2 (0.8)
Aspartate Aminotransferase Increased	78 (30.6)	21 (8.2)
Constipation	73 (28.6)	0

[redacted]

	LDK378 750 mg N=255	
	All Grades	**Grade 3/4**
Preferred term	**n (%)**	**n (%)**
Cough	62 (24.3)	0
Abdominal Pain Upper	58 (22.7)	2 (0.8)
Dyspnea	47 (18.4)	8 (3.1)
Asthenia	45 (17.6)	2 (0.8)
Blood Alkaline Phosphatase Increased	45 (17.6)	13 (5.1)
Back Pain	43 (16.9)	1 (0.4)
Headache	41 (16.1)	3 (1.2)
Weight Decreased	39 (15.3)	4 (1.6)
Blood Creatinine Increased	39 (15.3)	0
Pyrexia	38 (14.9)	0
Rash	32 (12.5)	0
Insomnia	31 (12.2)	0
Dyspepsia	26 (10.2)	1 (0.4)
Hypokalemia	26 (10.2)	11 (4.3)
Dizziness	26 (10.2)	0

Dose reductions due to adverse events occurred in 58.4% of patients treated with LDK378 at the 750 mg dose; 38.8% of patients had only 1 dose reduction. The most frequent AEs requiring dose adjustments or interruptions reported in ≥5% of the patients were: ALT increased, nausea, AST increased, vomiting, diarrhea, fatigue, and abdominal pain. Adverse events (AEs) leading to study drug discontinuations occurred in 10.2% of patients treated with LDK378 at the 750 mg dose. The most frequent AEs leading to study drug discontinuations were decreased appetite, pneumonia, ALP increased, pneumonitis, and respiratory failure.

Serious adverse events (SAEs) reported in 2% or more of the 255 patients treated at the recommended dose of 750 mg were convulsion, pneumonia, interstitial lung disease (ILD)/pneumonitis, dyspnea, hyperglycemia, and nausea. Fatal adverse reactions occurred in 5% of patients, consisting of: pneumonia (4 patients), respiratory failure, ILD/pneumonitis, pneumothorax, gastric hemorrhage, general physical health deterioration, pulmonary tuberculosis, cardiac tamponade, and sepsis (1 patient each). Adverse events of special interest to be monitored for LDK378 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 [Investigator's Brochure].

1.2.1.2.2 Clinical efficacy

[redacted] data from the ongoing Study [redacted] demonstrated a high rate of rapid and durable responses with LDK378 in 246 ALK-positive NSCLC patients treated in the 750 mg dose group (RD). In these patients the ORR was 58.5% (95% CI: 52.1, 64.8) based on investigator assessment (Table 1-2). Among the 144 ALK-positive NSCLC patients

[redacted]

with a confirmed CR or PR based on investigator assessment, 86.1% of those patients achieved a response within 12 weeks, with a median time to response of 6.1 weeks (range: 3.0 to 24.1) . The estimated median duration of response (DOR) based on investigator assessment was long at 9.69 months (95% CI: 7.00, 11.40). Based on the investigator assessment, the median PFS was 8.21 months (95% CI: 6.70, 10.12) with 53.3% of the patients censored.

Importantly, LDK378 showed this level of high anti-cancer activity regardless of prior ALK inhibitor status (i.e., whether or not the patient received previous treatment with an ALK inhibitor). A high ORR of 54.6% and 66.3% was observed in patients treated with a prior ALK inhibitor and in ALK inhibitor naïve patients, respectively, by investigator assessment (Table 1-2). Rapid responses were observed in patients regardless of prior ALK inhibitor status, 6.1 weeks (range: 4.6 to 24.1) in patients treated with a prior ALK inhibitor and 6.1 weeks (range: 3.0 to 24.1) in ALK inhibitor naïve patients. Further, the estimated median DOR was 7.39 months (95% CI: 5.42, 10.12) in patients treated with a prior ALK inhibitor and, the median DOR was not reached in ALK inhibitor naïve patients. However, the 12-month DOR rate was 65.2% (95% CI: 46.4, 78.8) for the latter. The estimated median PFS was 6.90 months (95% CI: 5.39, 8.41) in patients treated with a prior ALK inhibitor, while the median PFS was not reached in ALK inhibitor naïve patients (95% CI: 8.31, NE). Finally, LDK378 demonstrated activity in patients with brain metastasis at baseline. Among the 98 patients with brain metastasis who had received prior ALK-inhibitor treatment, the ORR was 50.0% (95% CI: 39.7, 60.3), median DOR was 6.9 months (95% CI: 4.8, 8.5), and median PFS was 6.7 months (95% CI: 4.9, 8.4). For additional details, refer to the [Investigator's Brochure].

[redacted]

Table 1-2 Summary of best overall response based on investigator assessment in NSCLC patients in the 750 mg dose group, by prior ALK inhibitor status (Full Analysis Set NSCLC 750 mg) (Cut-off date: [redacted])

	NSCLC with prior ALK inhibitor N=163 n (%)	NSCLC ALK inhibitor naïve N=83 n (%)	All NSCLC N=246 n (%)
Best overall response			
Complete response (CR)	2 (1.2)	1 (1.2)	3 (1.2)
Partial response (PR)	87 (53.4)	54 (65.1)	141 (57.3)
Stable disease (SD)	32 (19.6)	19 (22.9)	51 (20.7)
Progressive disease (PD)	16 (9.8)	0	16 (6.5)
Unknown	26 (16.0)	9 (10.8)	35 (14.2)
Overall response rate (ORR) (CR or PR), n (%)	89 (54.6)	55 (66.3)	144 (58.5)
95% CI	(46.6-62.4)	(55.1-76.3)	(52.1-64.8)

This table presents data for all patients with ALK-positive NSCLC in the 750 mg treatment dose group, **FAS-NSCLC 750 mg group**

Best overall response is based on investigator's assessment of disease status using RECIST 1.0 criteria

CR and PR are confirmed by repeat assessments performed not less than 4 weeks after the criteria for response are first met.

Exact binomial 95% Confidence Interval

1.2.1.2.3 Clinical pharmacodynamics

Data are not yet available from the ongoing clinical studies.

1.2.1.2.4 Clinical pharmacokinetics

In adult patients with tumors characterized by genetic abnormalities in ALK [redacted] and in healthy volunteers [redacted] and [redacted] the single-dose pharmacokinetics of LDK378 in humans has the following features: (1) LDK378 was slowly absorbed, with median peak plasma concentration occurring at approximately 4 to 6 h in patients, and approximately 6 to 8 h in healthy subjects. Following Cmax, LDK378 concentrations declined in a mono-exponential manner. The geometric mean apparent terminal half-life ranged from 31 to 41 h across the 400 to 750 mg dose groups in patients and 36 to 48 h across the 450 to 750 mg dose groups in healthy subjects. (2) Cmax and AUClast increased dose-proportionally following single oral administration of LDK378 across the 50 to 750 mg dose groups. (3) Moderate to high variability in LDK378 PK parameters has been observed in both healthy subjects and patients. Following single oral doses of 450 to 750 mg in healthy subjects when LDK378 was given alone, the inter-subject variability (geometric mean coefficient of variation; CV% range) was 42-74% and 35-72% for AUClast and Cmax, respectively. The corresponding values in patients were 93% and 87% following single oral doses of 50 to 750 mg based on a model developed for dose proportionality analysis.

[redacted]

The multiple-dose PK of LDK378 following repeated daily oral dosing in patients has the following features: (1) AUCtau at the maximum tolerated dose and recommended dose of 750 mg increased from first dose with geometric mean accumulation ratios of 4.7 on Cycle 1 Day 8 after 1 week of daily dosing and 6.2 on Cycle 2 Day 1 after 3 weeks of daily dosing, respectively. Evaluation of trough concentration at 750 mg that steady-state was achieved by Cycle 1 Day 15 following 2 weeks of daily dosing. (2) LDK378 demonstrated nonlinear PK over time, as indicated by the observed difference in apparent clearance (CL/F) between single-dose (88.5 L/h at 750 mg) and steady-state at Cycle 2 Day 1 (33.2 L/h at 750 mg). As LDK378 is a substrate as well as a time-dependent inhibitor of CYP3A, it is likely that this PK nonlinearity could be attributed to auto inhibition of LDK378. In contrast with single dose data, Ctrough on Cycle 2 Day 1 after repeated daily dosing increased with dose in a greater than dose-proportional manner.

[redacted]

CYP3A was identified as the major CYP isozyme responsible for the metabolism of LDK378. An inhibition DDI study conducted in healthy volunteers indicated that ketoconazole (200 mg bid for 14 days), a strong CYP3A inhibitor, increased the Cmax and AUCinf of a single 450 mg oral dose of LDK378 by 1.2-fold and 2.9-fold, respectively, compared with LDK378 alone [redacted] Therefore, concurrent use of strong CYP3A inhibitors should be avoided. An induction DDI study conducted in healthy volunteers indicated that rifampin (600 mg daily for 14 days), a strong CYP3A inducer, decreased the Cmax and AUCinf of a single 750 mg oral dose of LDK378 by 44% and 70%, respectively, compared with LDK378 alone [redacted] Concurrent use of strong CYP3A inducers should be avoided.

A food effect study was conducted in healthy volunteers [redacted] Compared to the fasted state, a low-fat meal increased Cmax and AUCinf of a single oral dose of LDK378 500 mg in healthy subjects by 43% and 58%, respectively, whereas a high-fat meal increased Cmax and AUCinf by 41% and 73%, respectively.

2 Rationale

2.1 Study rationale and purpose

LDK378 is a novel inhibitor of ALK that in preclinical studies is more potent and specific than crizotinib, and is active in a broad range of ALK-activated tumor models, including models driven by mutated versions of ALK known to be resistant to crizotinib, and by ALK gene amplification.

As described in Section 1.1, genetic alterations of ALK are found in subsets of several pediatric cancers, including about 10% of neuroblastomas, the majority of pediatric ALCL, and about half of inflammatory myofibroblastic tumors. Both *in vitro* and *in vivo* experiments have demonstrated that neuroblastoma, ALCL, and NSCLC models carrying ALK alterations

[redacted]

are frequently dependent on ALK for their growth, and are responsive to treatment with ALK inhibitors (Chiarle 2003, Soda 2007, Li 2011, Galkin 2007). Recent clinical data have also demonstrated that the ALK inhibitor crizotinib has antitumor activity in children with neuroblastoma and ALCL (Mosse 2012).

In the ongoing phase 1 study, [CLDK378X2101], LDK378 has demonstrated substantial antitumor activity in adult patients with ALK-rearranged NSCLC. Together, these preclinical and clinical data support evaluation of LDK378 in pediatric patients with malignancies carrying genetic alterations of ALK.

Safety data from studies in adult patients, as well as the pediatric patients already enrolled in this study show a high incidence of GI adverse events (nausea, vomiting, diarrhea, abdominal pain). These AE's seem to be generally low-grade and manageable with prophylactic medications. However, GI symptoms are uncomfortable and can affect patients' general well-being, as well as drug absorption and dosing compliance, with the latter potentially limiting efficacy. Dosing with food has been shown to improve the GI tolerability of other multi-kinase inhibitors, such as imatinib (Gleevec USPI) and bosutinib (Bosulif USPI). Therefore, a separate dose-escalation arm under fed conditions will be explored once the fasting MTD and/or RDE is reached.

The primary purpose of this study is to estimate the maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE) in pediatric patients, and to delineate a clinical dose to be used in any future pediatric studies. The MTD will first be determined in the fasted state, then a second dose escalation to determine the MTD in the fed state (low-fat light snack) will be conducted. This study will also assess the safety, tolerability, PK and preliminary evidence of antitumor activity of LDK378 in children with neuroblastoma, and other ALK-activated tumors.

2.2 Rationale for the study design

This is a multi-center, phase 1, open-label, dose escalation study limited to pediatric patients with malignancies that have a genetic alteration of ALK. The study includes an expansion part at the MTD or RDE in order to better evaluate safety, tolerability, and preliminary evidence of antitumor activity in neuroblastoma having a genetic alteration of ALK, and in other malignancies having a genetic alteration of ALK.

The current open-label dose escalation study design using a Bayesian logistic regression model (BLRM) is a well-established method to estimate the maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE) in cancer patients. The adaptive BLRM will be guided by the escalation with overdose control (EWOC) principle to control the risk of DLT in future patients on study. The use of Bayesian response adaptive models for small datasets has been accepted by EMEA ("Guideline on clinical trials in small populations", February 1, 2007) and endorsed by numerous publications (Babb 1998, Neuenschwander 2008, Neuenschwander 2010), and its development and appropriate use is one aspect of the FDA's Critical Path Initiative.

The study includes patients ranging from 12 months to <18 years of age. Patients must be diagnosed with a malignancy that has a genetic alteration of ALK (such as a mutation, translocation or amplification) and has progressed following standard therapy or for which no

[redacted]

standard treatment option exists. The study is limited to malignancies with a genetic alteration of ALK because LDK378 is only expected to be active against ALK-activated malignancies.

In order to ensure experience with LDK378 across this age range, at least 3 patients will be treated in each of the following age categories: 12 months - < 7 years, 7 - < 12 years, and 12 - <18 years.

2.3 Rationale for dose and regimen selection

The starting dose for the fasted dose escalation part is 66.7% of the MTD in adults, normalized to BSA. Based on the adult MTD of 750 mg qd, and a typical adult BSA of 1.7 m^2, the pediatric starting dose of LDK378 is 300 mg/m^2 ((750 mg x 0.667) /1.7 m^2 = 294 mg/m^2, rounded to 300 mg/m^2) dosed once daily by mouth. In adults, LDK378 is dosed once daily by mouth, and the half-life of approximately 36 hours supports proceeding with once daily dosing in children.

The starting dose of 300 mg/m^2 corresponds to an adult dose of approximately 500 mg qd. In the ongoing phase 1 study the combined response rate at the 400 mg qd and 500 mg qd dose levels was 63% (15/24), including unconfirmed responses only observed on a single evaluation as of the Aug 3, 2012 snapshot. In addition, considering that LDK378 is 20-fold more potent than crizotinib based on enzymatic inhibition assays of ALK kinase activity and at the clinical dose 500 mg qd, the median AUC of LDK378 is approximately 23.3 µM*hr (day 8 of cycle 1), which exceeds the steady state exposure of crizotinib of approximately 8.6 µM*hr, at its MTD (FDA Clin Pharm, Biopharm review of crizotinib, NDA 202570), the selected starting dose in the current study should produce anti-tumor activity. The probability of overdose at 500 mg qd is estimated to be <0.1% in the adult phase 1 study, based on the Bayesian logistic regression model. Thus, the starting dose of 300 mg/m^2 is expected to be active and well tolerated. The half-life of approximately 36 hours observed in adults supports once daily dosing in children.

[redacted]

Rodent xenograft experiments in ALK-rearranged tumor models that are resistant to crizotinib require higher LDK378 exposures to achieve maximum tumor growth inhibition; therefore, it is likely that higher doses of LDK378 will be more active in patients, and it is most appropriate to dose LDK378 at the MTD, not to target a minimal efficacious dose.

During the dose escalation parts of the study, dose escalation will be guided by the BLRM, but the maximum increase in dose for the fasted dose escalation part will be limited to 50% of the last prior dose level before reaching 450mg/m^2, and to 25% after reaching 450 mg/m^2, which is the MTD in adults, as shown in Table 6-1. Dose escalation for the fed dose escalation part will be limited to a 25% or smaller increase above the prior fed dose level. These restrictions are necessary to prevent excessive escalation, since the starting dose is relatively close to the adult MTD.

[redacted]

2.4 Rationale for choice of combination drugs

Not applicable.

2.5 Rationale for choice of comparators

Not applicable.

2.6 Risks and benefits

LDK378 dosed at 750 mg once daily has remarkable anti-tumor activity and induces a high rate of rapid and durable responses and prolonged PFS in patients with advanced, ALK-positive NSCLC, regardless of whether they had been previously treated with an ALK inhibitor or were ALK inhibitor naïve. The substantial anti-tumor activity and resulting clinical benefit combined with the clinically manageable safety profile of LDK378 strongly support a positive benefit/risk balance for ALK-positive NSCLC patients.

Efficacy

Patients with prior ALK inhibitor treatment: ALK-positive NSCLC patients previously treated with crizotinib who have progressed and patients intolerant to crizotinib have no effective treatment options, have a dismal prognosis, and represent a population with a high unmet medical need. In ALK-positive NSCLC patients failing treatment with crizotinib, independent from the resistance mechanism involved, ALK translocation is still present and is still the oncogenic driver in almost all of the cases. Chemotherapy is not expected to provide a meaningful clinical benefit in these patients, as was recently demonstrated in a Phase III study (PROFILE 1007) of crizotinib vs. chemotherapy in the second-line setting (Shaw et al 2013).

In ALK-positive NSCLC patients previously treated with an ALK inhibitor and multiple prior lines of anti-neoplastic therapy, based on an independent review of tumor assessments, as of 31-Oct-2013, the response rate was 45.1% (95% CI: 37.1 - 53.3) and the median DOR was 7.1 months (95% CI: 5.6 – NE). The median PFS was 6.7 months (95% CI: 5.5 - 7.7) in Study [CLDK378X2101]. The median PFS is similar (overlapping 95% CIs) to that reported for crizotinib in the second-line setting (7.7 months (95% CI: 6.0 - 8.8)) and similar or better than that reported for chemotherapy (4.2 months (95% CI: 2.8 - 5.7) with pemetrexed and 2.6 months (95% CI: 1.6 - 4.0) with docetaxel) in the PROFILE 1007 study (Shaw et al 2013) for patients with locally advanced or metastatic ALK-positive NSCLC who had received prior treatment with one platinum-containing chemotherapy regimen. Therefore, LDK378 fulfills an existing unmet medical need.

The efficacy of LDK378 seen in Study [CLDK378X2101] is highly encouraging in heavily pretreated patients with advanced disease, high tumor burden (including a high proportion of brain metastases at baseline), limited available therapeutic options, and dismal prognoses following prior ALK-targeted therapies, where the only options are chemotherapy and best supportive care.

ALK inhibitor naïve patients: As of 31-Oct-2013, based on an independent review of tumor assessments, the response rate in ALK inhibitor naïve NSCLC patients was 61.0% (95% CI: 49.2 - 72.0) in Study [CLDK378X2101]. The median DOR was not evaluable for treatment-naïve patients. The median PFS for LDK378 in ALK-inhibitor naïve patients was not

[redacted]

evaluable (95% CI: 13.7 - NE) as the majority of patients were ongoing without an event at the time of the data cut-off.

Overall, these data suggest that LDK378 as a first-line ALK inhibitor treatment has remarkable anti-tumor activity and induces a consistently high rate of durable responses in ALK inhibitor naïve patients.

Safety

The safety profile of LDK378 is manageable (Section 1.2.1.2), with a low rate of AEs leading to discontinuation. Furthermore, patients' perception of their quality of life was maintained or slightly improved with LDK378 treatment. The most common AEs were gastrointestinal (diarrhea, nausea, vomiting); increases in transaminases, decreased appetite, fatigue; abdominal pain, and constipation were also seen in ≥ 25% of patients. These AEs can be managed with symptomatic treatment and/or dose reductions or interruptions; only 8.8% of patients discontinued study drug due to an AE. No clinically meaningful differences in the safety profile were observed between ALK-positive NSCLC patients previously treated with an ALK inhibitor and ALK inhibitor naïve patients.

The risks identified with LDK378 treatment include hepatotoxicity, interstitial lung disease (ILD)/pneumonitis, QT interval prolongation, bradycardia, hyperglycemia, gastrointestinal toxicity (nausea, vomiting and diarrhea) and pancreatitis (including lipase and amylase elevations) (Section 8.1.3). These risks can be managed and ameliorated by early diagnosis and dose adjustment/interruption, or permanent discontinuation.

Risk management during study conduct

In order to manage the risks associated with LDK378 treatment, specific dose modifications and stopping rules during study conduct are described in the protocol. For patients who do not tolerate the initial protocol-specified dose, dose adjustments are provided in order to allow the patients to continue the study treatment (Section 6.3. and Table 6-3). Patients whose treatment is temporarily interrupted or permanently discontinued due to a study drug related AE or an abnormal laboratory value must be followed until resolution or stabilization of the event, whichever comes first, including all study assessments appropriate to monitor the event.

In addition, a thorough post-treatment safety follow-up is included (Section 7.1.4). Patients may voluntarily withdraw from study treatment at any time or on the advice of the investigator if he/she believes that continuation would be detrimental to the patient's well-being. When the patient discontinues from study treatment, an End of Treatment (EOT) visit must be performed as soon as possible and within 7 days of the last dose of LDK378. Patients will also be contacted for the safety follow-up 30 days after their last dose of LDK378 to determine if they have experienced any new AEs and/or to follow resolution of ongoing AEs.

Detailed information on allowed and prohibited concomitant medications is provided in Section 6.4. In vitro drug metabolism studies show that the metabolism of LDK378 is mediated by CYP3A4/5. Appendix 2 contains several tables listing medications that are prohibited, permitted or to be used with caution during treatment with LDK378. Prohibited medications should be discontinued at least 1 week prior to the start of treatment with LDK378.

[redacted]

Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced AEs, are extensively described in Section 6.3.

Furthermore, regarding adverse events of special interest (see Section 8.1.3):

- **Hepatotoxicity:** Hepatotoxicity, as defined by TB > 2xULN and ALT and/or AST > 3xULN and ALP < 2xULN, has been observed in <1% of patients treated with LDK378. to grade 3 or 4 ALT elevations were observed in 25% of patients receiving LDK378. Concurrent elevations in ALT >3xULN and total bilirubin >2xULN, with normal alkaline phosphatase, occurred in less than 1% of patients in clinical studies. The majority of cases were manageable with dose interruption and/or dose reduction. Few events required discontinuation of LDK378. Patients will be closely monitored by regular laboratory testing and related signs and symptoms. Risk to patients will also be minimized by restricting study enrollment to subjects with laboratory values for AST, ALT, ALP and bilirubin below certain thresholds (see exclusion criteria #3).
- **Interstitial lung disease/pneumonitis:** severe, life-threatening, or fatal interstitial lung disease (ILD)/pneumonitis have been observed in patients treated with LDK378 in clinical studies. Most cases improved or resolved with interruption of LDK378. Patients will be monitored for symptoms such as shortness of breath, cough or fever. Risk to patients will be minimized by excluding from study enrollment any patient with a history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention) (see exclusion criteria #10).
- **QT interval prolongation:** QTc prolongation has been observed in clinical studies in patients treated with LDK378, which may lead to an increased risk for ventricular tachyarrhythmias (e.g., Torsade de pointes) or sudden death. A pharmacokinetic analysis suggested that LDK378 causes concentration-dependent increases in QTc. Repeated ECG tracings will be performed throughout the study to closely monitor cardiovascular safety. Risk to patients will also be minimized by excluding from study enrollment those patients with clinically significant, uncontrolled heart disease and/or a recent cardiac event (within 6 months), including a corrected QT (QTcF) > 480 ms using Fridericia's correction on the screening ECG (see exclusion criteria #2).
- **Bradycardia:** asymptomatic cases of bradycardia have been observed in patients treated with LDK378 in clinical studies. Repeated ECG tracings will be performed throughout the study to closely monitor cardiovascular safety. Risk will also be minimized by monitoring concomitant use of other agents known to cause bradycardia (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin) to the extent possible. Heart rate and blood pressure will also be monitored regularly during the study.
- **Hyperglycemia:** events of hyperglycemia (all grades) have been reported in less than 10% of patients treated with LDK378 in clinical studies; 5% of patients reported a grade 3/4 event. The risk of hyperglycemia was higher in patients with diabetes mellitus and/or concurrent steroid use. Patients will be closely monitored throughout the study for any signs and symptoms related to elevated blood glucose levels. Risk will be minimized by including subjects with fasting plasma glucose levels < 175 mg/dL (< 9.8mmol/L) at screening (see exclusion #3).

[redacted]

- **Gastrointestinal toxicity:** diarrhea, nausea, and vomiting have been very commonly reported; 12.2% of patients reported a grade 3/4 event of diarrhea, nausea, or vomiting. Risk to patients will be minimized during the study by closely monitoring symptoms and managing patients using standards of care, including anti-diarrheals, anti-emetics, or fluid replacement, as indicated.
- **Pancreatitis (including lipase and amylase elevations):** in most cases, pancreatic enzyme elevations have been mild to moderate, and have typically reversed with interruption of LDK378. Few patients have experienced pancreatitis with severe upper abdominal pain. Patients will be monitored closely for any related signs and symptoms. In order to minimize the risk to patients during the study, patients with a history of pancreatitis or a history of increased lipase or amylase levels that was due to pancreatic disease will be excluded. In addition, serum amylase must be ≤2 x ULN and serum lipase must be within normal limits at screening.

Conclusion

The outstanding anti-tumor activity and resulting clinical benefit combined with the manageable safety profile of LDK378 strongly support a positive benefit-risk balance for ALK-positive NSCLC patients, regardless of whether the patients had received prior ALK inhibitor treatment or not.

The risk to subjects in this trial will be minimized and managed by compliance with the eligibility criteria, close clinical monitoring, dose modifications/interruptions and permanent discontinuation as required. There may be unforeseen risks with LDK378 which could be serious. Refer to the [Investigator's Brochure] for additional information regarding the safety profile of LDK378.

3 Objectives and endpoints

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

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4.
Estimate the MTD and/or RDE of LDK378 as a single agent when administered orally to pediatric patients with ALK-activated tumors in fasting and fed states	Incidence rate of Dose Limiting Toxicities (DLT) during the first cycle of LDK378 treatment.	
Secondary		Refer to Section 10.7.
(1) Characterize the safety and tolerability of LDK378 in the pediatric patients in fasting and fed states (2) Characterize single and multiple-dose PK of LDK378 in pediatric patients in fasting and fed states (3) Assess the anti-tumor activity of LDK378 in fasting and fed states	(1) Adverse events and serious adverse events, changes in laboratory values, assessments of physical examinations, vital signs and electrocardiograms. (2) Plasma concentration time profiles, PK parameters, including but not limited to, AUCtau, Cmin, Cmax, Tmax, Racc, and T1/2,acc (3) Overall response rate (ORR) and duration of response (DOR), progression-free survival (PFS) as per RECIST 1.1 in patients with neuroblastoma and other solid tumors, and by International Working Group (IWG) criteria in patients with lymphoma. MIBG response in patients with neuroblastoma.	

[redacted]

[redacted]

4 Study design

4.1 Description of study design

This is a two-part, phase 1 study, with a dose escalation part performed in the fasted and fed states, and an expansion part performed in the fasted and fed states. Eligible patients must be diagnosed with an advanced malignancy carrying a genetic alteration of ALK that has progressed following standard therapy, or for which no standard, effective therapy exists. LDK378 will be administered orally, once daily, continuously.

Because of the low incidence of cancers with abnormalities in ALK, the study sites will pre-screen patients for genetic alterations of ALK by sending a tumor sample to a central laboratory designated by Novartis. The tumor sample may be a previously obtained archival sample, or a sample obtained for the purpose of molecular pre-screening for this study. The ALK analysis results will be communicated to the study center within approximately 2 weeks of the lab's receipt of the sample. If the patient has already been identified to have a genetic alteration of ALK, he/she can be screened for the study without assessment of ALK at a designated laboratory, if Novartis reviews the local laboratory assessment, and agrees that it is sufficient for eligibility. The patient/guardian must provide signed informed consent on the molecular pre-screening consent form before a pre-screening tumor sample is sent to the designated laboratory. Patients found to have a genetic alteration of ALK, such as a mutation, translocation or amplification, may be screened for the study, after the patient/guardian provides signed informed consent. If the patient fulfills all other inclusion and exclusion criteria, the patient can begin treatment.

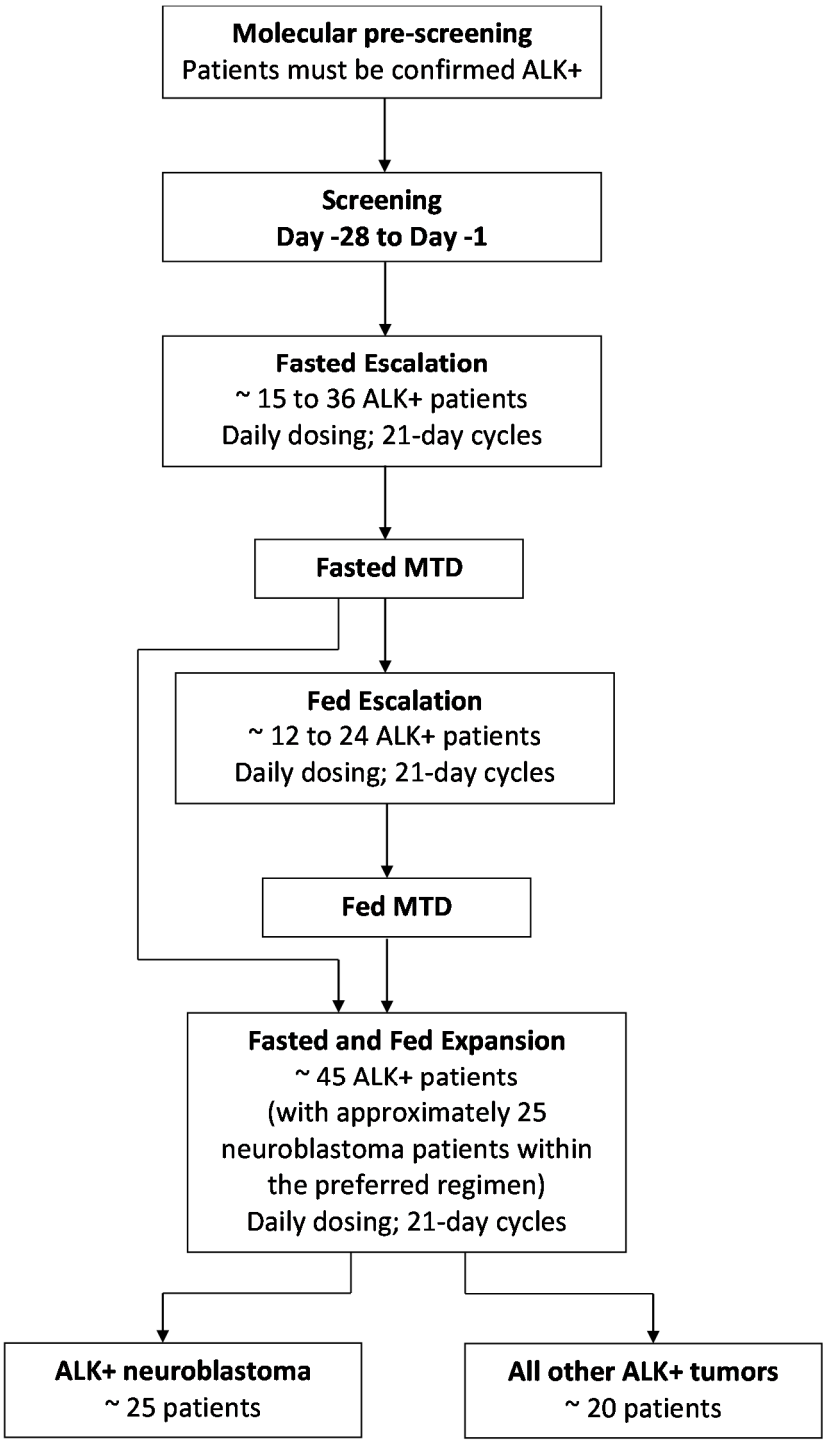
For the purpose of scheduling assessments, and establishing the MTD/RDE, a cycle is defined as 21 days in length, but there is no schedule break in dosing between cycles. It is anticipated that approximately 15-36 patients will be treated during the fasted escalation part (3-6 patients in approximately 5-6 dose levels, and a minimum of 6 at the MTD dose level). It is anticipated that approximately 12-24 patients will be treated during the fed escalation part (3-6 patients in approximately 3-4 dose levels, and a minimum of 6 at the MTD dose level). Patients will be categorized according to one of the age ranges as they enter the study.

The expansion part will start after the fasted MTD has been determined. During the expansion part patients will initially be dosed at the fasted MTD, or at a lower RDE, if the available data suggest that the MTD is not appropriate for multiple cycles of therapy. Once the fed dose escalation part is opened, patients will be enrolled on the open cohort of the fed dose escalation part. At times when the fed dose escalation part is closed to enrollment, such as during the observation period between cohorts, additional patients may continue to be enrolled in the expansion part at the fasted MTD/RDE. After the MTD/RDE is determined for the fed state and the available safety, PK and anti-tumor activity data have been reviewed, a decision will be made as to whether dosing in the fasted or fed state is preferred. Once this decision is made all subsequent patients will be enrolled on that dosing strategy to complete the planned expansion part. The expansion part will include 2 groups of patients, one restricted to patients with ALK-activated neuroblastoma and the second including all other ALK-activated tumors. Enrollment will proceed in parallel. The goals of the expansion part of

[redacted]

the study are to better characterize the safety, tolerability and PK profile of LDK378, and to make a preliminary assessment of antitumor activity. The neuroblastoma group will enroll approximately 25 patients on the preferred regimen (fed or fasted), and the mixed tumor group will enroll approximately 20 patients. See Section 10.10 for sample size rationale.

Figure 4-1 Overview of study design



[redacted]

4.2 Timing of interim analyses and design adaptations

Not applicable.

4.3 Definition of end of the study

End of study is defined as earliest occurrence of one of the following:

1. All patients have discontinued study treatment, and all required Study evaluation completion (SEC) follow-up visit have been completed, or
2. All patients have died, have been lost to follow-up or have withdrawn consent to further participation in the study, or the last patient on treatment has been enrolled into a separate rollover study or other option for continued treatment with LDK378, whichever comes first.

Patients who are still receiving treatment with LDK378 and deriving clinical benefit will be offered enrollment into a separate study or other option for continued treatment with LDK378 that are considered acceptable at the country level such as access to commercially available drug or managed access program. In the separate study, Novartis will continue to supply LDK378 to patients who may benefit from continued treatment as per the Investigator's opinion. Safety will be monitored and reported to Health Authorities per regulatory requirements. Prior to the end of the current study (CLDK378X2103), this separate protocol will be submitted to Health Authorities and IRBs involved in the current study.

The final analysis of study data will be conducted at the end of the study and all available safety and efficacy data from all patients will be analyzed. A final clinical study report (CSR) will be produced reporting all available data collected.

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. This includes early study termination if the investigators and Novartis determine that patients are experiencing excessive toxicity related to LDK378, and the available data indicate that continuation at a lower dose level is not appropriate. Should this be necessary, all patients should be seen as soon as possible and the same assessments should be performed as described in Section 7 for the EOT and SEC visits. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Patient population

This study with LDK378 as a single agent will be conducted in patients, aged 12 months to less than 18 years, with malignancies carrying a genetic alteration of ALK. Taking into account the distribution of ALK abnormalities in pediatric malignancies, it is expected that most patients will have neuroblastoma, ALCL, IMT, and rhabdomyosarcoma.

[redacted]

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

5.2 Inclusion criteria

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

1. Patients must be diagnosed with a locally advanced or metastatic malignancy that has progressed despite standard therapy, or for which no effective standard therapy exists.
2. Age ≥ 12 months and <18years.
3. The tumor must carry a genetic alteration of ALK including any of the following:
   - A point mutation, or any other mutation (e.g. insertion or deletion), , which results in a change of the amino acid sequence of the kinase domain of ALK.
   - An amplification of the ALK gene, defined as ≥ 9 copies per cell, or 4 copies per haploid genome. When assessed by FISH, ALK amplification must be observed in focal clusters of tumor cells (not only single cells) or in more than one-third of the tumor cells.
   - A rearrangement of the ALK gene (when rearrangement assessed by FISH positivity must be detected in ≥ 15% of the tumor cells).
   - In patients with rhabdomyosarcoma or anaplastic large cell lymphoma, expression of ALK protein based on immunohistochemistry is sufficient for eligibility.
4. Patients must have evaluable or measurable disease as defined by one of the following criteria: RECIST v1.1 for patients with non-hematologic malignancies (Appendix 5); MIBG scan for patients with neuroblastoma, International Working Group (IWG) criteria for patients with lymphoma (Appendix 6).
5. Performance status:
   - Karnofsky performance status score ≥ 60% for patients > 12 years of age.
   - Lansky score ≥ 50% for patients ≤ 12 years of age.

   Note: patients who are unable to walk because of paralysis, but who are mobile in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.
6. Written informed consent/assent before any study-specific molecular pre-screening and screening procedures. For pediatric patients (as defined by local standards), consent will be obtained from parent(s) or legal guardian(s) and the signature of at least 1 parent or guardian will be required. Investigators will also obtain assent of patients according to local, regional or national guidelines.

5.3 Exclusion criteria

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

1. Patients with symptomatic central nervous system (CNS) metastases who are neurologically unstable or require increasing doses of steroids or local CNS-directed therapy (such as radiotherapy, surgery or intrathecal chemotherapy) to control their CNS disease.

[redacted]

2. Patients with clinically significant, uncontrolled heart disease or corrected QT (QTc) interval > 480 milliseconds, using the Fridericia correction (QTcF).
3. Patients with the following laboratory values during screening:
   - Creatinine > 1.5 x ULN for age.
   - Total bilirubin > 1.5 x ULN for age, except for patients with Gilbert's syndrome, who may be included if total bilirubin is ≤ 3.0 x ULN and direct bilirubin is ≤ 1.5 x ULN.
   - Alanine aminotransferase (ALT) > 3 x ULN for age, except for patients that have tumor involvement of the liver, who must have a value ≤ 5 x ULN.
   - Serum aspartate aminotransferase (AST) > 3 x ULN for age, except for patients that have tumor involvement of the liver, who must have a value ≤ 5 x ULN.
   - Absolute neutrophil count (ANC) < 0.75 x 10^9/L without use of granulocyte growth factor for ≥ 14 days.
   - Platelet count < 50 x 10^9/L.
   - Hemoglobin (Hgb) < 8 g/dL.
   - Alkaline phosphatase (ALP) > 5.0 x ULN
   - Serum amylase > 2 x ULN
   - Serum lipase > ULN
   - Fasting plasma glucose ≥175 mg/dL (≥9.8 mmol/L)
   - Potassium, magnesium, calcium or phosphate abnormality > CTCAE grade 1.
4. Body surface area (BSA) < 0.35 m^2.
5. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of LDK378 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, or malabsorption syndrome).
6. Evidence of active viral hepatitis, including Hepatitis A, B or C (testing for viral hepatitis is not mandatory).
7. Known diagnosis of human immunodeficiency virus (HIV) infection (HIV testing is not mandatory).
8. Presence of ≥ CTCAE grade 2 toxicity (except alopecia, peripheral neuropathy, ototoxicity and lymphopenia, which are not excluded if grade 3 or less) due to prior cancer therapy.
9. Malignant disease, other than that being treated in this study. Exceptions to this exclusion include the following: malignancies that were treated curatively and have not recurred within 3 years prior to study entry; completely resected basal cell and squamous cell skin cancers; and completely resected carcinoma in situ of any type.
10. History of known interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention).
11. Patients who have received systemic anticancer therapy within 3 weeks of the first dose of LDK378. Patients whose immediate prior treatment was an ALK inhibitor may start treatment with LDK378 one week after the last dose of the ALK inhibitor.

[redacted]

12. Radiotherapy to lungs ≤ 4 weeks prior to starting the study treatment or patients who have not recovered from radiotherapy-related toxicities. For all other anatomic sites, radiotherapy ≤ 2 weeks prior to starting the study treatment.
13. Major surgery within 2 weeks of the first dose of LDK378. Insertion of a gastric feeding tube (G-tube), nasogastric feeding tube (NG-tube), and central venous access are not considered major surgery.
14. Patients receiving medications that are known to be strong inhibitors or inducers of CYP3A4/5 that cannot be discontinued at least 1 week prior to start of treatment with LDK378 and for the duration of the study (Appendix 2).
15. Patients receiving medications that are mainly metabolized by CYP3A4/5 or CYP2C9 and have low therapeutic index that cannot be discontinued at least 1 week prior to start of treatment with LDK378 and for the duration of the study (Appendix 2).
16. Medications with a known risk of prolonging the QT interval or inducing Torsades de Pointes (Appendix 2).
17. Pregnant or nursing (lactating) females.
18. Females of child-bearing potential, defined as all females physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 3 months after stopping dosing. **Highly effective** contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient) 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) total hysterectomy or tubal ligation at least six weeks before taking LDK378. In case of oophorectomy alone, only when the reproductive status of the female has been confirmed by follow up hormone level assessment.
    - Male sterilization (at least 6 months prior to screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient.
    - 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 females should have been stable on the same pill for a minimum of 3 months before taking LDK378.
19. Sexually active males, unless they use a condom during intercourse while taking LDK378 and for 3 months after stopping LDK378 treatment, and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.
20. Patient has other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may interfere with the interpretation of study results, and in the judgment of the investigator would make the patient inappropriate for the study.
21. Patient has a history of pancreatitis or history of increased amylase or lipase that was due to pancreatic disease.

[redacted]

6 Treatment

6.1 Study treatment

All dosages of LDK378 prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record (DAR) eCRF.

6.1.1 Dosing regimen

LDK378 dose will be scaled by BSA. The dose will be adjusted to the nearest 50 mg, and the minimum dose will be 50 mg. LDK378 will be administered once daily by mouth, or by NG tube or G tube. For patients who are not able to swallow the capsules, or who will receive LDK378 through a NG tube or G tube, the capsules will be opened, and the contents mixed with an appropriate food or liquid. Further detailed instructions regarding capsule opening and administration will be provided to all study sites separate from this protocol.

The study site staff will inform each patient of their actual daily dose, and this will be recorded on the appropriate eCRF. The actual dose for each patient will be calculated using a body surface area (BSA) conversion as follows:

- Actual dose in mg = (planned dose level (mg/m^2) x BSA) rounded to the nearest 50 mg

Individual patient BSA will be calculated using their height and weight as per standard site procedure. The actual dose for Cycle 1 will be based on the BSA calculation at screening. Dosage adjustments for changes in BSA in subsequent cycles will be made as per standard site practice (e.g., if the BSA changes by ± 10% from the previous dose calculation).

Individual doses will consist of the minimum number of capsules possible given based on the available capsule sizes, and will be rounded to the nearest 50 mg.

The investigator should instruct the patient to take the LDK378 exactly as prescribed below. All dosages prescribed and dispensed to the patient, and all dose changes during the study must be recorded on the appropriate eCRF. Patients/guardians will be asked to complete a paper dosing diary starting Cycle 1 Day 1 and will return the paper dosing diary to the study site at the beginning of each subsequent cycle (cycle 2 and on). A new diary will be dispensed to the patient at the beginning of each new cycle.

6.1.2 LDK378 administration

LDK378 should be taken as follows:

- Patients should take LDK378 once daily at approximately the same time each day. On days that PK samples are obtained, the patient will take LDK378 during the clinic visit, when instructed by the study staff.
- For patients enrolled in a fasted cohort each daily dose of LDK378 (including days which involve PK blood sampling) should be taken at least 2 hours after the last meal and patients should not eat until 1 hour after LDK378 is taken.
- Each daily dose of LDK378 should be taken with 1-2 tablespoons (15-30 mL) of an appropriate food (such as apple sauce or non-fat yogurt) and a glass of water, and consumed over as short a time as possible. Patients should be instructed to swallow capsules whole.

[redacted]

- For patients enrolled in a fed cohort each daily dose of LDK378 (including days which involve PK blood sampling) should be taken with, or within 30 minutes after finishing a low-fat light snack containing 100-300 calories and 1.5-2 grams of fat. Each daily dose of LDK378 should be taken with a glass of water, and consumed over as short a time as possible. Patients should be instructed to swallow capsules whole.
- For patients (including those in fasted cohorts and those in fed cohorts) who have difficulty swallowing intact capsule(s), the capsule(s) may be opened and the contents may be mixed with an appropriate food (such as apple sauce or non-fat yogurt) and eaten, or the contents may be mixed with water and administered via a NG tube or G tube. Once LDK378 is mixed with the carrier food or water it should be consumed within 2 hours. Further detailed instructions regarding capsule opening and administration will be provided to all study sites separate from this protocol. That document will also specify other foods and liquids that can be used as a carrier for LDK378, and updated as data become available.
- If vomiting occurs during the course of treatment, re-dosing is not allowed before the next scheduled dose.
- Patients should be instructed not to make up missed doses. A missed dose will include 1) when a patient forgets to take LDK378 within 12 hours after the approximate time of the usual daily dosing, or 2) a patient forgets to take his/her dose for that day. That day's dose should be omitted and the patient should continue treatment with the next scheduled dose.
- Patients or guardians should inform the study site staff of any missed or delayed doses.
- The investigator should instruct the patient to take the LDK378 exactly as prescribed. All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF. Patients/guardians will be asked to complete a paper dosing diary starting Cycle 1 Day 1 and will return the paper dosing diary to the study site at the beginning of each subsequent cycle (cycle 2 and on). A new diary will be dispensed to the patient at the beginning of each new cycle.

6.1.3 Treatment duration

Patients will continue treatment with the study drug until unacceptable toxicity that precludes any further treatment, disease progression, and/or treatment is discontinued at the discretion of the investigator or by patient refusal. Patients who have disease progression but who, in the opinion of the Investigator, have evidence of continued clinical benefit from LDK378 may continue to receive LDK378. A treatment cycle is defined as 21 days for the purposes of scheduling procedures and evaluations. There will be no scheduled break between cycles.

Patients whose treatment is interrupted or permanently discontinued due to an AE must be followed until resolution or stabilization of the event. Patients requiring interruptions greater than 2 cycles (42 days) will be discontinued from study treatment. In certain cases, if the Investigator and the Sponsor conclude that a patient, who has experienced a treatment interruption greater than 2 cycles (42 days), could benefit from additional treatment, continuation may be allowed.

6.2 Dose escalation guidelines

[redacted]

6.2.1 Starting dose rationale

The starting dose of LDK378 in this pediatric study is based on the clinical safety data, DLT and MTD data from the phase 1 study ([CLDK378X2101]) in adult NSCLC patients. In the adult phase 1 study the MTD was 750 mg on a once daily schedule. Based on the Bayesian logistic regression model (BLRM), at the 750 mg dose level the probability of unacceptable toxicity (DLT rate ≥ 33%) was 3.3% (satisfying the overdose criterion of < 25%), and the probability of being within the target toxicity interval (DLT rate ranging from 16% to < 33%) was 54%.

The starting dose for the fasted dose escalation, 300 mg/m^2, is 66.7% of the adult MTD (0.677 x 750 mg = 500 mg), scaled by BSA. Assuming an average adult BSA of 1.7 m^2, the starting dose is 300 mg/m^2 (rounded from 294 mg/m^2). In the adult phase 1 study most antitumor responses occurred at doses ≥ 400 mg qd, with < 0.1% probability of unacceptable toxicity at the 500 mg qd dose level, as determined by the BLRM. Thus, a starting dose of 300 mg/m^2 offers a high probability of beginning at an active dose, but a low probability of excessive toxicity. Additional information supporting the starting dose is provided in Section 2.3.

6.2.2 Provisional dose levels

Table 6-1 describes the starting dose and the dose levels that may be evaluated for the fasted dose escalation part during this trial.

Table 6-1 Provisional dose levels for fasted pediatric dose escalation[a]

Dose Level	Provisional Daily Dose[b]	Increment from previous dose
-1[c]	200 mg/m^2	33% reduction
1 (starting dose)	300 mg/m^2	Starting dose
2	450 mg/m^2	50% increase
3	560 mg/m^2	25% increase
4	700 mg/m^2	25% increase
5	875 mg/m^2	25% increase
6	1090 mg/m^2	25% increase

a. This table is intended as an example for guidance for the dose escalation part only. Intermediate or higher dose levels may be used if the dose-escalation rules presented in this protocol are followed. Actual dose levels will be confirmed in writing by Novartis and provided to all participating study sites before treatment of patients in a new cohort.

b. All doses will be dosed on a mg/m^2 basis, rounded to the nearest 50 mg (refer to Section 6.1.1 for details).

c. Dose level -1 may be used if appropriate (e.g., if the starting dose level is not well tolerated).

The fasted dose escalation will continue until the MTD and/or the RDE dose is reached. Following completion of the dose escalation part of the study, a dose will be chosen for the expansion part of the study. The dose for the expansion part will be opened at either the fasted MTD, or a lower dose that is determined to be the RDE.

After the fasted dose escalation has reached the MTD and/or RDE, the fed dose escalation will begin. The starting dose for the fed dose escalation part will be approximately 63% of the fasted MTD determined in this study. This is based on the data from adult healthy volunteers

[redacted]

taking LDK378 with a low-fat meal. It is estimated that the steady state exposure of LDK378 with a low-fat meal will be increased 1.58 fold. Dose escalations during the fed dose escalation part of the study will be limited to a 25% or smaller increase above the prior fed dose level.

Once the fed dose escalation begins, patients will be preferentially enrolled on the opened fed-dose escalation cohort; however, patients may continue to be enrolled into the expansion cohort at the fasted MTD/RDE if there is no availability on a fed-cohort.

6.2.3 Guidelines for dose escalation and determination of (MTD/RDE)

For the purposes of dose escalation decisions, each cohort will consist of 3 to 6 newly enrolled patients who will be treated at the specified dose level. The first fasted cohort will be treated with the starting dose of 300 mg/m^2. The first fed cohort will be treated with a starting dose of approximately 63% of the fasted MTD determined in this study.

Patients must complete a minimum of 1 cycle of treatment with the minimum safety evaluation and drug exposure or have had a DLT within the first cycle of treatment to be considered evaluable for dose escalation decisions. Dose escalation decisions will occur when the cohort of patients has met these criteria.

Dose escalation decisions will be made by Investigators and Novartis study personnel. Decisions will be based on a synthesis of all relevant data available from all dose levels evaluated in the ongoing study, including safety information, DLTs, all CTCAE Grade $\geq$ 2 toxicity data during Cycle 1 and available PK data from evaluable patients. The recommended dose for the next cohort of patients will be guided by the Bayesian logistic regression model (BLRM) with EWOC principle.

The adaptive Bayesian methodology provides an estimate of all dose levels of LDK378 that do not exceed the MTD and incorporates all DLT information at all dose levels for this estimation. In general, the next dose will have the highest chance that the DLT rate will fall in the target interval (16-33%) and will always satisfy the EWOC principle. In all cases, the dose for the next cohort will not exceed a 50% (25% after reaching 450 mg/m^2) increase from the previous dose. Smaller increases in dose may be recommended by the Investigators and Novartis upon consideration of all of the available clinical data.

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

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

1. at least 6 patients have been treated at this dose.
2. the dose satisfies one of the following conditions:
    a. the posterior probability of targeted toxicity at this dose exceeds 50% and is the highest among potential doses, or

[redacted]

b. minimum number of patients (15 for the fasted state dose escalation, 12 for the fed state dose escalation) have already been treated on the trial.

3. it is the dose recommended for patients, either per the model or by review of all clinical data by Novartis and Investigators in a dose-escalation teleconference, see Section 6.2.3.1.

Due to the rarity of pediatric cancers with genetic alterations of ALK and the small number of patients evaluated at each dose level, and consistent with the typical approach in phase 1 pediatric oncology studies, dose escalation decisions will not be based on age categories. However, if adequate data become available to indicate that the DLT rate is age-related, the protocol may be amended to define different MTDs in different age categories.

To better understand the safety, tolerability and PK of LDK378, additional cohorts of patients may be enrolled at preceding dose levels, or to intermediate dose levels before or while proceeding with further dose escalation.

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

6.2.3.1 Implementation of dose escalation decisions

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

6.2.3.2 Intra-patient dose escalation

Intra-patient dose escalation is not permitted at any time within the first 4 cycles of treatment. After the fourth cycle is completed, individual patients may be considered for treatment at a LDK378 dose higher than the dose to which they were initially assigned. In order for a patient to be treated at a higher dose of LDK378, he or she must have tolerated the lower dose for at least 4 cycles of therapy without any LDK378-related toxicity ≥ CTCAE grade 2. The proposed higher dose must be a dose that has completed evaluation and has not exceeded the maximum tolerated dose (MTD). Novartis must be consulted prior to an intra-patient dose escalation, and agree with the escalation decision. There is no limit to the number of times a patient may have his or her dose of LDK378 increased. The dose change must be recorded on the DAR eCRF.

Data from the first cycle of treatment at the new dose level will not be formally included in the statistical model describing the relationship between dose and occurrence of DLT. However, these data will be incorporated into the clinical assessment of safety when escalation to a new dose level is considered for the study.

[redacted]

6.2.3.3 Changing from Fasted to Fed Dosing

Changing from fasted dosing to fed dosing is allowed after the patient has completed at least six cycles of fasted dosing, provided the following:

- The MTD/RDE in the fed state has been determined, and dosing with food has been chosen for further expansion
- The dose level of LDK378 must remain the same, or be reduced to the MTD/RDE in the fed state, if that is lower than the patient's current dose
- The patient must have tolerated the fasted dose without any drug-related toxicity ≥ Grade 3, except for nausea, vomiting, diarrhea or abdominal pain
- If a patient on the fasted dosing has had a drug-related toxicity of ≥ Grade 3 other than nausea, vomiting, diarrhea or abdominal pain, the patient must have had a dose reduction and tolerated the reduced dose without a drug-related toxicity of ≥ Grade 3 for at least two cycles before changing from fasting dosing to fed dosing

6.2.4 Definitions of dose limiting toxicities (DLTs)

A DLT is defined as an adverse event or abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant therapies that occurs within the first 21 days (Cycle 1) of treatment with LDK378 and meets any of the criteria included in Table 6-2. Any adverse event is not considered a DLT if it does not happen within the first 21 days of treatment. However, medically significant events should be followed up as for DLTs. NCI CTCAE version 4.03 will be used for all grading. For the purpose of dose-escalation decisions, DLTs will be considered and included in the BLRM.

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

Table 6-2 Criteria for defining dose-limiting toxicities

Any adverse event of CTCAE grade 3 or higher during cycle 1 is a DLT, with the following exceptions	
Hematology	• Neutropenia is a DLT if it is CTCAE grade 4 lasting > 7 days • Thromobcytopenia is a DLT if it is CTCAE grade 3 lasting > 7 days or CTCAE grade 4 thrombocytopenia at any time • Anemia is a DLT if it is CTCAE grade 4 lasting > 7 days • Lymphopenia is a DLT if it is CTCAE grade 4
Renal	• Serum creatinine > 2 x ULN is a DLT Refer to Table 6-5 for additional follow up.
Hepatic	• AST or ALT increase is a DLT if CTCAE grade 3 or greater • Total bilirubin is CTCAE grade 2 with AST or ALT CTCAE grade 1 in the absence of cholestasis or hemolysis. Refer to Table 6-5 for additional follow up.
Pulmonary	• Pneumonitis or ILD of any grade without infectious etiology is a DLT

[redacted]

Any adverse event of CTCAE grade 3 or higher during cycle 1 is a DLT, with the following exceptions	
Gastrointestinal	● Nausea and vomiting are DLTs if they are ≥ CTCAE grade 2 despite optimal anti-emetic therapy ● Amylase and/or lipase elevation ≥ grade 3 is a DLT. Refer to Table 6-5 for additional follow up. ● Diarrhea is a DLT if it is ≥ CTCAE grade 3 despite optimal anti-diarrhea treatment
Infection	● Infection or fever in the absence of neutropenia are DLTs if they are ≥ CTCAE grade 3 and last > 5 days
Electrolytes	● Hypophosphatemia is a DLT if it is ≥ CTCAE grade 3 and lasts > 7 days
Fatigue	● Fatigue is a DLT if it is ≥ CTCAE grade 3 and lasts > 7 days
Other adverse events	Other unacceptable toxicities may be considered to be DLTs by the Investigators and Novartis, even if not CTCAE grade 3 or higher
Any toxicity resulting in an excess of missed doses	Inability to deliver ≥ 75% of the planned doses in a treatment cycle (i.e. at least 16 doses in a 21 day cycle) because of toxicity at least possibly related to LDK378 is a DLT
CTCAE version 4.03 will be used for all grading. Patients may receive supportive care as per local institutional guidelines. Optimal therapy for vomiting or diarrhea will be based on institutional guidelines, with consideration of the prohibited medications listed in this protocol.	

Dose modification related to DLTs

If a patient experiences a DLT, treatment with LDK378 should be held. Following resolution of the toxicity to grade 1 or to the patient's baseline value the patient may resume treatment with LDK378. In general patients who resume therapy following a DLT should resume at a lower dose level assessed to be safe with a minimum dose reduction of 50 mg. However, following recovery of a DLT that was not considered clinically important or can be managed if it recurs (e.g., replacement of an electrolyte), the patient may resume therapy without dose reduction, if the investigator considers that to be in the best interest of the patient. The dose should not be reduced below 150 mg/m^2. Provisional dose levels for LDK378 are listed in Table 6-1.

6.3 Dose modifications

6.3.1 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 patients to continue the study treatment. Any changes in LDK378 administration must be recorded on the Dosage Administration Record eCRF.

Patients whose treatment is interrupted or permanently discontinued due to an AE must be followed until resolution or stabilization of the event. Patients requiring interruptions greater than 2 cycles (42 days) will be discontinued from study treatment. In certain cases, if the Investigator and the Sponsor conclude that a patient, who has experienced a treatment

[redacted]

interruption greater than 2 cycles (42 days), could benefit from additional treatment, continuation may be allowed.

LDK378 dose reduction will follow the dose reduction steps described in Table 6-3. For each patient, a maximum of 3 dose modifications will be allowed after which the patient must be discontinued from treatment with LDK378. Once the dose of LDK378 has been reduced, it cannot be re-escalated. If a patient continues treatment with LDK378 after RECIST-defined PD confirmed by the investigator, the criteria for dose modification will also apply.

Table 6-3 Dose reduction steps for LDK378 at RDE (fasted and fed states)

LDK378 dose levels	Dose* and schedule
Starting dose level	RDE: 500/510 mg/m^2 QD continuously
Dose level -1	400 mg/m^2 QD continuously
Dose level - 2	300 mg/m^2 QD continuously
Dose level -3	200 mg/m^2 QD continuously

*Dose reduction should be based on the worst preceding toxicity as per NCI-CTCAE version 4.03
**Dose reduction below 200 mg/m2/day is not allowed. If a dose reduction below 200 mg/m2/day is required, the patient should be permanently discontinued from LDK378

Guidelines for dose interruptions and re-initiation of LDK378 treatment (with or without dose reduction) are described in Table 6-4.

Patients, who discontinue from the study for a study-related adverse event or an abnormal laboratory value, must be followed as described in Section 7.1.3.

General guidelines for dose modifications for toxicities other than those listed in Table 6-4:

For grade 1 and tolerable grade 2 treatment-related toxicities, patients are encouraged to continue at the current dose of study treatment. For intolerable grade 2 treatment-related toxicities, dosing should be interrupted until resolution to grade 1 or lower followed by dose reduction to the next dose level.

For grade 3 or grade 4 treatment-related toxicity that is not considered by the Investigator to be life-threatening, patients should interrupt study treatment until resolution of that toxicity, to grade 1 or lower. Study treatment may be resumed following a dose reduction to the next dose level if, in the opinion of the Investigator, the patient continues to experience clinical benefit. For any grade 3 or grade 4 treatment-related toxicity that is considered by the Investigator to be life-threatening, study treatment must be permanently discontinued.

In the case of a DLT of QTc prolongation (QTc >500 ms) LDK378 must be withheld until resolution to grade 1 or less. If LDK378 is resumed, the dose must be reduced by at least 1 dose level and at least 50 mg. In the case of grade 4 QTc prolongation (QTc >500 ms complicated by Torsades de pointes, polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia; or >60 ms change from baseline complicated by Torsades de pointes, polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia) LDK378 should be permanently discontinued.

Patients whose treatment is interrupted or permanently discontinued due to an AE must be followed until resolution or stabilization of the event. Patients requiring interruptions greater

[redacted]

than 2 cycles (42 days) will be discontinued from study treatment. In certain cases, if the Investigator and the Sponsor conclude that a patient, who has experienced a treatment interruption greater than 2 cycles (42 days), could benefit from additional treatment, continuation may be allowed.

[redacted]

Table 6-4 Criteria for interruption and re-initiation of LDK378 treatment

Worst toxicity (CTCAE 4.03 Grade)*	**Dose Modifications for LDK378**
HEMATOLOGICAL	
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
HEPATIC	
Alkaline phosphatase and/or **Gamma-glutamyl transpeptidase (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 liver function test (LFTs)*** monitored as per protocol

[redacted]

Worst toxicity (CTCAE 4.03 Grade)*	**Dose Modifications for LDK378**
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, discontinue patient from LDK378
Grade 4 (> 10.0 x ULN)	Permanently discontinue patient from LDK378
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
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 total bilirubin elevation to > 2.0 x ULN	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
AST or ALT and concurrent Total bilirubin	
AST or ALT > 3.0 x ULN with total bilirubin > 2.0 x ULN in the absence of cholestasis or hemolysis	Permanently discontinue patient from LDK378. Refer to Section 6.3.2.2 for additional follow-up.
AST or ALT > 5.0 and ≤ 20.0 x ULN with total bilirubin > 1.5 and ≤ 3.0 x ULN	Permanently discontinue patient from LDK378 if event reoccurs after dose reduction.
PANCREATIC	
Amylase and/or lipase evaluations (in 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 x ULN)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Note: Withhold LDK378 for acute onset of new or progressive unexplained abdominal symptoms, such as severe pain or vomiting; perform diagnostic procedures (e.g., abdominal CT scan or ultrasound) to exclude pancreatic pathology.	
RENAL	

[redacted]

Worst toxicity (CTCAE 4.03 Grade)*	**Dose Modifications for LDK378**
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	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 omit 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
Nausea***	
Grade 1 or 2	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	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

[redacted]

Worst toxicity (CTCAE 4.03 Grade)*	**Dose Modifications for LDK378**
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
GENERAL DISORDERS	
Fatigue (asthenia)	
Grade 1 or 2	Maintain dose level
Grade 3	If grade 3 fatigue resolves to Grade 2 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. ● For pneumonitis not treatment related: If pneumonitis/ILD of grade 2 or worse is confirmed, study drug should be permanently discontinued. If Grade 1 resolves within 6 weeks, LDK378 may be resumed reduced by 1 dose level, otherwise it must be discontinued. If grade 1 pneumonitis recurs after dose reduction, then LDK378 must be permanently discontinued.	
PNEUMONITIS	
Any Grade treatment-related ILD/pneumonitis	Permanently discontinue patient from LDK378
CARDIAC	
Electrocardiogram QT corrected (QTc) interval prolonged	
Grade 1 (QTc 450-480 ms) Grade 2 (QTc 481-500 ms)	Maintain dose level

[redacted]

Worst toxicity (CTCAE 4.03 Grade)*	**Dose Modifications for LDK378**
Grade 3 (QTc ≥ 501 ms on at least two separate ECGs)	Omit dose until QTc is less than 481 ms , 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 QTc < 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 After resumption of dosing: - Repeat ECGs 7 days after dose resumption for all patients who had therapy interrupted due to QTc ≥ 501 ms.
Grade 4 (QTc ≥ 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 Grade 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	Omit dose until recovery to asymptomatic bradycardia or to a heart rate ≥ 60 bpm Patient may resume LDK378 at ↓ 1 dose level with frequent monitoring
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 LDK378 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 patient from LDK378

[redacted]

Worst toxicity (CTCAE 4.03 Grade)*	Dose Modifications for LDK378
* Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. All dose modifications should be based on the worst preceding toxicity. ** 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 **** Dose modifications apply to patients who experience diarrhea despite appropriate antidiarrheal medication. This medication should be started at the first sign of abdominal cramping, loose stools or overt diarrhea (see Section 6.3.2.5) ***** Dose modifications apply to patients who experience nausea and/or vomiting despite appropriate antiemetic medication. This medication should be started at the first sign of nausea and/or vomiting (see Section 6.3.2.6)	

6.3.2 Follow-up for toxicities

An unscheduled visit should be performed in all cases below where toxicity monitoring is recommended more frequently than defined by the schedule of assessments in (Table 7-1). For details and frequency refer to Table 6-5.

6.3.2.1 Guidelines for the follow-up of laboratory hematologic abnormalities

In case of any occurrence of febrile neutropenia, neutropenia ≥ grade 3, anemia grade 4, or thrombocytopenia ≥ grade 3, white blood cell count with differential (including neutrophil count), platelet count and hemoglobin must be measured after 3 days and then at least once a week (or more frequently if clinically indicated) until the event resolves to ≤ grade 2 or baseline. Subsequent monitoring must be performed every 3 weeks (21 days).

Hematopoietic growth factors (e.g., erythropoietins, G-CSF, and GM-CSF) are not to be administered prophylactically. Use of these drugs should be reserved to patients with severe neutropenia and anemia as per the labeling of these agents.

6.3.2.2 Guidelines for the follow-up of liver laboratory abnormalities

In patients with any clinically relevant liver laboratory abnormality, as defined below, hepatic toxicity monitoring must include **ALL** of the following LFTs: albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 1.5x ULN, and any additional evaluation suggested by these results should be performed as clinically indicated), ALP. 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 ALT/AST/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 2 weeks (or more frequently if clinically indicated) for two additional cycles (e.g. 6 weeks). If there is no recurrence of ≥ grade 2 ALT/AST/total bilirubin elevations during this period, subsequent monitoring must be performed every 3 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 ALT/AST/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. Thereafter monitoring must be continued every 2 weeks (or more frequently if clinically indicated) for four additional cycles (e.g., 12 weeks). If there is no recurrence of ≥ grade 2 ALT/AST/total bilirubin elevations during this period, subsequent monitoring must be performed every 3 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 3 weeks). Refer to Table 6-5.

Patients with transaminase increase combined with total bilirubin (TBIL) increase may be indicative of potential DILI, 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:

- 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 (ALT/ALP in x ULN) < 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 or hepatocellular 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, creatinine 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.
- 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 after repeat testing and meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as "medically significant", these cases will meet the definition of SAE (Section 7.2.1) and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

6.3.2.3 Guidelines for the follow-up of renal laboratory 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 3 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 3 weeks.

[redacted]

6.3.2.4 Guidelines for monitoring pneumonitis

Monitor patients for pulmonary symptoms indicative of pneumonitis. In addition, 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. Exclude other causes of pneumonitis, and follow dose modification guidelines as described in Table 6-4.

6.3.2.5 Guidelines for the treatment of study treatment-induced diarrhea

The investigator should consider/investigate potential concomitant medication-, food-, or comorbidity-driven causes of diarrhea (including infectious causes) and remedy these causes if possible (e.g., discontinuation of concomitant medication, dietary modification, treatment of comorbidity).

The patient should be actively monitored for signs of dehydration and instructed to take preventive measures against dehydration as soon as diarrhea occurs.

Antidiarrheal medication must be initiated at the first sign of abdominal cramping, loose stools or overt diarrhea. Concomitant medication for the treatment of diarrhea should follow local practices and the Investigator's best judgment and may follow "the recommended guidelines for the treatment of cancer treatment-induced diarrhea" (Benson et al 2004). For example:

- For uncomplicated diarrhea (grade 1 or 2 without complicating signs or symptoms), loperamide given at the usual pediatric dose as per local Label, along with oral hydration, and dietetic measures should be considered. Note: complicating signs or symptoms include: moderate to severe cramping, decreased performance status, fever, neutropenia, frank bleeding or dehydration.
- For complicated diarrhea (all grade 3 or 4, grade 1-2 with complicating signs or symptoms), management should involve IV fluids, and consider treatment with antibiotics (e.g., fluoroquinolone) should be given.

Dose adaptation of LDK378 in case of treatment-related diarrhea must follow the guidelines presented above in Table 6-4.

6.3.2.6 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 also 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.

[redacted]

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

Dose adaptation of LDK378 in case of treatment related nausea and/or vomiting must follow the guidelines presented above in Table 6-4.

6.3.2.7 Guidelines for the treatment of hypophosphatemia

In the phase I study [CLDK378X2101] conducted in adult patients, as of 31-Oct-2013, there were 9 cases of grade 3 hypophosphatemia observed 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 a 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 not among the commonly reported AE (6.3%), regardless of relationship to LDK378 treatment.

Therefore, phosphate levels will be checked during treatment. 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.

6.3.2.8 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. 3 weeks). If there is no recurrence of ≥ grade 2 amylase or lipase elevations during this period, subsequent monitoring must be performed every 3 weeks.

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 3 weeks). Refer to Table 6-5.

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

See also dose modification guidelines described in Table 6-4.

[redacted]

Table 6-5 Follow up evaluations for selected toxicities

Toxicity	Follow-up evaluation*
Investigations (hematologic)	**Febrile neutropenia or thrombocytopenia ≥ CTCAE Grade 3 or Neutropenia or anemia ≥ CTCAE Grade 4** White blood cell count with differential (including neutrophil count), platelet count and hemoglobin must be measured after 3 days and then at least once a week until resolution to ≤ CTCAE grade 2 or baseline. **Neutropenia ≥ CTCAE Grade 3** Test after 3 days and then at least once a week until ≤ Grade 2 or baseline Subsequent monitoring must be performed every cycle (3 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 (6 weeks) If no recurrence of ≥ Grade 2 event, continue monitoring every cycle (3 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 (12 weeks) If no recurrence of ≥ grade 2 event, continue monitoring every cycle (3 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 (3 weeks) **Serum creatinine ≥ Grade 3**: Test twice weekly (or more frequent) until ≤ Grade 1 Thereafter, test every cycle (3 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 (3 weeks). If no reoccurrence of ≥ Grade 2 event, continue monitoring every cycle (3 weeks)**.**
Investigations (gastrointestinal)	**Vomiting or diarrhea** Measure blood electrolytes at least once a week until the symptoms have resolved to ≤ CTCAE grade 1 or baseline. If nausea occurs in the absence of clinically relevant vomiting or diarrhea, the patient must be followed weekly as deemed clinically appropriate until resolved to ≤ CTCAE grade 2 or baseline.

*Note: this table refers to the evaluation schedule only. Refer to Table 6-4 for dose modifications required for applicable toxicities

[redacted]

6.4 Concomitant medications

6.4.1 Permitted concomitant therapy

6.4.1.1 Corticosteroids

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 initiating study therapy

6.4.1.2 Bisphosphonates

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.

6.4.1.3 Drugs that are metabolized by CYP450 enzymes

In vitro drug metabolism studies show that the metabolism of LDK378 is mediated by CYP3A4/5. LDK378 is a time-dependent CYP3A4/5 inhibitor and is also a potent reversible inhibitor of CYP2A6, 2E1, 2C9 and 3A4/5 and may consequently increase exposure to drugs metabolized by these enzymes at clinically relevant concentrations. Clinical studies have not yet been performed to confirm the potential effect of LDK378 on substrate drugs metabolized by these enzymes in patients. The risk for CYP2A6 and CYP2E1 is largely mitigated by the low potential for drugs metabolized by these enzymes to be co-administered with LDK378.

Concomitant treatment of LDK378 with weak inhibitors or inducers of CYP3A4/5 is permitted. Caution is advised when LDK378 is co-administered with drugs that are moderate inhibitors or inducers of CYP3A4/5 (Appendix 2). Duration of concomitant treatment should be kept as short as possible (e.g., less than 1 week), or completely avoided whenever possible. Patients receiving such medications must be monitored closely for any potentiation of toxicity or decrease of clinical benefit due to any individual concomitant medications, and may require

[redacted]

dose titration or adjustment. Note that co-administration of LDK378 with strong inhibitors or inducers of CYP3A4/5 is prohibited (refer to Section 6.4.2).

Concomitant treatment of LDK378 with medications known to be metabolized by CYP2C9 and CYP3A4 is allowed with caution (Appendix 2), except for drugs which have narrow therapeutic index/sensitive substrates for these CYP isoforms (Appendix 2).

6.4.1.4 Non-enzyme inducing anti-epileptic drugs

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

6.4.1.5 Palliative radiotherapy and surgery

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 ceritinib therapy, as determined by the Investigator may undergo radiotherapy and/or surgical resection as palliative localized therapy to treat metastatic lesions. Ceritinib should be held for at least 4 days prior to radiotherapy and at least 1 day prior to any surgery. Ceritinib may be resumed ≥3 days after completing radiotherapy or minor surgery, and ≥2 weeks after major surgery.

6.4.1.6 Gastric protection agents

The use of gastric protection agents including antacids, H2-antagonists, and proton pump inhibitors (PPIs) is allowed (Appendix 2). 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).

6.4.2 Prohibited concomitant therapy

6.4.2.1 Other anticancer therapy

Anticancer therapy (chemotherapy, targeted therapy, biologic therapy or radiation therapy [except palliative radiotherapy and palliative surgery as described in Section 6.4.1.5], and anti-cancer surgery), 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.

6.4.2.2 Other investigational therapies

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

[redacted]

6.4.2.3 Warfarin and coumarin derivatives

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.

6.4.2.4 Enzyme inducing anti-epileptic drug

Use of EIAEDs is not permitted. Refer to Appendix 2 for a list of prohibited EIAED.

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.

6.4.2.5 Strong CYP3A inhibitors and inducers

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 receiving concomitant medications known to strongly inhibit and/or induce CYP3A4/5 that are deemed medically necessary should be excluded from the study. Refer to Appendix 2 for a list of these medications. Please note that this list may not be comprehensive.

6.4.2.6 Medications that are CYP2C9 and CYP3A4/5 substrates with narrow therapeutic index

LDK378 is a potent inhibitor of drugs metabolized by CYP2C9 and CYP3A4/5 *in vitro*. Because of the potential risk for drug-drug interactions, using medications known to be metabolized by these enzymes and that have a narrow therapeutic index is not permitted concomitantly with LDK378. Refer to Appendix 2 for a list of these medications. Please note that this list may not be comprehensive.

6.4.2.7 Herbal medications

Herbal preparations/medications are not allowed throughout the study, as a potential drug-drug interaction is always possible. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng.

Patients should stop using herbal medications at least 7 days prior to first dose of study treatment and may be resumed 9 days (5 ceritinib half life) after study drug discontinuation.

6.4.2.8 Medications that may prolong the QT interval or have a known risk of inducing Torsades de Pointes

LDK378 has potent activity on the hERG channel with an IC_{50} of 0.4 µM. There were no LDK378-related effects *in vivo* in monkeys at doses as high as 100 mg/kg (human equivalent dose [HED] of 1950 mg).

[redacted]

Serial ECGs were collected following a single dose and at steady-state to evaluate the effect of LDK378 on the QT interval in an open-label, dose-escalation, and expansion [Study CLDK378X2101]. A total of 304 patients were treated with LDK378 doses ranging from 50 to 750 mg with 255 patients treated with LDK378 750 mg. One of 304 patients (<1%) was found to have a QTc >500 msec and 10 patients (3.3%) had an increase from baseline QTc >60 msec. A central tendency analysis of the QTc data at average steady-state concentrations demonstrated that the upper bound of the 2-sided 90% CI for QTc was 16 msec at LDK378 750 mg. A pharmacokinetic/pharmacodynamic analysis suggested concentration-dependent QTc interval prolongation

Concomitant use of LDK378 and any medication included in Appendix 2, Table 14-11 titled "List of prohibited QT prolonging drugs" (i.e., drugs that are generally accepted by the Qtdrugs.org Advisory Board of the Arizona CERT to have a known risk of causing Torsades de Pointes) is not permitted.

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

Each patient is identified in the study by a Patient Number (Patient No.), assigned when the patient is first pre-screened and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Patient No. consists of a 4-digit Center Number (Center No.) (as assigned by Novartis to the study site) with a sequential 5-digit patient number suffixed to it, so that each patient is numbered uniquely across the entire database. Upon signing the pre-screening informed consent/assent form (ICF), the patient is assigned to the next sequential Patient No. available to the investigator.

6.5.2 Treatment assignment or randomization

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

6.6 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient/guardian to take/dispense LDK378 as per protocol. LDK378 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 DAR eCRF.

Patients/guardians will be asked to complete a paper dosing diary starting Cycle 1 Day 1 and will return the paper dosing diary to the study site at the beginning of each subsequent cycle (cycle 2 and on). A new diary will be dispensed to the patient at the beginning of each new cycle.

[redacted]

[redacted]

6.6.2 Drug supply and storage

LDK378 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, LDK378 should be stored according to the instructions specified on the drug labels.

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug 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. Patients/guardians will be asked to complete a paper dosing diary starting Cycle 1 Day 1 and will return the paper dosing diary to the study site at the beginning of each subsequent cycle (cycle 2 and on). A new diary will be dispensed to the patient at the beginning of each new cycle.

On days when LDK378 is administered to the patient by the study site staff (e.g. PK sampling days), compliance will be assured by administration of the LDK378 under the supervision of investigator or his/her designee, and will be verified by determinations of LDK378 in plasma.

6.6.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of LDK378 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 LDK378 and packaging on a regular basis, at the end of the study or at the time of LDK378 discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused LDK378, 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 study site.

6.6.4 Disposal and destruction

LDK378 supply can be destroyed at the local Novartis facility, at the study site or third party, as appropriate.

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

[redacted]

documentation. No eCRF will be used as a source document. Visit windows can be found for procedures starting with Section 7.2.

[redacted]

Table 7-1 Visit evaluation schedule

	Category	Protocol Section	Pre-screening	Screening/ Baseline	Treatment Period														End of study treatment (EoT)	Study Evaluation Completion (SEC)
					Cycle 1				Cycle 2			Cycles 3-4		Cycles 5-16		Odd # Cycle ≥ 17 (telephone call)		Even # Cycle ≥ 18 (on site visit)			
Visit Name			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**14+**	**15+**	**36 +**	**37 +**	**38+**	**39+**	**777**	**778**
Day of cycle				**-28 to-1**	**1**	**2**	**8**	**15**	**1**	**2**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**Last**	**30-day follow-up**
Obtain molecular pre-screening informed consent	D	7.1.1.	X																		
Obtain main informed consent	D	7.1.1.		X																	
Collection of tumor paraffin block or slides (archival tumor or tumor collected specifically for this study) for ALK assessment (only if ALK testing being performed at central lab)	D	7.1.1.	X																		
Patient history																					
Demography	D	7.1.1.3.	X	X																	
Inclusion/exclusion criteria	D	5.2/5.3.		X																	
Medical History	D	7.1.1.3.		X																	
Diagnosis and extent of cancer	D	7.1.1.3.		X																	
Prior/concomitant therapies (including prior antineoplastic therapies)	D	7.1.1.3.		Continuous																	
Antineoplastic therapies since discontinuation of LDK378	D	7.1.3.																			X

[redacted]

	Category	Protocol Section	Pre-screening	Screening/ Baseline	Treatment Period															End of study treatment (EoT)	Study Evaluation Completion (SEC)
					Cycle 1				Cycle 2			Cycles 3-4		Cycles 5-16		Odd # Cycle ≥ 17 (telephone call)		Even # Cycle ≥ 18 (on site visit)			
Visit Name			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**14+**	**15+**	**36 +**	**37 +**	**38+**	**39+**	**777**	**778**
Day of cycle				**-28 to-1**	**1**	**2**	**8**	**15**	**1**	**2**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**Last**	**30-day follow-up**
Physical examination, including neurological exam	S	7.2.2.1.		X	X		X	X	X			X		X				X		X	
Performance status Karnofsky (> 12 years old) OR Lansky (≤ 12 years old)	D	7.2.2.4.		X	X				X			X		X				X		X	
Height	D	7.2.2.3.		X					X			X		X				X		X	
Weight	D	7.2.2.3.		X					X			X		X				X		X	
BSA	D	7.2.2.3.		X					X			X		X				X			
Vital signs	D	7.2.2.2.		X	X		X	X	X			X		X				X		X	
Laboratory assessments																					
Hematology ** done at local laboratory	D	7.2.2.5.1.		X	X		X	X	X		X	X	X	X		X**		X		X	
Chemistry ** done at local laboratory	D	7.2.2.5.2.		X	X		X	X	X		X	X	X	X		X**		X		X	
Pregnancy test ** done at local laboratory	D	7.2.2.5.3.		X	X				X			X		X		X**		X		X	

[redacted]

	Category	Protocol Section	Pre-screening	Screening/ Baseline	Treatment Period															End of study treatment (EoT)	Study Evaluation Completion (SEC)
					Cycle 1				Cycle 2			Cycles 3-4		Cycles 5-16		Odd # Cycle ≥ 17 (telephone call)		Even # Cycle ≥ 18 (on site visit)			
Visit Name			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**14+**	**15+**	**36 +**	**37 +**	**38+**	**39+**	**777**	**778**
Day of cycle				**-28 to-1**	**1**	**2**	**8**	**15**	**1**	**2**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**Last**	**30-day follow-up**
Tumor evaluations																					
Radiological tumor evaluation (± 7 days) * post Cycle 14, collect on D15 every six cycles: Cycles 20, 26, 32, etc. until off study	D	7.2.1.		X							X		C4		C6 C10 C14				X*	X	
MIBG imaging (neuroblastoma patients only) (± 7 days) *post Cycle 14, collect on D15every six cycles: Cycles 20, 26, 32, etc. until off study	D	7.2.1.		X							If positive at Baseline		If positive at Baseline C4		If positive at Baseline C6, C10 C14				If positive at Baseline*	If positive at baseline	
Bone marrow bilateral aspirate and biopsy (neuroblastoma and lymphoma patients only) (±7 days)	D	7.2.1.		X							Optional except in case of radiological CR		Optional except in case of radiological CR						Optional except in case of radiological CR	Optional except in case of radiological CR	
ECG	D	7.2.2.5.4.		X	X				X			X		X				X		X	

[redacted]

	Category	Protocol Section	Pre-screening	Screening/ Baseline	Treatment Period															End of study treatment (EoT)	Study Evaluation Completion (SEC)
					Cycle 1				Cycle 2			Cycles 3-4		Cycles 5-16		Odd # Cycle ≥ 17 (telephone call)		Even # Cycle ≥ 18 (on site visit)			
Visit Name			1	2	3	4	5	6	7	8	9	10	11	14+	15+	36 +	37 +	38+	39+	777	778
Day of cycle				-28 to-1	1	2	8	15	1	2	15	1	15	1	15	1	15	1	15	Last	30-day follow-up
Safety																					
Adverse events	D	8.1.		Continuous																	
[redacted]																					
LDK378 administration	D	6.1.			Continuous																
PK sampling (* indicates during Escalation only)	D	7.3.1.			X*	X*		X*	X	X		X									
Meal record (* indicates during Escalation only)	D				X	X*		X	X	X*		X									

[redacted]

7.1.1 Molecular pre-screening and screening examination

Only patients with tumors carrying a genetic alteration of ALK are eligible for this study. Patients will be considered potentially eligible if their tumor carries a mutation (including point mutations, insertions and deletions), rearrangement (including translocations and intra-chromosomal rearrangements), or amplification involving the ALK gene, as long as the alteration does not clearly result in inactivation of the kinase activity, such as deletion of the kinase domain, or a stop codon preventing translation of the kinase domain.

If the ALK tumor status is unknown when the patient is initially considered for this study, patients/guardians will be asked to sign the molecular pre-screening ICF. The study sites will pre-screen patients for genetic alterations of ALK by sending a tumor sample to a laboratory designated by Novartis. The tumor sample may be a previously obtained archival sample, or a sample obtained for the purpose of molecular pre-screening for this study (tumor paraffin block or slides). Additionally, a pathology report should be submitted along with the patient's archival tumor block/slides. The ALK analysis results will be communicated to the study center within approximately 2 weeks of receipt of the sample. If the patient is already known to have a genetic alteration of ALK at pre-screening, the laboratory result may be used for eligibility assessment, if Novartis reviews the laboratory assessment and agrees that it is sufficient for eligibility.

7.1.1.1 Molecular pre-screening and screening period

[redacted]

Patient re-screening is allowed and should be discussed with Novartis on a case by case basis before re-screening procedures are performed.

7.1.1.2 Information to be collected on screening failures

Patients who sign the molecular pre-screening ICF but do not meet the pre-screening requirements will be considered a screen failure. The reason will be entered on the Screening Log eCRF, and each patient's demographic information will be added to the Demography eCRF. No other data will be entered into the clinical database for patients who are screen failures.

Patients who meet molecular pre-screening requirements and sign the main ICF but do not start treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the Screening Log eCRF, and each patient's demographic information will be added to the Demography eCRF. No other data will be entered into the clinical database for patients who are screen failures.

7.1.1.3 Patient demographics and other baseline characteristics

The data that will be collected on patient characteristics at molecular pre-screening and baseline include general demographics, relevant medical history, the diagnosis and extent of their tumor/s and details regarding anti-neoplastic treatments that they have received in the past.

7.1.2 Treatment period

The treatment period commences on the first day of the first cycle (C1D1) of LDK378 and ends after the last dose of LDK378.

Patients who enter the study will be treated with continuous once daily dosing of oral LDK378 until objective evidence of progression of disease, occurrence of unacceptable toxicities, or patient withdrawal.

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

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

7.1.3 End of treatment visit

At any time, patients may voluntarily withdraw from the study or be removed from it at the discretion of the investigator. If withdrawal occurs, or if the patient fails to return for visits, effectively withdrawing, the investigator should make a reasonable effort (e,g. telephone, e-amil, letter) to understand the primary reason for a patient's premature withdrawal, record this information on the End of Treatment eCRF, and notify Novartis. Patients may be withdrawn from LDK378for one of the following reasons:

1. Adverse event(s).
2. Disease progression.
3. Protocol violation/deviation.

[redacted]

4. Patient withdrew consent.
5. Lost to follow-up.
6. Death.

Patients who discontinue LDK378 for any of the above reasons (except death) should be scheduled for an end of treatment (EOT) visit 14 days (up to 21 days) after discontinuing LDK378, at which time all of the assessments listed for the EOT visit will be performed. An EOT eCRF will be completed, giving the date and reason for stopping the LDK378.

The EOT completion evaluations include the following:

- A physical examination, including an assessment of any tumor lesions; Karnofsky/Lansky performance status; height/weight and vital signs; hematology; chemistry; pregnancy test for FCBP.
- Radiological tumor evaluation of all tumor sites, if not evaluated ≤ 28 days prior to the EOT visit, and if objective evidence of disease progression has not previously been documented.
- For neuroblastoma patients: MIBG imaging, if positive at baseline and not evaluated ≤ 28 days prior to the EOT visit.
- For neuroblastoma and lymphoma patients: If bone marrow bilateral aspirate and biopsies were performed and were positive at screening, it will be left to the investigator's discretion to monitor the bone marrow aspirate at each disease evaluation. In order to confirm a Complete disease Response (CR), bone marrow biopsy or aspirate may be required when a radiological CR has been achieved.
- ECG.
- Occurrence of new AEs and status of current AEs.
- Collection of a fresh tumor biopsy, if medically feasible, and the patient and/or guardian agrees.

All patients who discontinue LDK378, including those who refuse to return for a final visit, should be contacted 30 days (up to 37 days) after discontinuing LDK378 for safety evaluations and a list of concomitant medications, including antineoplastic therapies received since discontinuation (Study Evaluation Completion (SEC) visit). See Section 7.1.4. A SEC eCRF will then be completed, giving the date and reason for study discontinuation.

For patients who refuse to return for visits or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone. Patients lost to follow up should be recorded as such on the Study Evaluation Completion eCRF. A patient is considered "lost-to-follow up" if the patient fails to show up for a scheduled follow-up visit and no response despite at least 3 documented failed attempts to contact the patient, such as via phone calls and / or registered letters. 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).

Patients whose treatment is interrupted or permanently discontinued due to an AE must be followed until resolution or stabilization of the event. Patients requiring interruptions greater than 2 cycles (42 days) will be discontinued from study treatment. In certain cases, if the Investigator and the Sponsor conclude that a patient, who has experienced a treatment

[redacted]

interruption greater than 2 cycles (42 days), could benefit from additional treatment, continuation may be allowed.

Patients who discontinue from the study for a study-related adverse event will be followed for toxicity, as described above. All patients should be followed for adverse events and serious adverse events for 30 days (up to 37 days) following the last dose of LDK378 (Study Evaluation Completion (SEC) visit).

Patients who discontinue from LDK378 (e.g., due to disease progression) during Cycle 1 should have all the remaining evaluations for Cycle 1 performed prior to LDK378 completion.

The EOT visit is not considered the end of the study.

7.1.3.1 Patient replacement

Escalation:

Patients will not be replaced on study. However, if a patient is considered as non-evaluable for the DDS (Dose Determining Set), enrollment of a new patient to the current cohort will be considered if there is less than the required number of evaluable patients. Enrollment of new patients may be considered until at least the minimum number (3) or at most the maximum number (6) of evaluable patients is achieved within the cohort. Minimum and maximum numbers of evaluable patients per cohort are defined in Section 6.2.3.

Expansion:

Patients will not be replaced.

7.1.3.2 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 allow further collection of personal data.

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table. Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

[redacted]

All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

7.1.4 Follow-up period

All patients will have a Study Evaluation Completion (SEC) visit 30-days (up to 37 days) after the last dose of LDK378. At this time AE, SAE and concomitant medication (including subsequent antineoplastic therapy) information during the follow-up period will be recorded on the AE eCRF and Novartis will be informed as necessary.

Patients lost to follow-up should have this documented on the appropriate eCRF and attempts made to contact the patient to ascertain the reason and required study information, as described in Section 7.1.3.

7.1.5 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 eCRF page.

7.2 Assessment types

7.2.1 Efficacy

Disease will be assessed as per RECIST v1.1 (Appendix 5) in patients with solid tumors, and per IWG criteria (Appendix 6) for patients with lymphoma. In addition, patients with neuroblastoma will be assessed by MIBG scanning and bone marrow bilateral aspirate and biopsy at screening. Disease response and progression will be determined by the local investigator. When the revised International Neuroblastoma Response Criteria (INRC) currently in development are final they will be incorporated into this protocol.

At screening (within 28 days of the start of LDK378), all patients will undergo CT with i.v. contrast or MRI of the brain, chest, abdomen and pelvis. If there is clinical evidence of disease in the neck, a CT or MRI of the neck will also be performed. If a patient is intolerant of iodine-based contrast agents, CTs may be performed without contrast or MRI may be used. Visible skin lesions and easily palpable subcutaneous tumors may be measured by physical examination using a ruler or calipers. Ultrasound should not be used to measure sites of disease. Patients with neuroblastoma will undergo MIBG scanning, and bone marrow bilateral aspirate and biopsy at screening. Patients with lymphoma will undergo bone marrow bilateral aspirate and biopsy at screening. MIBG scans should be performed within 28 days of the start of treatment, and bone marrow bilateral aspirates and biopsies should be performed within 42 days of the start of treatment.

[redacted]

Subsequent disease evaluations will be performed on Day 15 (±7 days) of cycles 2, 4 and 6. After cycle 6, disease evaluations will be performed on Day 15 (±7 days) of every 4th cycle (e.g., C10, C14), or sooner if there is clinical evidence of disease progression. Post Cycle 14, disease evaluations will be performed every 6 cycles (e.g., C20, C26, C32, etc.) and also performed at EOT. If the last prior disease evaluation was within 28 days of EOT or objective evidence of progressive disease has already been documented, then evaluations do not need to be repeated at EOT.

Disease evaluations after the screening assessment will include evaluation of all sites of disease identified at baseline, using the same technique that was used at screening. If there was no evidence of disease in a body region at baseline, that region does not need to be imaged at subsequent assessments, unless there is clinical concern for a new lesion in that body region. Bone marrow bilateral aspirate and biopsies, and MIBG scans are not required after screening if they were negative at screening. If bone marrow bilateral aspirate and biopsies were performed and were positive at screening, it will be left to the investigator's discretion to monitor the bone marrow aspirate at each disease evaluation. In order to confirm a Complete disease Response (CR), bone marrow biopsy or aspirate may be required when a radiological CR has been achieved.

MIBG scans if positive at screening will be required at each disease evaluation unless 2 consecutives MIBG scan post screening were negative and tumor response is a confirmed Complete or partial response. MIBG scan will be required if radiological assessment demonstrates a progression of the disease.

7.2.2 Safety and tolerability

Safety and tolerability assessments will include adverse event reporting and changes from baseline in laboratory measures and vital signs. Tolerability will be assessed by the incidence of AEs leading to LDK378 delay or discontinuation.

After cycle 16, for odd numbered cycles, safety assessments can be reduced to a phone call and local laboratory tests (see Table 7-1) to assess patient safety. It is left to the investigator's discretion to monitor patient's safety more closely as suggested for even cycles if judged necessary.

7.2.2.1 Physical examination

A full physical examination (PE) that evaluates all major organ systems will be performed at baseline. This should include a brief neurological exam (examination by a neurologist is not required). A gynecological exam should be included if clinically indicated. Subsequent PEs should be focused on sites of disease, and clinical signs and symptoms.

During the PE the patient's history related to their diagnosis and extent of cancer should be collected. Significant findings that were present prior to the signing of ICF must be included in the Relevant Medical History/Current Medical Conditions page on the patient's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's eCRF.

Note: PE may be performed within 4 days prior to the start of a cycle and ±1 day for other visits.

[redacted]

PE to be performed:

- Screening/baseline.
- Cycle 1 Day 1.
- Cycle 1 Day 8 and 15.
- Cycle 2 and subsequent cycles Day 1.
- End of treatment.

7.2.2.2 Vital signs

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

Note: Vital signs may be performed within 4 days prior to the start of a cycle and ±1 day for other visits.

Vital signs to be obtained:

- Screening/baseline.
- Cycle 1 Day 1 (pre-dose).
- Cycle 1 Day 8 and 15.
- Cycle 2 and subsequent cycles Day 1.
- End of treatment.

7.2.2.3 Height, weight and body surface area

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured. Body surface area (BSA) will be measured using the patient's weight and height, in accordance with local site procedure. The baseline BSA will be used to determine the dose at C1D1.

Note: Height, weight and BSA may be performed within 4 days prior to the start of a cycle and ±1 day for other visits.

Assessments will be obtained on:

- Screening/baseline.
- Cycle 2 and subsequent cycles Day 1.
- End of treatment (except BSA).

7.2.2.4 Performance status

Performance status will be scored using the Karnofsky or Lansky performance scales, depending on the patient's age (Appendix 3 and Appendix 4).

Note: Performance status may be performed within 4 days prior to the start of a cycle and ±1 day for other visits.

Performance status to be obtained:

- Screening/baseline.
- Cycle 1 Day 1.

[redacted]

- Cycle 2 and subsequent cycles Day 1.
- End of treatment.

For patients that have their 13th birthday during the study, performance status will continue to be assessed by the Lansky scale for the duration the patient is on study. This approach will preserve continuity for these patients.

7.2.2.5 Laboratory evaluations

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

All efforts should be made to minimize the volume of blood drawn during the course of the study. For each test the smallest tube required by the local laboratory should be used, and all blood required at a time point, including that for routine safety labs and PK samples should be drawn simultaneously to minimize wastage and venipunctures. If a patient has an indwelling venous catheter appropriate for drawing blood, it should be used whenever possible to reduce venipunctures. The maximum volume of blood that may be drawn over a 24 hour period is 0.8 mL/kg, and the maximum volume of blood that may be drawn over a 4 week period is 2.4 mL/kg. The maximum blood volumes required by this protocol over 24 hr and 4 week periods are provided in Table 7-2. If the volume of blood requested in the protocol will exceed the limit in a particular patient, blood samples exceeding the limit should not be performed, unless necessary for the medical care of the patient. If it is anticipated that the volume limit will be exceeded, hematology, chemistry and pregnancy test samples should be drawn preferentially over PK samples. If PK samples must be skipped, PK samples should be prioritized as shown in Table 7-5.

Table 7-2 Maximum blood volumes

	Maximum Sample Volume	24 hr (Cycle 1 Day 1)		Cycle 1 (4 wk)	
		No. Samples	Total Volume	No. Samples	Total Volume
Hematology	1 mL	1	1 mL	3	3 mL
Chemistry	1 mL	1	1 mL	3	3 mL
Pregnancy test[a]	1 mL	1	1 mL	2	2 mL
PK[b]	1 mL	5	5 mL	6	6 mL
Total			8 mL		14 mL

a. Urine test may be performed at all time-points after screening/baseline, and samples are not required in females not of child-bearing potential.

b. PK sample volume may be reduced from 1 mL to.5 mL as necessary.

Maximum allowed blood volumes: 0.8 mL/kg over a 24 hr period, 2.4 mL/kg over a 4 week period.

At any time during the study, abnormal laboratory parameters which are clinically relevant (e.g., require dose modification and/or interruption of LDK378, lead to clinical signs or symptoms, or require therapeutic intervention), whether specifically requested in the protocol or not, must be recorded in the AE eCRF.

[redacted]

Novartis will be provided with a copy of the laboratory certification and tabulation of the normal ranges for each parameter required. In addition, if at any time a patient has laboratory parameters obtained from a different outside laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges for that laboratory.

Note: Laboratory tests may be performed within 4 days prior to the start of a cycle and ±1 day for other visits. In order to reduce the volume of blood drawn, tests performed during screening/baseline within 4 days of Cycle 1 Day 1 should not be repeated on Cycle 1 Day 1, unless repeat testing is considered medically necessary.

For timing of assessments, refer to Table 7-1.

7.2.2.5.1 Hematology

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

Hematology to be performed:

- Screening/baseline.
- Cycle 1 Day 1, 8 and 15.
- Cycles 2 – 4 Day 1 and 15.
- Cycle 5 and subsequent cycles Day 1.
- End of treatment.

7.2.2.5.2 Clinical chemistry

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

Clinical chemistry to be performed:

- Screening/baseline.
- Cycle 1 Day 1, 8 and 15.
- Cycles 2 – 4 Day 1 and 15.
- Cycle 5 and subsequent cycles Day 1.
- End of treatment.

Table 7-3 Local clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hemoglobin, White blood cells with differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils) and Platelets
Chemistry	Albumin, ALT (SGPT), AST (SGOT), Bicarbonate, Calcium, Chloride, Creatinine, Blood Urea Nitrogen (BUN) or Urea, LDH (only required in patients with lymphoma), Magnesium, Phosphate, Potassium, Sodium, Total Bilirubin (measure direct and indirect bilirubin if total bilirubin elevation ≥ grade 2 occurs), ALP, Serum amylase, Serum lipase , plasma glucose

7.2.2.5.3 Pregnancy assessments

All females of childbearing potential should complete a serum β-hCG or urine pregnancy test.

Note: Pregnancy testing should be performed within 1 day prior to Cycle 1 Day 1.

[redacted]

Pregnancy test to be performed:

- Screening/baseline (serum).
- Cycle 1 Day 1 (urine or serum).
- Subsequent cycles Day 1 (urine or serum).
- End of treatment (urine or serum).

A positive pregnancy test is cause for immediate withdrawal.

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

- Pre-menarchal.
- Surgically sterile for at least 6 months (hysterectomy with bilateral oophorectomy or tubal ligation). Documentation of sterilization method must be provided. The date of sterilization will be recorded.

To ensure patient safety, each pregnancy in a patient receiving LDK378 must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to and including the baby's date of birth 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 local Novartis Drug Safety and Epidemiology (DS&E) follow-up should be recorded on the same form and should include an assessment of the possible relationship to LDK378 of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

7.2.2.5.4 Electrocardiogram (ECG)

A standard 12-lead ECG will be performed in accordance with Table 7-4.

Interpretation of the tracing will be made by a central ECG lab. Each ECG tracing should be labeled with the study number, patient initials, patient number, date, and kept in the source documents at the study site. Only clinically significant abnormalities will be recorded in the AE eCRF page. Clinically significant abnormalities at screening/baseline should be recorded on the Relevant Medical History/Current Medical Conditions eCRF page. Clinically significant findings must be discussed with the Novartis Medical Monitor prior to enrolling the patient in the study. In the case of QTc >500 ms an ECG should be repeated daily until the QTc prolongation has resolved to grade 1 or less.

[redacted]

Table 7-4 Central ECG collection plan

Cycle	Day	Time	ECG Type
Screening/ Baseline	**-28 to -1**	**Anytime**	**12 Lead**
1	1	Post-dose 4 hours (ECG should be performed just prior to drawing PK sample if both are scheduled simultaneously	12 Lead
1	1	Post-dose 6 hours (ECG should be performed just prior to drawing PK sample if both are scheduled simultaneously	12 Lead
2	1	Post-dose 4 hours (ECG should be performed just prior to drawing PK sample if both are scheduled simultaneously	12 Lead
2	1	Post-dose 6 hours (ECG should be performed just prior to drawing PK sample if both are scheduled simultaneously	12 Lead
3	1	Pre-dose (ECG should be performed just prior to drawing PK sample if both are scheduled simultaneously	12 Lead
4	1	Pre-dose (ECG should be performed just prior to drawing PK sample if both are scheduled simultaneously	12 Lead
5-16	1	Pre-dose	12 Lead
Even # cycles ≥18	1	Pre-dose	12 Lead
EOT	1	Within 14 days (up to 21 days) of last dose	12 Lead

7.3 Pharmacokinetics

Blood samples for PK analysis of LDK378 will be collected during the study. Table 10-1 lists non-compartmental PK parameters for LDK378 which will be calculated from the individual plasma concentration versus time profiles using Phoenix® (Pharsight, Mountain View, CA). The individual and mean plasma concentration versus time profiles of LDK378 will be displayed graphically. In addition, a population PK model may be developed to characterize inter-patient variability and covariate effects on LDK378 by pooling all available data.

[redacted]

Blood sampling schedules for PK assessment during the escalation and expansion parts of the study can be found in Table 7-5 and Table 7-6, respectively.

7.3.1 Pharmacokinetic blood sample collection and handling

PK blood samples will be collected in the escalation parts (Table 7-5) and the expansion part (Table 7-6). For the determination of LDK378 concentrations, 1 mL of whole blood will be drawn for each time point. For smaller patients where collection of PK samples may compromise local blood volume limits, 0.5 mL of whole blood may be drawn for each PK time point, in order to permit all samples to be collected without exceeding the maximum blood volume limits (Section 7.2.2.5). If the maximum blood volume limit will be exceeded in a particular patient, hematology, chemistry and pregnancy test samples should be drawn

preferentially over PK samples. If a PK sample needs to be omitted due to blood volume limits, the 4 hour samples on Cycle 1 Day 1 and/or Cycle 2 Day 1 should be omitted first.

A total of approximately 13 mL blood will be collected for each patient treated in the dose escalation part. The amount of blood for PK analysis required from patients participating in the expansion part is approximately 8 mL.

The collection of plasma with exact dates and clock times of drug administration and sample collection will be recorded on the appropriate Blood collection eCRF. All blood samples will be taken by either direct venipuncture or venous catheter or indwelling cannula inserted in a forearm vein. Samples should be processed and labeled as detailed in the [Laboratory Manual]. Plasma fractions will be split in 2 aliquots and all samples should be stored frozen at ≤ -70°C within 90 minutes of venipuncture at the site until sample shipment.

Meal records, including start and stop times and amount of meal consumed, will be collected on PK collection days for patients taking LDK378 with food. Refer to below Table 7-5 and Table 7-6. LDK378 administration method, including if the capsule was opened or swallowed whole, and type of vehicle, will also be collected on all PK collection days for all patients.

Table 7-5 Pharmacokinetic blood collection log – dose escalation (fasted and fed)

Cycle	Day	PK collection number	Sample number	Scheduled time points (hours)
Cycle 1	Day 1	1	1	pre-dose*
Cycle 1	Day 1	1	2	2h post-dose (± 15 min)
Cycle 1	Day 1	1	3	4h post-dose (± 15 min) (If it is anticipated that the maximum allowed blood volume will be exceeded (Section 7.2.2.5) sample should be skipped)
Cycle 1	Day 1	1	4	6h post-dose (± 15 min)
Cycle 1	Day 2	2	5	pre-dose* (i.e. 24h post-dose on Cycle 1 day 1)
Cycle 1	Day 15	3	6	pre-dose*
Cycle 2	Day 1	4	7	pre-dose*
Cycle 2	Day 1	4	8	2h post-dose (± 15 min)
Cycle 2	Day 1	4	9	4h post-dose (± 15 min) (If it is anticipated that the maximum allowed blood volume will be exceeded (Section 7.2.2.5) sample should be skipped)
Cycle 2	Day 1	4	10	6h post-dose (± 15 min)
Cycle 2	Day 2	5	11	pre-dose* (i.e. 24h post-dose on Cycle 2 day 1)
Cycle 3	Day 1	6	12	pre-dose*
Cycle 4	Day 1	7	13	pre-dose*
Unscheduled			1001+	Anytime

*Take sample immediately prior to LDK378 administration.

[redacted]

Table 7-6 Pharmacokinetic blood collection log – dose expansion (fasted and fed)

Cycle	Day	PK collection number	Sample number	Scheduled time points (hours)
Cycle 2	Day 1	103	203	pre-dose*
Cycle 2	Day 1	103	206	2h post-dose (± 15 min)
Cycle 2	Day 1	103	207	4h post-dose (± 15 min)
Cycle 2	Day 1	103	208	6h post-dose (± 15 min)
Cycle 2	Day 2	106	209	pre-dose* (i.e. 24 h post dose on Cycle 2 Day 1)
Cycle 3	Day 1	104	204	pre-dose*
Cycle 4	Day 1	105	205	pre-dose*
Unscheduled			2001+	Anytime

*Take sample immediately prior to LDK378 administration.

[redacted]

[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/guardian signed ICF has been obtained.

For patients whose ALK status is unknown and who sign the molecular pre-screening ICF, AEs which occur after signature of this consent 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 ICF is signed, all AEs per the descriptions below will be captured in the Adverse Event eCRF.

Patients whose ALK status is known will sign the main ICF.

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).

Except for screening failures, adverse events that begin or worsen after informed consent should be recorded in the Adverse Events eCRF. Conditions that were already present at the time of informed consent should be recorded in the Relevant Medical History/Current

[redacted]

Medical Conditions of the patient's eCRF. Adverse event monitoring should be continued for at least 30 days following the last dose of LDK378. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

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

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected on the EOT or the SEC eCRF.

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

1. The severity grade (CTCAE Grade 1-4).
2. Its duration (Start and end dates) or Ongoing at End of Study.
3. Its relationship to LDK378 (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. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1.

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

Any AE that constitutes a DLT should be reported like a grade 3 and 4 adverse event.

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

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to LDK378, 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 1.1 criteria for solid tumors or as per IWG 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

[redacted]

be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

Adverse events of a special interest to be monitored for LDK378 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 Investigator's Brochure.

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 LDK378), should be recorded on the Adverse Events eCRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. 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 4.03 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.

8.1.3 Adverse events of special interest

[redacted]

Details regarding these adverse events are provided in the [Investigator's Brochure] for LDK378. Potential emergent new AEs will be monitored during the course of the study.

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.

[redacted]

- 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.
- 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.

For patients with unknown ALK status and who sign the molecular pre-screening ICF, 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.

For patients with known ALK status who sign the main ICF, SAE collection starts at time of main ICF whether the patient is a screen failure or not.

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has signed the main ICF and until at least 30 days after the patient has stopped LDK378 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 LDK378. 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 LDK378, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department.

The telephone and telefax number of the contact persons in the local department of Drug Safety and Epidemiology (DS&E), specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

[redacted]

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original 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, 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 LDK378, 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.

To ensure patient safety, each pregnancy occurring while the patient is on LDK378 must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up from the estimated date of delivery plus 3 months 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 LDK378. 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 LDK378 in this study up to and including the baby's date of birth. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

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 [Investigator's Brochure] updates will be communicated in the form of Investigator Notifications. This information will be included in the patient ICF and should be discussed with the patient during the study as needed.

8.3 Data Monitoring Committee

Not applicable.

8.4 Steering Committee

Not applicable.

[redacted]

9 Data collection and management

[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 eCRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that LDK378 is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

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

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/assent, 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.

[redacted]

9.3 Data collection

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

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

[redacted]

Patient drug diary data will be entered into a paper diary by the patient/guardian. Patient diaries will be part of the study source documentation and be kept at the study site.

9.4 Database management and quality control

For studies using eCRFs, 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 study site via the EDC system. Designated study 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. Relevant medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

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

For EDC studies, after database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the study site.

10 Statistical methods and data analysis

The data from this study will be analyzed by Novartis or a designated CRO. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

It is planned that the data from participating centers in this protocol will be combined, so that an adequate number of patients will be available for analysis. The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and all relevant PK measurements using descriptive statistics (quantitative data) and contingency tables (qualitative data).

The study data will be analyzed and reported based on all patients' data of both dose escalation and safety expansion parts at the end of study, and a final CSR will be written.

[redacted]

Patients treated with the MTD, or RDE if different, on the regimen (fasted or fed) during the dose escalation part, will be pooled with those receiving both the same dose and the same regimen during the expansion part. For patients undergoing intra-patient dose escalation to doses other than their initially received dose level, their post-escalation data will be listed separately. However, only data before the first intra-patient escalation will be used in summary statistics. A treatment group is defined by dose level and regimen (fasted versus fed).

10.1 Analysis sets

10.1.1 Full analysis set

The full analysis set (FAS) (Full Analysis Set) includes all patients who received at least one dose of LDK378. Patients will be classified according to the planned 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

The safety set includes all patients who received at least one dose of LDK378.

On the specified regimen, patients will be classified according to dose level received, where dose level received is defined as:

1. The dose level assigned if it was received at least once, or
2. The first dose level received in the study, if the assigned dose level was never received.

10.1.3 Per-protocol set

Not applicable.

10.1.4 Dose-determining analysis set

The dose determining set (DDS) consists of all patients from the safety set who either meet the following minimum exposure criterion and have sufficient safety evaluations or discontinue earlier due to DLT. A patient is considered to have met the minimum exposure criterion if having received at least 16 out of the 21 planned once daily doses of LDK378 in the first 21 days of dosing. Patients who do not experience DLT during the first cycle are considered to have sufficient safety evaluations if they have been observed for at least 21 days following the first dose, and are considered by both the Sponsor and Investigators to have sufficient safety data to conclude that a DLT did not occur.

Patients who do not meet these minimum safety evaluation requirements will be regarded as ineligible for the DDS.

10.1.5 Pharmacokinetic analysis set

The pharmacokinetic analysis set (PAS) consists of all patients who have receive at least one dose of LDK378 and have at least one evaluable PK sample. Additional criteria for the PAS will be defined in the RAP. The PAS will be used for summaries of PK data (tables and figures) as well as for listings of derived parameters. The definition of an evaluable PK blood sample will be further specified in the SAP.

[redacted]

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline will be summarized descriptively for all patients in the FAS. 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.

10.3 Treatments (study treatment, concomitant therapies, compliance)

10.3.1 Study treatment

The actual dose and duration in days of LDK378 treatment, as well as the dose intensity (computed as the ratio of actual dose received and actual duration) and the relative dose intensity (computed as the ratio of dose intensity and planned dose received/planned duration), will be listed and summarized by means of descriptive statistics in the clinical study report. The summary data will be presented for each treatment cycle individually, as well as for all study days as a single category. The FAS will be used.

10.3.2 Concomitant therapies

Concomitant medications and significant non-drug therapies prior to and after the start of LDK378 will be listed by patient, and summarized by ATC term and treatment group by means of contingency tables. The FAS will be used.

[redacted]

10.4 Primary objective

The primary objective of the escalation part is to estimate the MTD/RDE respectively on fasted regimen and on fed regimen of the single agent LDK378 when administered orally on a once daily schedule to pediatric patients with ALK-activated tumors. The corresponding primary analysis method is an adaptive Bayesian logistic regression model (BLRM) guided by the escalation with overdose control (EWOC) principle (Neuenschwander et al 2008).

10.4.1 Variable

The primary endpoint is the incidence of dose limiting toxicities (DLTs) in Cycle 1. Estimation of the MTD of the treatment will be based upon the estimation of the probability of DLT in Cycle 1 for patients in the DDS. This probability is estimated by the model in Section 10.4.2.

[redacted]

10.4.2 Statistical hypothesis, model, and method of analysis

Dose escalation

The BLRM with 2 parameters, guided by the EWOC principle, will be used to make dose recommendations and estimate the MTD/ RDE during both the fasted escalation part and the fed escalation part of the study.

The DLT relationship in the escalation part of the study will be described by the following Bayesian logistic regression model:

$$\text{logit}(\pi_{(d)}) = \log(\alpha) + \beta \log(d/d^*), \qquad \alpha>0, \beta>0 \qquad [1]$$

where $\text{logit}(\pi_{(d)}) = \ln(\pi_{(d)}/(1-\pi_{(d)}))$, and $\pi_{(d)}$ is the probability of a DLT at dose d. Doses are rescaled as d/d* with reference dose of $d^* = 400$ mg/m^2. As a consequence α is equal to the odds of toxicity at d*. Note that for a dose equal to zero, the probability of toxicity is zero.

The same 2-parameter form of the BLRM described in equation [1] will be used to estimate the dose-DLT relationships separately for fasted and fed patients. The Bayesian approach requires the specification of prior distributions for the model parameters. Dose escalation in fed patients will begin once the MTD/RDE is determined in fasted patients. Data from fasted patients will be utilized to formulate a prior distribution for the BLRM parameters for fed patients. The prior distributions and the process of their derivation are provided in the statistical appendix (Appendix 1).

Dose recommendation

After each cohort is completed the posterior distributions for the probabilities of DLT at different dose levels are obtained. The results of this analysis are summarized in terms of the estimated probabilities that the true rate of DLT at each dose-level will lie within each of the following intervals:

- (0, 0.16) under-dosing.
- (0.16, 0.33) targeted toxicity.
- (0.33, 1.00) excessive toxicity.

Following the principle of EWOC, after each cohort of patients the recommended dose is the one with the highest posterior probability of the DLT rate falling in the target interval (16%, 33%) among the doses fulfilling EWOC, i.e. it is unlikely (< 25% posterior probability) that the DLT rate at the dose falls in the excessive toxicity interval. In addition, the maximum dose escalation for the fasted regimen is limited to 50% before reaching 450 mg/m^2, and to 25% after reaching 450 mg/m^2, which correspond to the adult MTD. Dose escalations for the fed dose escalation part will be limited to a 25% or smaller increase above the prior fed dose level.

Note that the dose that maximizes the posterior probability of targeted toxicity is the best estimate of the MTD, but it may not be an admissible dose according to the overdose criterion if the amount of data is insufficient. If vague prior information is used for the probabilities of DLT, in the early stages of the study this escalation procedure will reflect a cautious strategy.

[redacted]

The dose recommended by the adaptive Bayesian logistic model may be regarded as guidance and information to be integrated with a clinical assessment of the toxicity profiles observed at the time of the analysis in determining the next dose level to be investigated.

Details of the criteria for dose escalation and the determination of the MTD are provided in Section 6.2.3.

Listing/summary of DLTs

DLTs will be listed and their incidence summarized by primary system organ class, worst grade based on the CTCAE version 4.03, type of adverse event, and by treatment. The DDS will be used for these summaries.

Dose expansion

Upon completion of the first cycle of treatment for at least 10 patients within the dose expansion part, if the observed DLT rate exceeds 33%, the BLRM will be re-run to confirm that the estimated MTD/RDE on either regimen still satisfies the overdose criteria of the model. If the dose fails to satisfy the criteria a change to the dose under study may be made according to the Bayesian model recommendation, after review of the clinical data.

10.5 Handling of missing values/censoring/discontinuations

Patients in the dose-escalation part who are ineligible for the dose-determining set may be replaced if necessary. Patients in the safety expansion part will not be replaced.

As of the date of data-cutoff for the final CSR for the purposes of reporting:

- Time to event data (i.e. PFS) will be censored if no event is observed before the cut-off date or before the start date of a new anti-neoplastic therapy, whichever occurs earlier. The censoring date will be the date of last adequate tumor assessment before either of these two dates. If a PFS event is documented after two or more missing or non-adequate tumor assessments, then the date of PFS will be censored at the date of the last adequate tumor assessment. If a PFS event is observed after a single missing or non-adequate tumor assessment, the actual date of event will be used.
- Continuing events (e.g. adverse events, concomitant therapies, etc.) will be summarized using the data cut-off date as the date of completion, with an indication within listings that the event is continuing.

For patients who discontinue the study with ongoing events, the discontinuation date will be used as the completion date of the event with the appropriate censoring as described in the above paragraph.

The reason for discontinuation from study will be summarized and listed, along with dates of first and last LDK378, duration of exposure to LDK378 and date of discontinuation for each patient.

Other missing data will simply be noted as missing in appropriate tables/listings. The FAS will be used.

[redacted]

10.6 Supportive analyses

[redacted]

10.7 Secondary objectives

Refer to Section 3 for secondary objectives.

10.7.1 Safety objectives

10.7.1.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used. Unless otherwise specified, all listings and tables will be presented by treatment group (regimen (fasted versus fed) and dose level) in the clinical study report, with patients classified according to treatment received as described in Section 10.1.

Data from patients of the expansion part will be pooled with the patients of the escalation part receiving the same dose.

10.7.1.2 Adverse events (AEs)

All AEs recorded during the study will be summarized. The incidence of treatment-emergent AEs (new or worsening from baseline) will be summarized by primary system organ class, severity based on CTCAE version 4.03, type of adverse event, and relationship to LDK378, by treatment group. Deaths reportable as SAEs and non-fatal SAEs will be listed by patient and tabulated by primary system organ class, type of adverse event, and treatment group.

Any other information collected (e.g. start/end dates and duration of adverse event, severity or relatedness to study medication) will be listed as appropriate.

10.7.1.3 Laboratory abnormalities

All laboratory values will be converted into SI units, as appropriate, and the severity grade calculated using CTCAE, version 4.03. Parameters for which a grading does not exist will be classified into low/normal/high group by means of laboratory normal ranges.

For each laboratory test (e.g. hematology, biochemistry etc.) a listing of laboratory values will be provided by laboratory parameter, patient and treatment group. The frequency of notable lab abnormalities (i.e. newly occurring CTCAE grade 3 or 4 laboratory toxicities), will be reported by parameter, cycle and treatment group. Similarly, the frequency of all laboratory abnormalities will be tabulated by parameter, worst CTCAE v4.03 grade experienced, and treatment group. Laboratory data will be summarized by presenting grade shift tables for those parameters that can be classified using CTCAE version 4.03. All remaining data will be summarized by presenting shift tables based on normal ranges.

Laboratory data will be also be displayed by presenting summary statistics of raw data and change from baseline values (means, medians, standard deviations, ranges).

[redacted]

10.7.1.4 Other safety data

ECG

- shift table baseline to worst on-treatment result for overall assessments.
- listing of ECG evaluations for all patients with at least one abnormality.

Vital signs

Definitions of notably abnormal results will be included in the analysis plans.

- 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 the post-baseline time points.

Data from other tests will be listed, notable values will be flagged, and any other information collected will be listed as appropriate. Any statistical tests performed to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration.

10.7.1.5 Supportive analyses for secondary objectives

[redacted]

10.7.1.6 Tolerability

Tolerability of LDK378 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 and summarized. Cumulative dose, dose intensity and relative dose intensity of LDK378 will be listed by patient and summarized. Categories for relative dose intensity of LDK378 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.

10.7.2 Pharmacokinetics

All PK analyses will be performed based on the PAS unless otherwise specified.

Pharmacokinetic variables:

Pharmacokinetic parameters will be determined using non-compartmental method(s), using Phoenix WinNonlin (Pharsight, Mountain View, CA). The PK parameters listed in Table 10-1 will be estimated and reported, as appropriate. PK data generated from this study may be used in conjunction with PK data from other adult clinical studies in future meta-analyses for population PK assessment. These data will be reported separately.

[redacted]

Table 10-1 Noncompartmental pharmacokinetic parameters

AUCtau	The AUC calculated to the end of the dosing interval, tau.
Cmin	Observed concentration at the end of a dosing interval (taken directly before next administration).
Cmax	The maximum observed plasma, blood, serum, or other body fluid drug concentration.
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration.
T1/2,acc	Effective half-life can be calculated from Racc.
CLss/F	Apparent oral total body clearance of drug from the plasma calculated from steady-state exposure.
Racc	Accumulation ratio calculated using AUCtau values obtained from a dosing interval at steady-state divided by AUCtau at day 1.

10.7.2.1 Data handling principles

Any missing PK parameters will not be imputed. All concentrations of LDK378 below their respective LLOQs (lower limits of quantification) or missing data will be labeled as such in the concentration data listings. Concentrations below the LLOQ will be treated as zero in summary statistics and for the calculation of PK parameters.

10.7.2.2 Data analysis principles

Basic tables, figures and listings

Summary statistics, including n, mean, SD, coefficient of variation CV (%) for mean, geometric mean, geometric CV (%), median, minimum and maximum, will be tabulated for evaluable PK plasma concentration of LDK378 by treatment group and scheduled time point separately for the fasted and fed patients. Graphical representation of individual plasma concentration-time profiles will be generated too.

Descriptive statistics will also be provided for all PK parameters by treatment group separately for fasted and fed patients. Summaries by age group may be provided as appropriate.

Advanced analysis methods

Dose linearity will be assessed by graphic presentation and model-based method with respect to AUCtau and Cmax at steady state. To assess the attainment of steady state, median Cmin will be plotted by study day and treatment group.

[redacted]

10.7.3 Efficacy

Anti-tumor activity of LDK378 will be evaluated using investigator-assessed tumor response based on RECIST 1.1 for patients with neuroblastoma and other solid tumors, and IWG

[redacted]

criteria for patients with lymphoma, and summarized in terms of overall response rate (ORR), duration of response (DOR), and progression-free survival (PFS). In patients with neuroblastoma, disease assessable only by MIBG scans and by bone marrow evaluation at screening will be treated as non-target lesions. When the revised International Neuroblastoma Response Criteria (INRC) currently in development are final they will be incorporated into this protocol.

For analysis by treatment group, patients from the expansion part and patients from the escalation treated at the MTD/RDE on the same regimen (either fasted or fed) will be combined to be included in the same dose level.

For analysis of patients at the MTD/RDE on one regimen (either fasted or fed), patients from the dose escalation part treated at the MTD/RDE on the same regimen will be classified into one of the expansion groups.

For patients with neuroblastoma, resolution of disease assessable by MIBG scans will also be summarized by treatment group separately from the response assessment by RECIST 1.1.

ORR will be summarized by treatment group and by expansion group, and exact 95% confidence intervals will be presented. To assess anti-tumor activity in pediatric patients previously treated with an ALK inhibitor, BOR and ORR will be tabulated for this subset of patients.

Kaplan Meier analyses of PFS and DOR will be provided overall and by treatment group, if sufficient number of patients allow. For MTD/RDE patients, Kaplan Meier analyses of PFS and DOR will be done by expansion group, if appropriate.

In addition, for the expansion group patients with ALK activated neuroblastoma, a Bayesian approach will be used to estimate the ORR along with a 95% credible intervals based on the posterior distributions, using minimally informative unimodal Beta prior distributions. The prior clinical assumption for LDK378 in this selected patient population will be used in order to derive a minimally informative unimodal Beta prior distribution that reflects the level of uncertainty around the ORR before starting the current trial. At completion of the study, this prior distribution will be updated with all data available from the expansion group patients with ALK activated neuroblastoma (including those treated at the MTD in the dose escalation part) in the FAS. Once updated, the posterior probability that the true ORR at the MTD/RDE for these patients lies in the following categories will be presented:

- (0, 10%) insufficient antitumor activity.
- (10%, 20%) limited antitumor activity.
- (20%, 30%) moderate antitumor activity.
- (30%, 100%) substantial antitumor activity.

If the observed ORR is equal to or greater than 30%, then this will be considered as preliminary evidence of substantial antitumor activity of LDK378 in ALK activated neuroblastoma. If the observed ORR is between 20% and 30% then this will be considered as evidence of moderate antitumor activity, and as limited antitumor activity if it is between 10% and 20%. If the observed ORR is less than 10% (i.e. $\leq$ 2 CR or PR out of 25), then insufficient antitumor activity will be declared.

[redacted]

Note that for a sample size of n = 25 (see Section 10.8), if the observed ORR is greater than or equal to 20% (i.e. ≥ 5 CR or PR), then the true ORR has a posterior risk of less than 10% of being in the insufficient antitumor activity category.

A minimally informative unimodal Beta prior distribution of the true ORR is derived as follows. A priori it is assumed that the true mean of the ORR equals 20%. A true ORR of 20% is the midpoint between limited and moderate antitumor activity and serves as a compromise between a skeptical view assuming the treatment has only limited antitumor activity and an optimistic view assuming the treatment has moderate antitumor activity. The parameters of the minimally informative Beta prior distribution of the ORR are then derived as a=1/4 and b=1.

[redacted]

10.9 Interim analysis

No formal interim analyses are planned. However, the dose-escalation design foresees that decisions based on the current data are made before the end of the study. More precisely, the next dose of LDK378 has to be chosen after each cohort in the dose escalation part, and the decision is dependent on the observed data.

10.10 Sample size calculation

10.10.1 Dose Escalation

Cohorts of 3 to 6 evaluable patients will be dosed in the dose-escalation including at least 6 patients at the MTD/RDE level separately on each regimen, as described in Section 6.2.3. Multiple cohorts may be sequentially enrolled to the same dose level. Additional cohorts of 1 to 6 patients may be enrolled at any dose level below the estimated MTD/RDE for further elaboration of safety and pharmacokinetic parameters as required. At least 15 patients for the fasted dose escalation and at least 12 patients for the fed dose escalation are respectively expected to be treated, for the model to have reasonable operating characteristics relating to its MTD recommendation (Appendix 1).

10.10.2 Dose Expansion

During the expansion part, approximately 45 patients will be treated on the preferred regimen (including all patients treated at the MTD on that regimen during the dose escalation who are eligible for the safety set), approximately 25 patients in group 1 on the preferred regimen, and approximately 20 patients in group 2.

Group 1: ALK-activated neuroblastoma

Based on the ORR (per RECIST 1.1) intervals described in Section 10.4.2, it was assessed how likely it is to wrongly declare activity as defined by observing at least “moderate antitumor activity” (i.e. seeing at least 5 responses out of 25 patients) given the true ORR = 10%, and how likely it is to correctly declare activity given the true ORR = 30% when 25 patients are evaluated.

- If the true ORR = 10%, the probability to wrongly declare activity is 9.8%.
- If the true ORR = 30%, the probability to correctly declare activity is 91.0%.

Given a sample size of 25 in group 1, if 5 responses are seen, the observed ORR is 20% with an 80% credible interval of (10.7%, 30.3%). This will be considered as preliminary evidence of antitumor activity of LDK378 at the MTD/RDE within this group.

[redacted]

Group 2: other ALK-activated tumors, such as IMT and ALCL

For group 2, sample size estimation is based on safety. A sample size of 20 will result in an 87.8% probability of detecting an AE with an incidence rate of ≥ 10%.

10.11 Power for analysis of key secondary variables

Not applicable.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

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

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed molecular pre-screening and main ICFs must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. A signed and dated statement that the protocol and ICFs have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written ICF or a separate assent form.

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

Novartis will provide to investigators, in separate documents, proposed molecular pre-screening and main ICFs that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to these ICFs suggested by the

investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and copies of the approved versions must be provided to the Novartis monitor after IRB/IEC/REB approval.

Females 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 and for 3 months after stopping dosing. 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 assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of patients. As part of participating in 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, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and patient files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the study staff at the site under the supervision of the site Principal Investigator. The electronic case report form (eCRF) 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 eCRFs and all other required reports. Data reported on the eCRF, that are derived from source documents, should be consistent with the

[redacted]

source documents or the discrepancies should be explained. All data requested on the eCRF must be recorded. Any missing data must be explained. Any change or correction to a paper eCRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic eCRFs an audit trail will be maintained by the system.

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

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

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed ICFs and patient screening logs 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

[redacted]

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.

[redacted]

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14 Appendices

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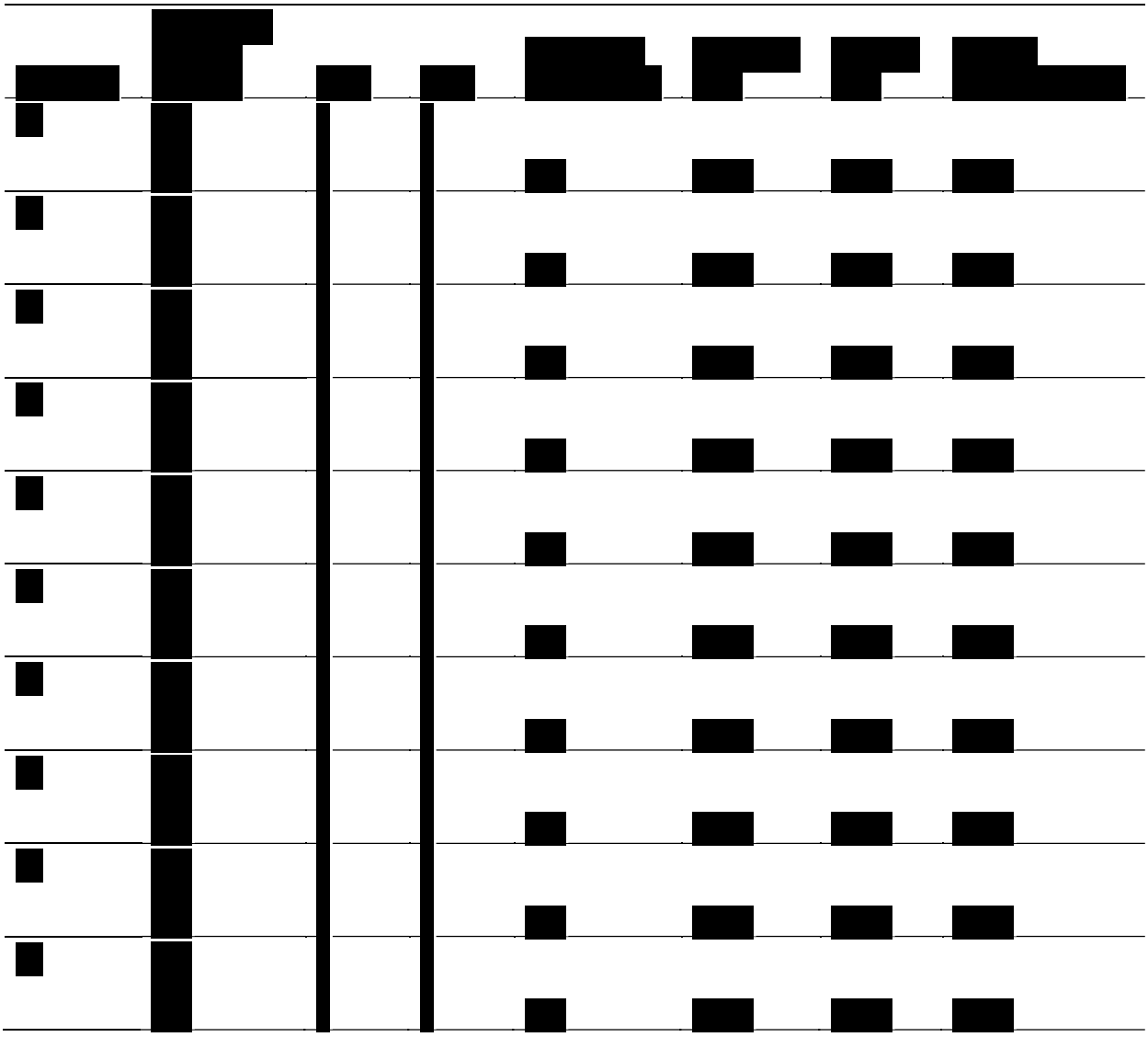

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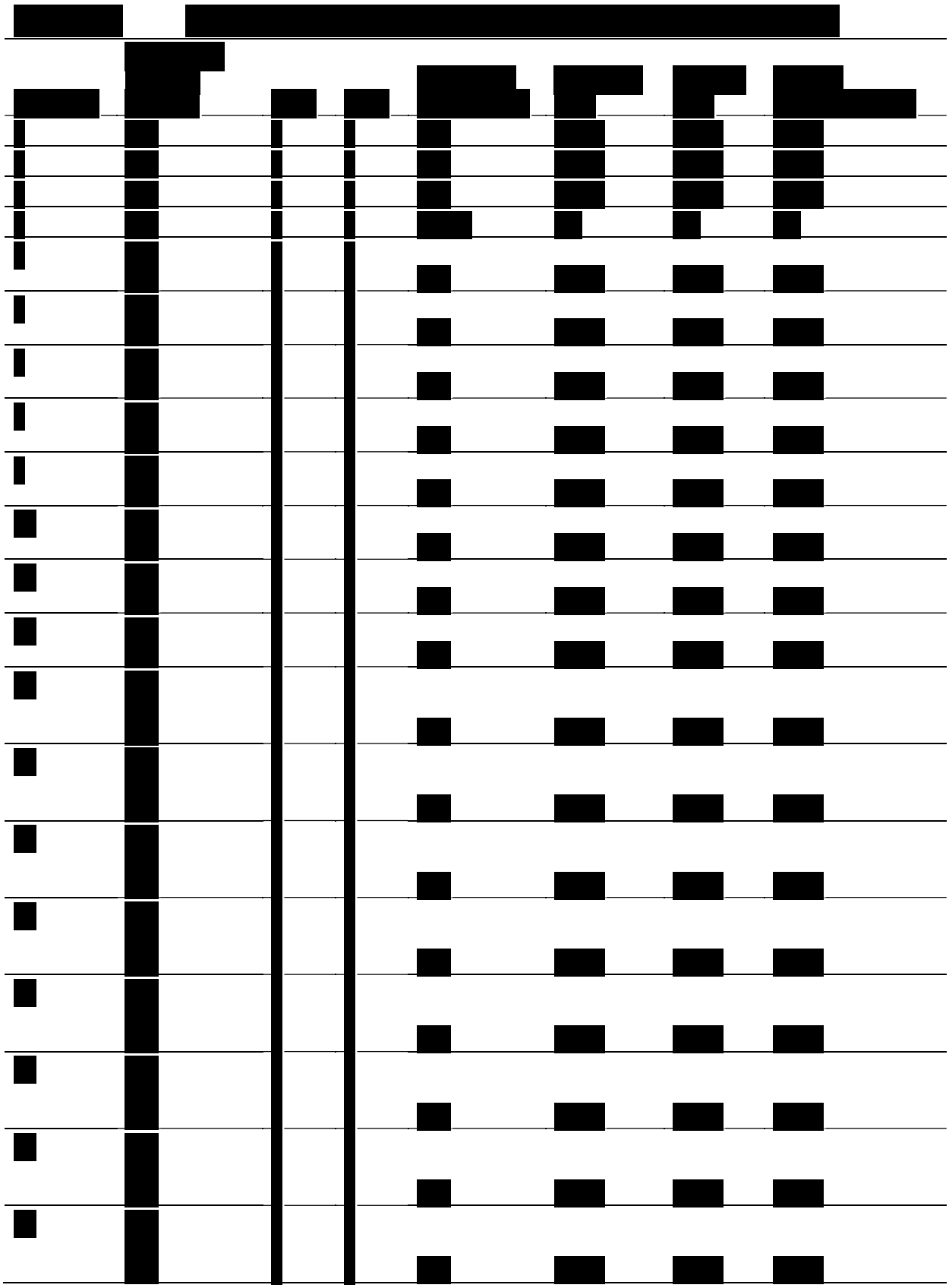

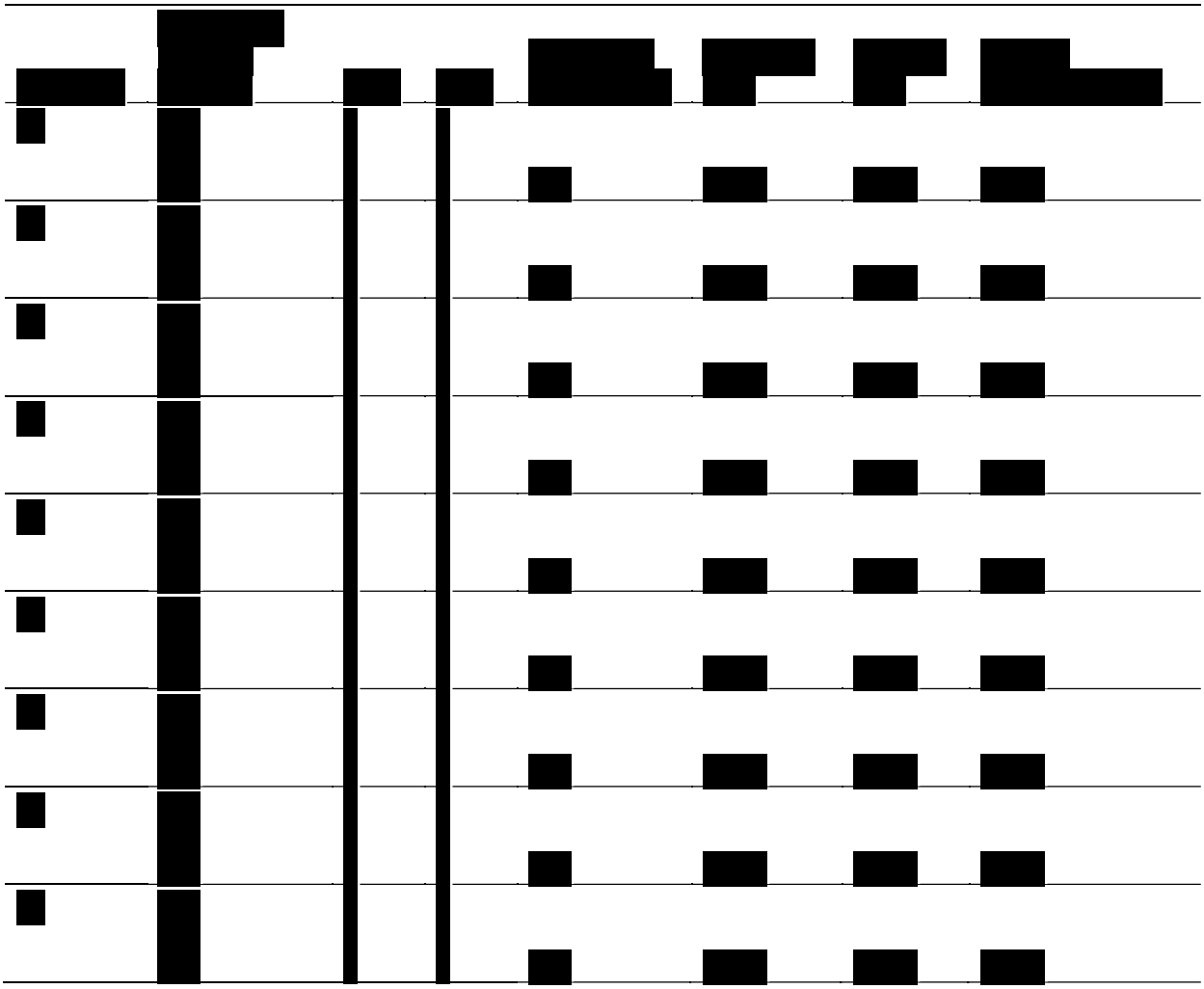

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14.3 Appendix 3: Karnofsky Performance Status Scale (for patients greater than 12 years old)

Able to carry on normal activity and to work; no special care needed	100%	Normal no complaints
	90%	Able to carry on normal activity; minor signs or symptoms of disease.
	80%	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70%	Cares for self; unable to carry on normal activity or to do active work.
	60%	Requires occasional assistance, but is able to care for most of his personal needs.
	50%	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40%	Disabled; requires special care and assistance
	30%	Severely disabled; hospitalization is indicated though death not imminent.
	20%	Very sick; hospitalization necessary; active supportive treatment necessary.
	10%	Moribund; fatal processes progressing rapidly.
	0	Dead

[redacted]

14.4 Appendix 4: Lansky score (for patients less than or equal to 12 years old)

100	Fully active, normal
90	Minor restrictions in physically strenuous activity
80	Active, but tires more quickly
70	Both greater restriction of play and less time spent in play activity
60	Up and around, but minimal active play; keeps busy with quieter activities
50	Gets dressed but lies around much of the day; no active play but able to participate in all quiet play and activities
40	Mainly in bed; participates in quiet activities
30	Bed-bound; needs assistance even for quiet play
20	Often Sleeping; play entirely limited to very passive activities
10	No play; does not get out of bed
0	Unresponsive

[redacted]

14.5 Appendix 5: Response Evaluation Criteria in Solid Tumors (RECIST 1.1) Harmonization of Efficacy Analysis of Solid Tumor Studies

Harmonization of Efficacy Analysis of Solid Tumor Studies

Guidelines for Response, Duration of Overall Response, TTF, TTP, Progression-Free Survival and Overall Survival (based on RECIST 1.1)

Document type:	TA Specific Guideline
Document status:	Version 3.1: 29-Nov-2011 Version 3:0: 19-Oct-2009 Version 2:0: 18-Jan-2007 Version 1:0: 13-Dec-2002
Release date:	29-Nov-2011

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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
LPLV	Last patient last visit
MRI	Magnetic resonance imaging
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
RAP	Reporting and Analysis Plan
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]

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).

The efficacy assessments described in Section 2 and the definition of best response in Section 3.1 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 3.2 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 4 of this guideline describes data handling and programming rules. This section is to be referred to in the RAP (Reporting and Analysis Plan) to provide further details needed for programming.

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.

2.1 Definitions

2.1.1 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 3.2.8.

Measurable lesions (both nodal and non-nodal)

- Measurable non-nodal - As a rule of thumb, the minimum size of a measurable non-nodal target lesion at baseline should be no less than double the slice thickness or 10mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components, that can be evaluated by CT/MRI, can be considered as measurable lesions, if the soft tissue component meets the definition of measurability.
- Measurable nodal lesions (i.e. lymph nodes) - Lymph nodes ≥15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring ≥10 mm and <15 mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at baseline, regardless of the slice thickness, are normal and not considered indicative of disease.

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

2.1.2 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 3.2.8.

2.2 Methods of tumor measurement - general guidelines

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

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

- All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.
- For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5 mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If, at baseline, a patient is known to have a medical contraindication to CT contrast or develops a contraindication during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.

[redacted]

- A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change in methodology will result by default in a UNK overall lesion response assessment. However, another response assessment than the Novartis calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.
- **FDG-PET**: can complement CT scans in assessing progression (particularly possible for 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - No FDG-PET at baseline with a positive FDG-PET at follow-up:
- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT are needed to determine if there is truly progression occurring at that Site (if so, the date of PD will be the date of the initial abnormal CT scan).
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- **Chest x-ray**: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Ultrasound**: When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- **Endoscopy and laparoscopy**: The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- **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, alpha-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

[redacted]

and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).

- **Clinical examination**: Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

2.3 Baseline documentation of target and non-target lesions

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

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

Minimum target lesion size at baseline

- **Non-nodal target**: Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination, photography) should be at least 10 mm in longest diameter. See Section 2.1.1.
- **Nodal target**: See Section 2.1.1.

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

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

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

To assess tumor response, the sum of diameters 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 2-1) and non-target lesions (Table 2-2) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 2-3) as well as the presence or absence of new lesions.

2.4.1 Follow-up and recording of lesions

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

2.4.1.1 Non-nodal lesions

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

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

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

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

2.4.1.2 Nodal lesions

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

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

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

[redacted]

2.4.2 Determination of target lesion response

Table 2-1 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 <10 mm in size. In this case, the target lesion response is CR
3. Methodology change See Section 2.2.

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 2-1 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 with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to patients who have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.
- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.

[redacted]

- **Missing measurements**: In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is 100 mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit is 140 mm (with data for 2 other lesions missing) then a PD should be assigned. However, in other cases where a PD cannot definitely be attributed, the target lesion response would be UNK.
- **Nodal lesion decrease to normal size**: When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size they should still have a measurement recorded on scans. This measurement should be reported even when the nodes are normal in order not to overstate progression should it be based on increase in the size of nodes.
- **Lesions split**: In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.
- **Lesions coalesced**: Conversely, it is also possible that two or more lesions which were distinctly separate at baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the "merged lesion" should be used when calculating the sum of diameters for target lesions. On the case report form, the diameter of the "merged lesion" should be recorded for the size of one of the original lesions while a size of "0"mm should be entered for the remaining lesion numbers which have coalesced.
- The **measurements for nodal lesions**, even if less than 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.
- Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm and all non-nodal target lesions have disappeared.
- Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
- Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion "reappears" or if any single nodal lesion is at least 10 mm and there is at least 20% increase in sum of the diameters of all nodal target lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.

[redacted]

2.4.3 Determination of non-target lesion response

Table 2-2 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]
Non-CR/Non-PD:	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. < 10 mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e. ≥ 10 mm) the response can only be '**Non-CR/Non-PD**' unless any of the lesions was not assessed (in which case response is **UNK**) or there is unequivocal progression of the non-target lesions (in which case response is **PD**).
- **Unequivocal progression**: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 2.4.2 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

2.4.4 New lesions

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

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm

[redacted]

there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion.

- If new disease is observed in a region which was **not scanned at baseline** or where the particular baseline scan is not available for some reason, then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment (see Section 2.5).
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ≥ 10 mm for the first time in the study plus 5 mm absolute increase.
  FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 2.2.

2.5 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 2-3.

Table 2-3 Overall lesion response at each assessment

Target lesions	Non-target lesions	New Lesions	Overall lesion response
CR	CR	No	CR[1]
CR	Non-CR/Non-PD[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 2.4.

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

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

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

[redacted]

3 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 3.2.8 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

3.1 Best overall response

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

The best overall response will usually be determined from response assessments undertaken while on treatment. However, if any assessments occur after treatment withdrawal the protocol should specifically describe if these will be included in the determination of best overall response and/or whether these additional assessments will be required for sensitivity or supportive analyses. As a default, any assessments taken more than 30 days after the last dose of study treatment will not be included in the best overall response derivation. If any alternative cancer therapy is taken while on study any subsequent assessments would ordinarily be excluded from the best overall response determination. If response assessments taken after withdrawal from study treatment and/or alternative therapy are to be included in the main endpoint determination, then this should be described and justified in the protocol.

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

Longer intervals may also be appropriate. However, this must be clearly stated in the protocol. The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

- For non-randomized trials where response is the primary endpoint, confirmation is needed.
- For trials intended to support accelerated approval, confirmation is needed.
- For all other trials, confirmation of response may be considered optional.

The best overall response for each patient is determined from the sequence of overall (lesion) responses according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required.
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required.
- SD = at least one SD assessment (or better) > 6 weeks after randomization/start of treatment (and not qualifying for CR or PR).
- PD = progression ≤ 12 weeks after randomization/ start of treatment (and not qualifying for CR, PR or SD).

[redacted]

- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks).

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

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

Example: In a case where confirmation of response is required the sum of lesion diameters is 200 mm at baseline and then 140 mm - 150 mm - 140 mm - 160 mm - 160 mm at the subsequent visits. Assuming that non-target lesions did not progress, the overall lesion response would be PR - SD - PR - PR - PR. The second assessment with 140 mm confirms the PR for this patient. All subsequent assessments are considered PR even if tumor measurements decrease only by 20% compared to baseline (200 mm to 160 mm) at the following assessments.

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

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

The best overall response for a patient is always calculated, based on the sequence of overall lesion responses. However, the overall lesion response at a given assessment may be provided from different sources:

- Investigator overall lesion response.
- Central Blinded Review overall lesion response.
- 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:

[redacted]

Overall response rate (ORR) is the proportion of patients with a best overall response of CR or PR. This is also referred to as 'Objective response rate' in some protocols or publications.

Disease control rate (DCR) is the proportion of patients with a best overall response of CR or PR or SD.

Another approach is to summarize the progression rate at a certain time point after baseline. In this case, the following definition is used:

Early progression rate (EPR) is the proportion of patients with progressive disease within 8 weeks of the start of treatment.

The protocol should define populations for which these will be calculated. The timepoint for EPR is study specific. EPR is used for the multinomial designs of Dent and Zee (2001) and counts all patients who at the specified assessment (in this example the assessment would be at 8 weeks ± window) do not have an overall lesion response of SD, PR or CR. Patients with an unknown (UNK) assessment at that time point and no PD before, will not be counted as early progressors in the analysis but may be included in the denominator of the EPR rate, depending on the analysis population used. Similarly when examining overall response and disease control, patients with a best overall response assessment of unknown (UNK) will not be regarded as "responders" but may be included in the denominator for ORR and DCR calculation depending on the analysis population (e.g. populations based on an ITT approach).

3.2 Time to event variables

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

3.2.1 Progression-free survival

Usually in all Oncology studies, patients are followed for tumor progression after discontinuation of study medication for reasons other than progression or death. If this is not used, e.g. in Phase I or II studies, this should be clearly stated in the protocol. Note that randomized trials (preferably blinded) are recommended where PFS is to be the primary endpoint.

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

3.2.2 Overall survival

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

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

[redacted]

3.2.3 Time to progression

Some studies might consider only death related to underlying cancer as an event which indicates progression. In this case the variable "Time to progression" might be used. TTP is defined as PFS except for death unrelated to underlying cancer.

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

3.2.4 Time to treatment failure

This endpoint is often appropriate in studies of advanced disease where early discontinuation is typically related to intolerance of the study drug. In some protocols, time to treatment failure may be considered as a sensitivity analysis for time to progression. The list of discontinuation reasons to be considered or not as treatment failure may be adapted according to the specificities of the study or the disease.

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

3.2.5 Duration of response

The analysis of the following variables should be performed with much caution when restricted to responders since treatment bias could have been introduced. There have been reports where a treatment with a significantly higher response rate had a significantly shorter duration of response but where this probably primarily reflected selection bias which is explained as follows: It is postulated that there are two groups of patients: a good risk group and a poor risk group. Good risk patients tend to get into response readily (and relatively quickly) and tend to remain in response after they have a response. Poor risk patients tend to be difficult to achieve a response, may have a longer time to respond, and tend to relapse quickly when they do respond. Potent agents induce a response in both good risk and poor risk patients. Less potent agents induce a response mainly in good risk patients only. This is described in more detail by Morgan (1988).

It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. An analysis of responders should only be performed to provide descriptive statistics and even then interpreted with caution by evaluating the results in the context of the observed response rates. If an inferential comparison between treatments is required this should only be performed on all patients (i.e. not restricting to "responders" only) using appropriate statistical methods such as the techniques described in Ellis et al (2008). It should also be stated in the protocol if duration of response is to be calculated in addition for unconfirmed response.

For summary statistics on "responders" only the following definitions are appropriate. (Specific definitions for an all-patient analysis of these endpoints are not appropriate since the status of patients throughout the study is usually taken into account in the analysis).

Duration of overall response (CR or PR): For patients with a CR or PR (which may have to be confirmed the start date is the date of first documented response (CR or PR) and the end date and censoring is defined the same as that for time to progression.

The following two durations might be calculated in addition for a large Phase III study in which a reasonable number of responders is seen.

Duration of overall complete response (CR): For patients with a CR (which may have to be confirmed) the start date is the date of first documented CR and the end date and censoring is defined the same as that for time to progression.

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

3.2.6 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 3.2.5. It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. Where an inferential statistical comparison is required, then all patients should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all patients, patients who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

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

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

[redacted]

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

Assessment date

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

Start dates

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

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

- Date of first documented response is the assessment date of the first overall lesion response of CR (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.
- 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 3.2.8).

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 correspond 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 known date patient alive from the 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.

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

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

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

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also be incorporated in an appropriate manner. The overall response for patients with measurable disease is derived slightly differently according to Table 3-1.

Table 3-1 Overall lesion response at each assessment: patients with non-target disease only

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

[1] As defined in Section 2.4.

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

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

For ORR it is recommended that the main (ITT) analysis includes data from patients with only non-measurable disease at baseline, handling patients with a best response of CR as "responders" with respect to ORR and all other patients as "non-responders".

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

[redacted]

3.2.9 Sensitivity analyses

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

Based on definitions outlined in Section 3.2.7, 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 3-2 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 RAP**	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment[3]	Censored
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[2]	Progressed Progressed
C1	Progression or death after **exactly one** missing assessment	(1) Date of progression (or death) (2) Date of next scheduled assessment[2]	Progressed Progressed
C2	Progression or death after **two or more** missing assessments	(1) Date of last adequate assessment[2] (2) Date of next scheduled assessment[2] (3) Date of progression (or death)	Censored Progressed Progressed
D	No progression	(1) Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) N/A (2) Date of discontinuation (visit date at which clinical progression was determined)	Ignored Progressed
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, duration of response)

1. Definitions can be found in Section 3.2.7.

2. After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 3.2.7.

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.

[redacted]

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

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

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

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

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

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

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g. by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 3-2 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.

4 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).

[redacted]

4.1 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).

4.2 End of treatment phase completion

Patients **may** voluntarily withdraw from the study treatment or may be taken off the study treatment at the discretion of the investigator at any time. For patients who are lost to follow-up, the investigator or designee should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

The end of treatment visit and its associated assessments should occur within 7 days of the last study treatment.

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

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

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

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

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

- Adverse event.
- Lost to follow-up.
- Physician decision.

[redacted]

- Pregnancy.
- Protocol deviation.
- Technical problems.
- Subject/guardian decision.
- Death.
- New therapy for study indication.
- Progressive disease.
- Study terminated by the sponsor.

4.4 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' or central reader's opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the investigator or central reader's response assessment will never be overruled.

If Novartis elect to invalidate an overall lesion response as evaluated by the investigator or central reader 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.

4.5 Programming rules

The following should be used for programming of efficacy results:

4.5.1 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.

4.5.2 Incomplete assessment dates

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

[redacted]

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 3.2.7). 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.

4.5.3 Incomplete dates for last known date patient alive 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.

4.5.4 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)'.

4.5.5 Study/project specific programming

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

4.5.6 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 3-2).
- Death due to reason other than underlying cancer (only used for TTP and duration of response).
- Initiation of new anti-cancer therapy.

*Adequate assessment is defined in Section 3.2.7. 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

[redacted]

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="Sponsor decision" 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 to censor in case of no baseline assessment.

[redacted]

5 References (available upon request)

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

Eisenhauer E, et al (2009) New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). European Journal of Cancer, Vol.45: 228-47.

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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]

14.6 Appendix 6: Guidelines for efficacy evaluation in lymphoma studies (based on Cheson response criteria). International Working Group guidelines for hematological malignancies

Authors:	[redacted]
Document type:	TA Specific Guideline
Development phase:	Final Version 1: 17-Nov-2009

[redacted]

1 Introduction

The purpose of this document is to provide the working definitions and rules necessary for a consistent and efficient analysis of efficacy in Oncology Lymphoma studies where Cheson response criteria apply.

This document is based on the International Working Group response criteria (Cheson et al 1999), and the International Harmonization Project revised response criteria (Cheson et al 2007b). Further clarification on these criteria has been published by (Cheson 2007a).

As Positron emission tomography (PET) is not yet widely accepted (Cheson 2009) for assessing response to treatment in lymphoma it is not considered for standard use in Novartis Oncology Lymphoma studies and therefore it is not considered in this document.

In general, this document is intended for studies where patients currently have measurable disease to be assessed, and therefore does not specifically address studies when the eligible patient population has no measurable disease (such as studies in patients who achieved complete response to first line treatment, or in post-transplantation settings). However, this guidance should be readily adaptable to these settings (see Appendix E).

2 Definitions and criteria for normalization

2.1 Definitions

Throughout this document, the following definitions will apply (See also Appendix A).

Nodal vs extranodal lesion

A lesion is categorized based on the location as:

- **Nodal lesion,**
- **Extranodal lesion**, if it is located in organs other than lymph node or nodal mass, but including spleen and liver.

Measurability

Throughout this document, a lesion will be called **measurable** if it can be measured accurately in 2 perpendicular dimensions and:

- For nodal lesion, if the long axis is > 15 mm, regardless of the length of the short axis,
- For extranodal lesion, if the long and short axes are ≥ 10 mm.

Classification of lymph nodes

Lymph nodes are classified according to their size and/or relationship to the disease:

- A lymph node meeting the measurability requirement above will constitute a **measurable nodal lesion**.
- A lymph node not meeting the measurability requirement but with long axis > 15 mm (e.g. short axis cannot be measured accurately) will constitute a **non-measurable nodal lesion**.

[redacted]

- A lymph node not meeting the measurability criteria but with a size of 11 mm to 15 mm in the long axis and > 10 mm in the short axis will be checked for relationship to disease:
  - If it is thought to be disease related, it will constitute a **non-measurable nodal lesion** (referred to as "involved node" in Cheson et al 2007b).
  - If it is not thought to be disease related, it will constitute an **abnormal lymph node** but not a lesion.
- All other lymph nodes will be considered normal and will not constitute nodal lesions.

2.2 Criteria for normalization of lesions

The normalization of lesions is defined as follow:

- A measurable nodal lesion must become ≤ 15 mm in long axis to be considered normalized.
- A non-measurable nodal lesion must decrease to ≤ 10 mm in the short axis and be ≤ 15 mm in long axis to be considered normalized.
- An extranodal lesion must disappear completely (assigned a size of 0 mm x 0 mm) to be considered normalized.

3 Efficacy assessments

3.1 Eligibility

Studies will be intended to include patients with measurable disease.

Patients should have **at least one measurable nodal lesion greater than 20 mm** in the long axis.

In cases where the patient has no measurable nodal lesions greater than 20 mm in the long axis at baseline, then the patient must have at least one measurable extranodal lesion.

3.2 Methods of disease assessment

All radiological measurements should be taken in two perpendicular dimensions and recorded in metric notation, using a ruler or calipers.

All baseline evaluations should be performed as closely as possible to the randomization/start of treatment (preferably within 7 days) and never more than **3** weeks (**21 days**) before the randomization/start of treatment.

The protocol should state if randomization or start of treatment is used as start date (baseline). This is then used in all definitions.

If different window for baseline assessments is allowed in the study this must be justified in the Study Protocol.

3.2.1 CT scan (or MRI)

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

[redacted]

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 "Unknown" overall radiological response assessment. However, another overall radiological response than the Novartis calculated "Unknown" response may be accepted from the investigator or the central blinded reviewer if a definitive overall radiological response can be justified to be based on the available information.

In order to calculate the sum of the product of the diameters (SPD) of all index lesions (or extranodal lesions), their size must be entered throughout the study.

Actual lesion measurements should be entered on the corresponding CRFs. If, during the course of the study, either of the perpendicular diameters of a lesion can not be reliably measured because of its small size, it is recommended to enter the minimum limit of detection as the diameter size (e.g. 5 mm for spiral CT). In other cases when, during the course of the study, the diameter cannot be reliably measured for reasons other than its size (i.e. borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

If lesions become confluent over time, it is recommended to measure them as one lesion, report the overall diameters to one of the lesions and assign 0 mm x 0 mm to each of the other previously measured lesions. If a lesion splits during the study, each sub-lesion should be measured separately for all subsequent assessments and all sub-lesions contribute to the SPD.

3.2.2 Bone marrow assessment

Documentation of status of bone marrow involvement by lymphoma based on prior bone marrow biopsy or aspirate findings is required at baseline for all patients.

If no such documentation is available then a bone marrow biopsy or aspirate should be performed at baseline.

Further collection or confirmation of bone marrow status at baseline beyond the above requirement and/or at time of radiological CR may be required for some or all patients depending on disease/study/setting basis. A time window should be specified for when the biopsy or aspirate date would be expected with respect to the inclusion date (resp. the date of radiological CR). Full details should be provided in the Study Protocol.

If bone marrow involvement is assessed by biopsy, the biopsy sample should have a goal of > 20 mm unilateral core. If the biopsy sample is indeterminate by morphology (immunohistochemistry), then flow cytometry may be performed on bone marrow aspirate to confirm the findings.

[redacted]

3.2.3 Physical examination and assessment of B-symptoms

Skin lesions, if the size is ≥ 20 mm in at least one diameter, must be histologically confirmed for lymphoma involvement (the investigational site must document the histological confirmation (yes or no) on the corresponding CRF) and photographed including a ruler (color photography using digital camera). Tumor assessment will be performed and results will be recorded on the corresponding CRF at baseline and at the time of each radiological assessment.

B-symptoms are of importance in determining prognosis and should resolve completely in patients who have achieved complete response. B-symptoms in lymphoma patients are disease related clinical symptoms and are not caused by anticancer therapy (or drug toxicity).

B-symptoms are defined as follows :

- Significant unexplained fever (≥ 38°C),
- Unexplained, recurrent drenching night sweats,
- Unexplained loss of > 10% body weight within the previous 6 months,

as assessed and reported (present vs. absent) by the Investigator.

3.3 Documentation of disease

For the evaluation of disease at baseline and throughout the study, the following are recorded.

Index nodal lesions

Index nodal lesions are selected from the measurable nodal lesions. A minimum of one measurable index nodal lesion and maximum of six of the largest dominant nodal lesions should be documented at baseline and assessed throughout the study. If a patient has no measurable nodal disease at baseline, then it would be acceptable that no index nodal lesions be identified. Index nodal lesions should be from disparate regions of the body including mediastinal and retroperitoneal areas of disease whenever these sites are involved. Two perpendicular dimensions must be recorded on the corresponding CRF at each assessment of a measurable lesion selected to be an index lesion.

Non-index nodal lesions

All other nodal lesions (both measurable and non-measurable) are considered as non-index lesions.

Non-index lesions should be documented at baseline and assessed throughout the study. Measurements of these lesions are not required to be documented on the CRF. Their response status will be determined from investigator assessment as described in Section 3.4.2.

Spleen and liver (index and non-index) lesions

The spleen and liver will be assessed by CT scan (or MRI scan).

A maximum four of the largest dominant measurable nodules representing all involved anatomic locations should be selected as splenic and hepatic index lesions to be measured at

[redacted]

baseline and followed up during the treatment. Two perpendicular dimensions will be recorded into the CRF at each assessment.

All other splenic or hepatic nodules (both measurable and non-measurable) are considered as non-index lesions. They should be documented at baseline and assessed throughout the study. Measurements of these lesions are not required to be documented on the CRF. Their response status will be determined from investigator assessment as described in Section 3.4.2.

Other extranodal (index and non-index) lesions

Organs other than lymph nodes, liver, spleen and bone marrow (such as breast and lung) can be occasionally involved by lymphoma. Determination of lymphoma involvement of these organs should be confirmed histologically.

If such organs are confirmed to be involved with measurable lesions, then index lesions should be selected from those organs. Up to four measurable lesions will be selected as index extranodal lesions from disparate regions (other than liver and spleen) at baseline and followed during the study.

Additional measurable lesions and all non-measurable extranodal disease will be documented at baseline and assessed throughout the study as non-index lesions. Other non-measurable disease, such as pleural effusion or bone lesions that are documented to be due to malignant disease, will be recorded at baseline as non-index lesions and followed during the study. Measurements of these lesions are not required to be documented on the CRF. Their response status will be determined from investigator assessment as described in Section 3.4.2.

Enlarged spleen or liver

The presence of enlarged spleen or liver before randomization/start of treatment on the basis of CT scan should be recorded on the corresponding CRF at baseline, and reassessed if the patient has a radiological CR.

Bone marrow involvement

Status of bone marrow involvement by lymphoma before randomization/start of treatment will be collected (see Section 3.2.2).

If specifically required by the Study Protocol, a confirmatory bone marrow biopsy or aspirate may be performed at baseline and following a radiological CR, and will be reviewed by pathology laboratory to confirm the status of bone marrow involvement of the disease. Report will be recorded on the corresponding CRF.

B-symptoms

B-symptoms (unexplained fever $\geq$ 38°C; unexplained, recurrent drenching night sweats; unexplained loss of > 10% body weight within the previous 6 months) will be recorded before randomization/start of treatment (baseline) and reevaluated if patients have achieved radiological CR as well as at the end of therapy.

[redacted]

3.4 Evaluation of radiological response

For the sake of simplicity, complete remission (as defined in Cheson et al 2007b) and complete response will both be referred to as complete response in this document.

To evaluate disease response to treatment, all index and non-index lesions will be followed and assessed throughout the study. At each assessment, response is evaluated separately for the **index lesions** (Table 14-14) and **non-index lesions** (Table 14-15) identified at baseline, then a combined overall radiological response is determined (Table 14-16).

3.4.1 Evaluation of index lesions (nodal and extranodal)

3.4.1.1 When index nodal lesions are not in complete response

The response for index lesions is evaluated by calculating the Sum of the Products of Diameters (SPD) of all index lesions (see Table 14-12), except when there is a Complete Response for index nodal lesions (i.e. complete normalization of all index nodal lesions) (see Section 3.4.1.2).

Table 14-12 Table radiological status based on SPD calculation for all index lesions

Response Criteria[1]	Evaluation of index lesions
Complete Response (CR)	See Table 14-14 below (not based on SPD calculation for all index lesions)
Partial Response (PR)	At least 50% decrease from baseline in the SPD of all index lesions
Stable Disease (SD)	Failure to attain the criteria needed for CR or PR and failure to fulfill the criteria for PD
Progressive Disease (PD)	At least a 50% increase from nadir[2] in the SPD of all index lesions

[1] At each assessment (if the index nodal lesions are not in CR status), the response status based on SPD calculation will be first assessed for meeting PD status criteria, then PR status and SD status.

[2] Nadir is defined as the smallest sum of the product of the diameters of all index lesions recorded so far, at or after baseline.

3.4.1.2 When index nodal lesions are in complete response

When there is a Complete Response for index nodal lesions (i.e. complete normalization of all index nodal lesions as defined in Section 2.2: all index lesion ≤ 15 mm in long axis), the SPD for these index nodal lesions may not be equal to zero and therefore a calculation of a SPD for all index lesions may be misleading. Therefore, by default, a specific response for extranodal index lesions needs to be evaluated, based on the SPD calculation restricted to all index extranodal lesions only (see Table 14-13).

Table 14-13 Radiological response criteria for index extranodal lesions in case of CR in index nodal lesions

Response Criteria[1]	Evaluation of index extranodal lesions
Complete Response (CR)	Complete disappearance of all index extranodal lesions
Partial Response (PR)	At least 50% decrease from baseline in the SPD restricted to all index extranodal lesions

[redacted]

Response Criteria[1]	Evaluation of index extranodal lesions
Stable Disease (SD)	Failure to attain the criteria needed for CR or PR and failure to fulfill the criteria for PD
Progressive Disease (PD)	At least a 50% increase from nadir[2] in the SPD restricted to all index extranodal lesions

[1] At each assessment, response will be first assessed for meeting CR status. If CR status is not met, response will be assessed for PD status, then PR status and SD status.

[2] Nadir is defined as the smallest sum of the product of the diameters restricted to all index extranodal lesions recorded so far, at or after baseline.

The algorithm for evaluating the response integrating index extranodal lesions and the SPD calculated on all index lesions (where appropriate) provides an overall response for index lesions (see Table 14-14).

3.4.1.3 Evaluation of response for all index lesions

The evaluation of response for all index lesions is based on the combination of the response for index nodal lesions (CR or non-CR), the response for index extranodal lesions (as calculated in Table 14-13), and the status based on the SPD calculated on all index lesions (nodal and extranodal), as described in Table 14-14 and Appendix B.

Table 14-14 Radiological response for index lesions

Response for index nodal lesions[1]	Response for index extranodal lesions[1]	Status based on SPD calculation for all index lesions	Response for index lesions
CR	CR	Not calculated	CR
CR	SD/ PR	Not calculated	PR
CR	PD	PD	PD
CR	PD	PR	PR
CR	PD	SD	SD
Non-CR	Not evaluated	PD	PD
Non-CR	Not evaluated	PR	PR
Non-CR	Not evaluated	SD	SD

[1] If no index nodal lesions are present at baseline, then index lesions response is equal to the index extranodal lesions response. A similar rule applied if no index extranodal lesions are present at baseline, then index lesions response is equal to the index nodal lesions response.

In case of a missing measurements of any of the index lesions, the radiological response for index lesions at that assessment will be “Unknown (UNK)”, unless progression was seen.

All lesions must have been measured with the same method as the one used at baseline, otherwise the radiological response for index lesions at that assessment will be “Unknown (UNK)”.

[redacted]

3.4.2 Evaluation of non-index lesions (including nodal, splenic and/or hepatic nodules and other extranodal lesions)

At each reassessment, a non-index lesion (or a group of non-index lesions) will be given one of the following designations:

- Normalization (non-index nodal lesion has regressed to normal size; non-index extranodal lesion is no longer present). Normalization of non-index nodal lesions should be determined based on their size at baseline as described in Section 2.2.
- Improved, stable or worsened, but without unequivocal evidence of disease progression (non-index lesion is present but there is not sufficient worsening to declare PD based on the existing non-index lesions).
- Unequivocal evidence of disease progression (worsening of existing non-index lesions is sufficient to declare PD)
- Not assessed

Then, this status for each non-index lesion (or group of non-index lesions) will lead to a global response for non-index lesions (Table 14-15 and Appendix C):

Table 14-15 Response criteria for non-index lesions (nodal, splenic and/or hepatic nodules and other extranodal lesions)

Response Criteria	Evaluation of non-index lesions
Complete Response (CR)	Complete normalization of all non-index nodal and extranodal lesions: Radiological regression to normal size of all lymph nodes and complete disappearance of all extranodal (including splenic and/or hepatic nodules) lesions
Stable Disease (SD)	Failure to attain the criteria needed for CR and failure to fulfill the criteria for PD
Progressive Disease (PD)	Unequivocal disease progression of any existing non-index lesions (nodal or extranodal)

In case of a missing status of any of the non-index lesions, the radiological response for non-index lesions at that assessment will be “Unknown (UNK)”, unless progression was seen.

All lesions must have been measured with the same method as the one used at baseline, otherwise the radiological response for non-index lesions at that assessment will be “Unknown (UNK)”.

3.4.3 New lesions

The appearance of

- any new nodal lesion >15 mm in any axis. New nodal lesion is defined by:
  - either a previously normal lymph node becoming > 15 mm in any axis,
  - or a previously identified abnormal lymph node showing an increase of at least 50% in the long axis,

as assessed by investigator (or Central Review if applicable).

OR

[redacted]

- any discrete extranodal (including splenic and/or hepatic nodules) lesions reliably appearing on CT scan or MRI after baseline,

is always considered as Progressive Disease (PD) and has to be recorded as a new lesion in the appropriate module of the CRF. Determination of new lymphoma involvement in organs other than lymph nodes or liver or spleen should be confirmed histologically and the site must document that in a comment to the corresponding CRF.

3.4.4 Overall radiological response

Overall radiological response is calculated as shown in Table 14-16.

Table 14-16 Overall radiological response at each assessment

Index lesions	Non-index lesions[1]	New lesions	Overall radiological response
CR	CR	No	CR
CR	SD	No	PR
PR	CR or SD	No	PR
SD	CR or SD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

[1] If no non-index lesions are present at baseline, then this column is not used in evaluating overall radiological response.

If the evaluation of any of the index or non-index lesions identified at baseline could not be made during follow-up or if the index or non-index response is "Unknown (UNK)", the overall response status at that assessment must be "Unknown (UNK)" unless progression or a new lesion was seen.

3.5 Evaluation of overall disease response

The evaluation of overall disease response at each assessment is a composite of the individual radiological responses (index and non-index lesions, new lesions), laboratory test (bone marrow) and clinical responses (lymphoma related clinical symptoms).

3.5.1 Bone marrow re-assessment at time of radiological CR

In order to confirm a Complete disease Response (CR), bone marrow biopsy or aspirate may be required when a radiological CR has been achieved (see Section 3.2.2). Details are provided in the Study Protocol. The infiltrate of lymphoma in bone marrow must have cleared on repeat bone marrow biopsy or aspirate. Patients who achieve a CR by other criteria but who have persistent morphologic positive or inconclusive bone marrow involvement will be considered partial responders. New or recurrent bone marrow involvement anytime during the follow up will be considered PD. Bone marrow biopsy or aspirate will be performed after the first assessment of CR or when clinically indicated.

The biopsy sample of bone marrow must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry.

[redacted]

3.5.2 Overall disease response

If a patient has an overall radiological response of CR as defined in Table 14-16, then this response must be confirmed by bone marrow biopsy or aspirate (if required as per the Study Protocol), presence of normal liver and spleen size, and evaluation of lymphoma related B-symptoms. The patient's overall response will be calculated as follows (see also Appendix D):

A patient will be deemed to have overall disease response of CR if bone marrow biopsy or aspirate becomes negative for tumor involvement (if the bone marrow was involved by lymphoma at baseline) and the liver and spleen are normal in size and there are no lymphoma related B-symptoms in addition to radiological CR.

If assessments of any of the following: lymphomatous infiltration of bone marrow (If required as per the Study Protocol), or evaluation of B-symptoms is not done, unknown or indeterminate or B-symptoms are still present when the overall radiological response is assessed as CR or the liver or spleen are enlarged, then the overall disease response will be assessed as PR until evaluation of these factors have shown normalized results and recorded on the corresponding CRF.

For patients whose radiological response is anything other than CR, assessment of bone marrow, liver, spleen and B-symptoms will not be required in evaluating overall response and overall disease response is the same as radiological response. However any new or recurrent bone marrow involvement at any time during follow-up will be considered PD.

Of note, appearance of B-symptoms or enlarged spleen or liver will not in themselves constitute documentation of progression. They are however expected to be associated with progressive disease. Every effort should be made to document that evidence radiologically and report the corresponding tumor assessments. Such tumor assessments are expected to be performed within 2 months of appearance of B-symptoms or enlarged spleen or liver.

4 Efficacy analysis definitions

4.1 Best overall disease response

The best overall disease response is the best disease response recorded from randomization/start of treatment until progressive disease or start of new anticancer therapy, whichever comes first.

A best overall disease response of SD will be declared when at least one SD assessment is available at least 6 weeks after randomization/start of treatment (and the patient would not qualify for CR or PR).

If a different minimum follow-up period is required to classify for best overall disease response= 'stable disease', this must be specified in the Study Protocol.

A patient will have a best overall disease response of PD if the progressive disease was observed less than 17 weeks after randomization/ start of treatment (and the patient does not qualify for CR, PR or SD).

The 17 weeks period corresponds to the time period when two tumor assessments are expected (i.e. tumor assessments performed every 8 weeks ± 1 week). If the PD is first

[redacted]

observed after 2 missing assessments from baseline, the best overall disease response of the patient is UNK. If a different follow-up period is considered for PD to lead to a best overall disease response= 'progressive disease', this must be specified in the Study Protocol.

The best overall disease response for a patient is always calculated, based on the sequence of overall disease responses. However, the overall disease response at a given assessment may be provided from different sources:

- Investigator overall disease response based on local radiological assessments, clinical and pathological (bone marrow in patients with CR) response.
- Central Blinded Review of radiological response, with or without blinded adjudication integrating clinical and pathological (bone marrow in patients with CR) response.
- Novartis calculated overall disease response, based on measurements / lesion status from either Investigator or Central Review and clinical and pathological (bone marrow in patients with CR) response.

The Study Protocol should state which source will be used for the primary analysis.

Based on the patients' best overall disease response during the study, the following rate is then calculated:

Overall response rate (ORR) is the proportion of patients with a best overall disease response of CR and PR.

4.2 Time to event variables

Most of the time to event variables are defined in this section according to the International Working Group response criteria (Cheson et al 2007b). Further details on dates and censoring rules are provided respectively in Section 4.3 and Section 4.4.

4.2.1 Overall survival

Overall survival (OS) is defined as the time from the date of randomization/start of treatment to the 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.

4.2.2 Progression-free survival

Progression-free survival (PFS) is defined as the time from the 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 the last adequate assessment.

4.2.3 Time to progression

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

[redacted]

4.2.4 Duration of response

If the following variables are analyzed, it should be stated that this analysis might introduce a bias as it includes only responders. There have been reports where a treatment with a significantly higher response rate had a significantly shorter duration of response. The analysis of duration of responses should only be used as a descriptive analysis. If they are used as inferential comparison between treatments, clear justification must be given in the Study Protocol.

Duration of overall response (CR or PR) applies only to patients whose best overall disease response was CR or PR. It is defined as the time from the date of first documented disease response (CR or PR) to the date of first documented progression or death due to lymphoma. If a patient has not had an event, duration of overall response is censored at the date of the last adequate assessment.

The following duration might be calculated in addition for a large Phase III study in which a reasonable number of responders is seen. Justification must be given in the Study Protocol when these endpoints are used for any comparison between treatments.

Duration of overall complete response (CR) applies only to patients whose best overall disease response was CR. It is defined as the time from the date of first documented disease complete response to the date of first documented progression or death due to lymphoma. If a patient has not had an event, duration of overall complete response is censored at the date of the last adequate assessment.

4.2.5 Time to response

Time to overall disease response (CR or PR) is defined as the time from the date of randomization / start of treatment to the date of first documented disease response (PR or CR). This analysis will include all patients/responders. If all patients are included, then patients who did not achieve a PR or CR will be censored:

- At maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients who had a PFS event (i.e. either progressed or died due to any cause).
- At the date of the last adequate assessment otherwise.

Time to overall disease complete response (CR) is defined as the time from the date of randomization / start of treatment to the date of first documented disease complete response (CR). This analysis will include all patients/responders. If all patients are included, then patients who did not achieve a CR will be censored:

- At maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients who had a PFS event (i.e. either progressed or died due to any cause)
- At the date of the last adequate assessment otherwise.

Indicate whether this analysis should include only the responders (in which case please delete ‘patients/’ and the sentence on patients who did not respond) or should estimate the time to response for the whole study population (in which case please delete ‘/responders’). If both methods should be used, please state that in the Study Protocol.

[redacted]

4.2.6 Lymphoma specific survival

Lymphoma specific survival (LSS) is defined as the time from the date of randomization/ start of treatment to the date of death documented as a result of lymphoma. If a patient has not had an event, lymphoma specific survival will be censored:

- at the date of last contact if the patient is not known to have died,
- at the date of death if the patient died for other reason than lymphoma.

4.2.7 Event free survival

This endpoint is often appropriate in studies of advanced disease where early discontinuation is typically related to intolerance of the study drug. In some protocols, time to treatment failure may be considered as a sensitivity analysis for time to progression. The list of discontinuation reasons to be considered or not as treatment failure may be adapted according to the specificities of the study or the disease.

Event-free survival (Time to treatment failure (TTF)) is defined as the time from the date of randomization to the earliest date of any of the following:

- death.
- progressive disease as overall disease response assessed by the local investigator prior to treatment discontinuation.
- study treatment discontinuation due to:
  - disease progression.
  - adverse event(s).
  - abnormal laboratory value(s).
  - abnormal test procedure results.
  - patient withdrew consent.
  - lost to follow-up.
  - death.
  - new cancer therapy.

Patients who discontinue study treatment for reasons other than those listed above (i.e., as a result of protocol violation, administrative problems) are censored at the date of the last adequate assessment prior to discontinuation. Patients with neither an event nor study treatment discontinuation are censored at the date of the last adequate assessment.

4.3 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 date of all radiological measurement dates (e.g. CT-scan (or MRI), and excluding both bone marrow biopsy and B-symptoms assessment), if the overall disease response at that assessment is CR/PR/SD/UNK,

[redacted]

- the earliest date of all measurement dates (e.g. CT-scan (or MRI), including bone marrow biopsy, but excluding B-symptoms assessments) if the overall disease response at that assessment is PD.

Start dates

For all "time to event" variables, other than the duration of responses, the date of randomization /start of treatment 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 disease response of CR (for duration of overall complete response) or CR / PR (for duration of overall response) respectively.

End dates

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

- **Date of death** as reported on the CRF (on the treatment completion page, the study evaluation completion page or survival follow-up page).
- **Date of last contact** is defined as the last date the patient was known to be alive as derived from different CRF pages (see details in Section 5).
- **Date of progression** is the first assessment date at which the overall disease response was recorded as PD.
- **Date of last adequate assessment** is the date the last assessment with overall disease response of CR, PR or SD which was made before an event or a censoring reason occurred. 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 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 radiological assessment as per protocol.
  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 correspond to 9 months.
- **Date of treatment discontinuation** is the last known date subject took study drug.
- **Date of secondary anti-cancer therapy** is defined as the start date of first additional (secondary) antineoplastic therapy or surgery (see details in Section 5)

[redacted]

[redacted]

[redacted]

[redacted]

5 Data handling and programming conventions

The following could be used for programming of efficacy results, but should be specified in the RAP documentation:

Calculation of 'time to event' variables

Time to event = enddate - startdate + 1 (in days).

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

Date of last contact

The date of last contact will be derived for patients alive using the latest complete date among the following:

- All assessment dates (e.g. vital signs assessment, performance status assessment, and also assessment date in third-party data such as tumor imaging, central laboratory, ECG etc).
- Medication dates including study medication, concomitant medications, antineoplastic therapies administered after study treatment discontinuation.
- Adverse events dates.

[redacted]

- Last contact date collected on the 'Survival information' eCRF.
- Randomization date.

Date of secondary anti-cancer therapy

The date of secondary anti-cancer therapy is the date of the 1st antineoplastic therapy or surgery reported in the concomitant medications page, further antineoplastic therapy page or from other sources (e.g. Dosage administration record page).

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 4.3). If all measurement dates have no day recorded, the 1st of the month is used.

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

Incomplete dates for last contact or death

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

Study/project specific programming

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

6 References (available upon request)

Cheson BD (2007a) The international harmonization project for response criteria in lymphoma clinical trials. Hematol Oncol Clin N Am 21:841-854.

Cheson BD (2009) The case against heavy PETing. J Clin Oncol 27:1742-1743.

Cheson BD, Horning SJ, Coiffier B, et al (1999) Report of an International Workshop to standardize response criteria for non-Hodgkin's lymphomas. J Clin Oncol 17:1244-1253.

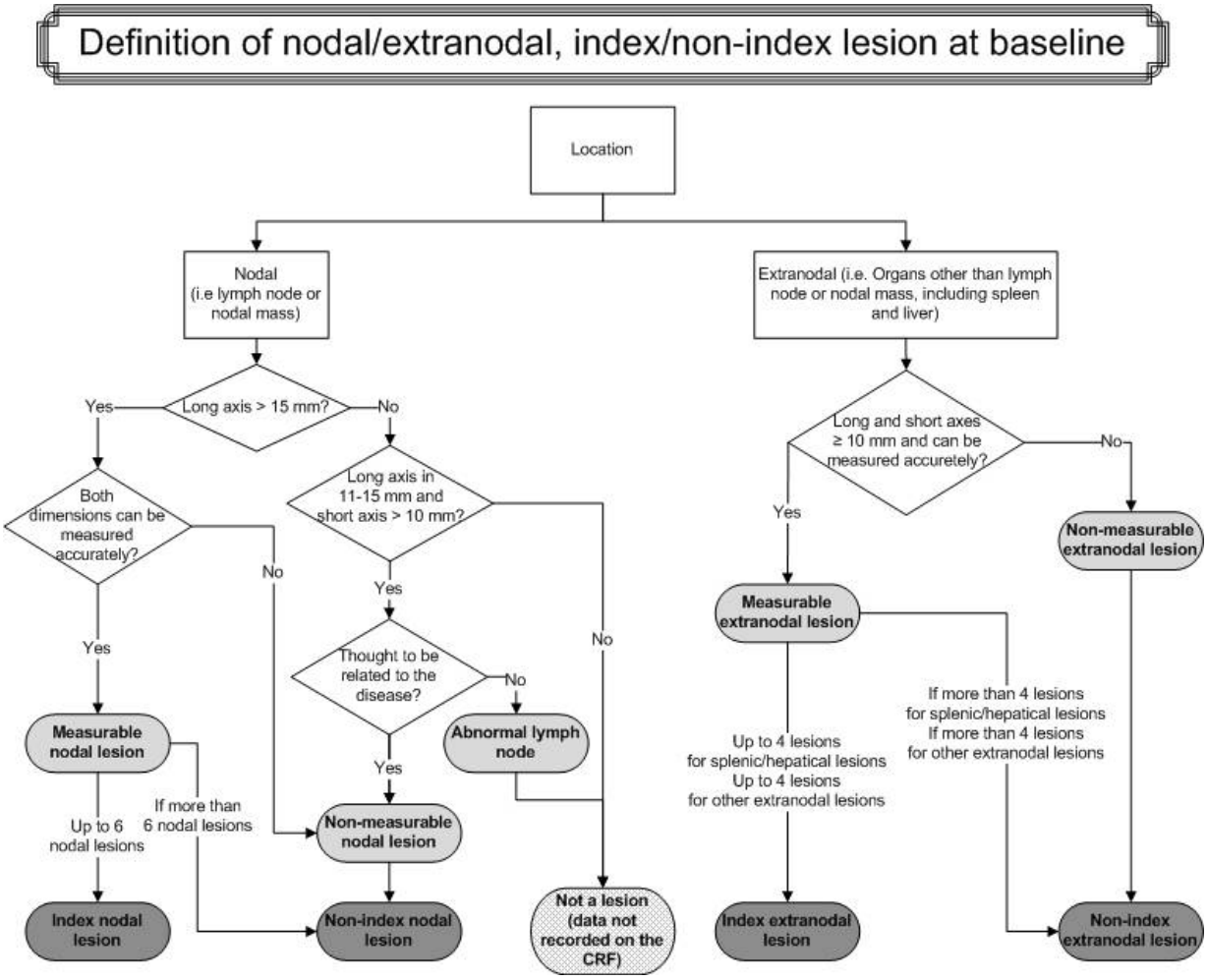
Cheson BD, Pfistner B, Juweid ME, et al (2007b) Revised response criteria for malignant lymphoma. J Clin Oncol 25:579-586.

FDA Guideline (2005) Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005.

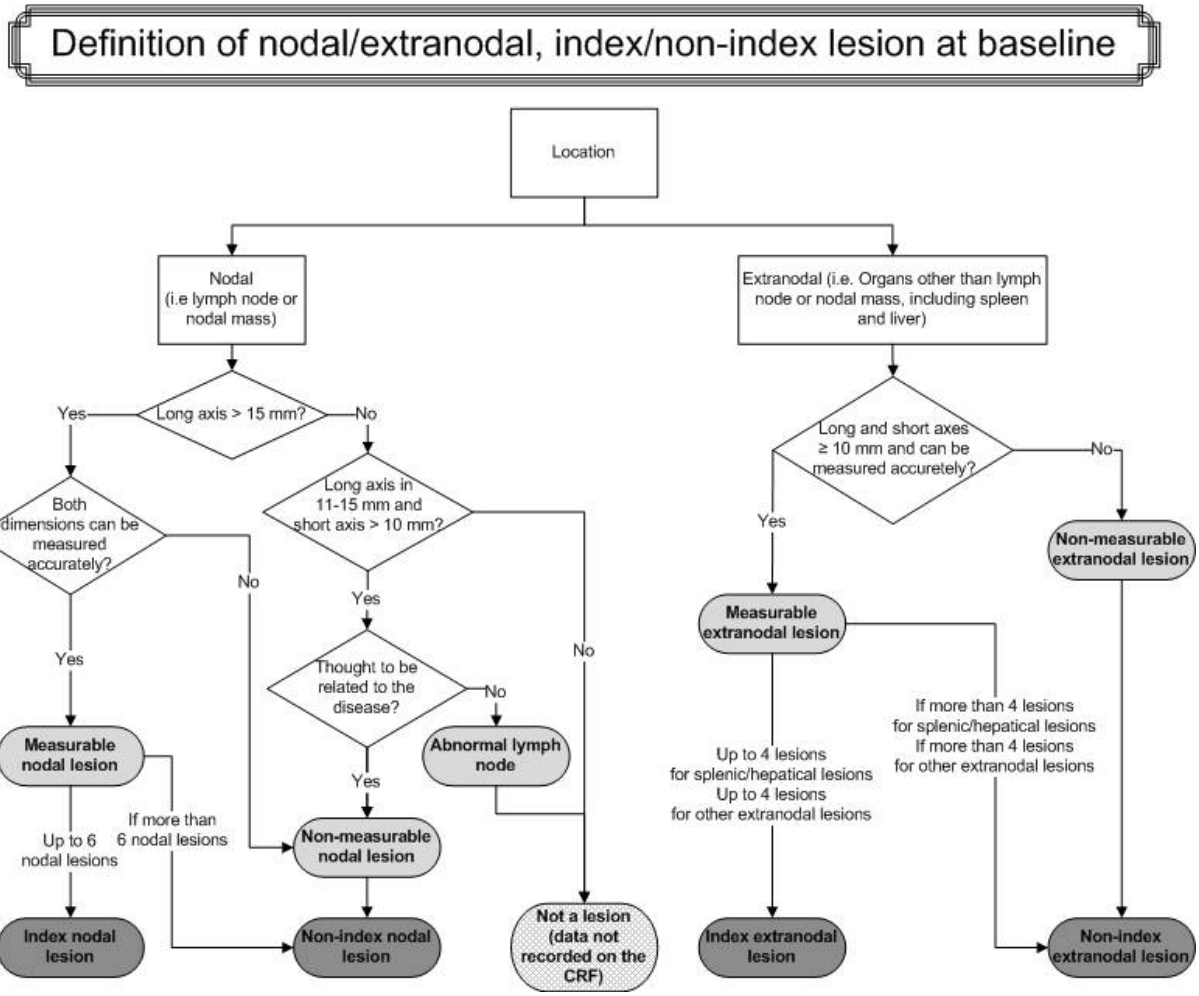
[redacted]

7 Appendices

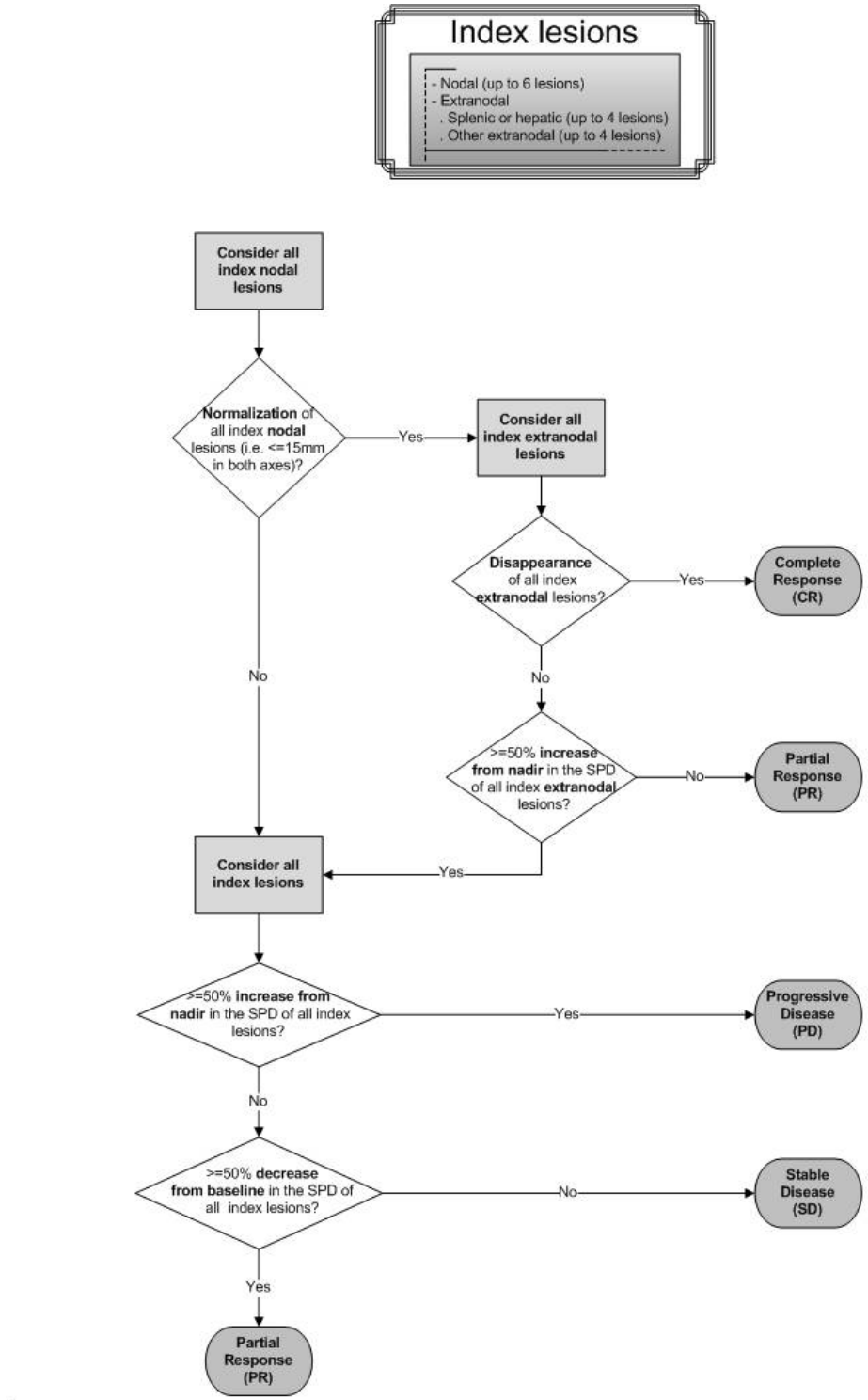
Appendix A: Definition of index nodal lesion, non-index nodal lesion, index extranodal lesion, non-index extranodal lesion



[redacted]

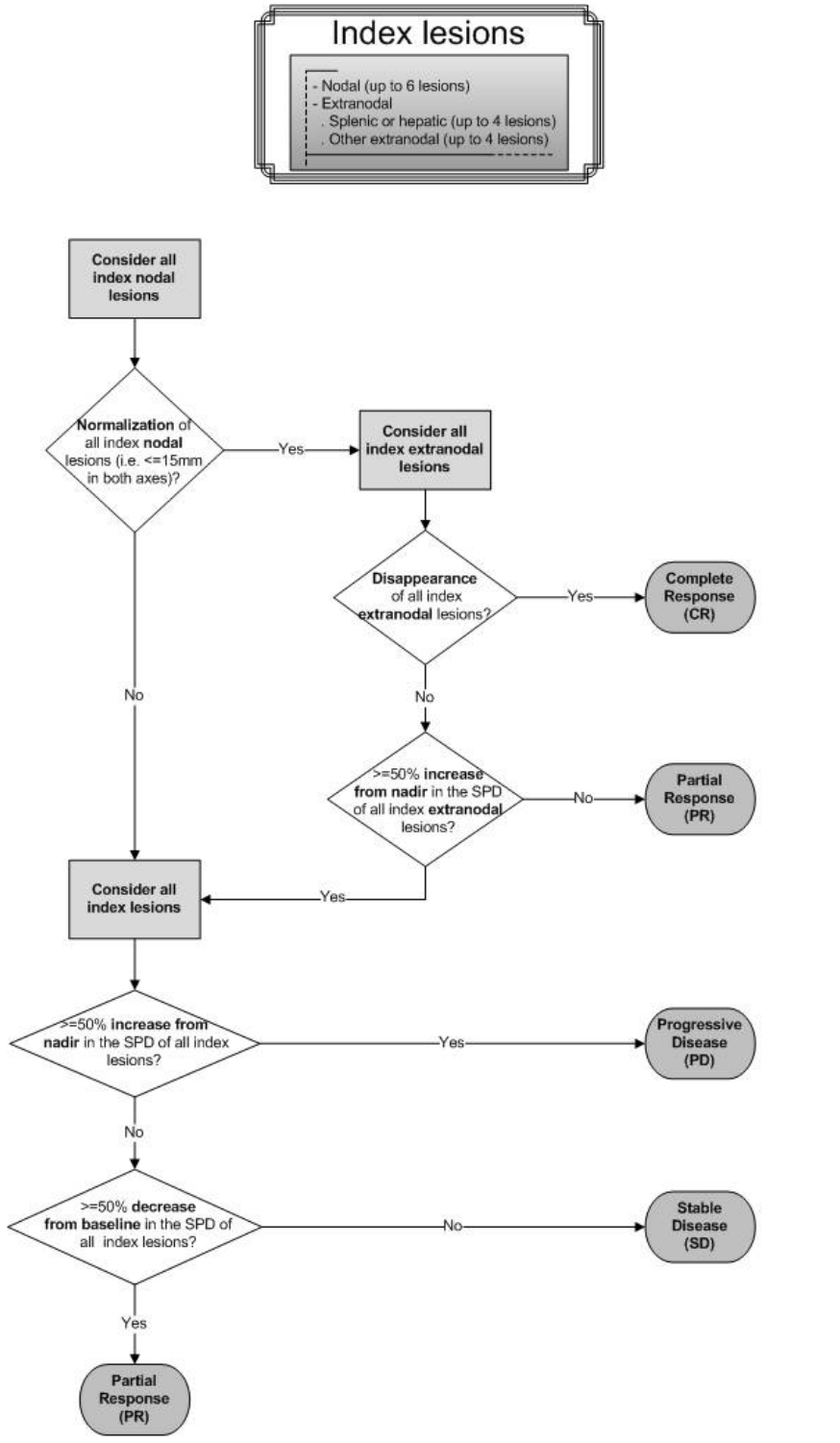

Definition of nodal/extranodal, index/non-index lesion at baseline
Location
Nodal (i.e lymph node or nodal mass)
Extranodal (i.e. Organs other than lymph node or nodal mass, including spleen and liver)
Long axis > 15 mm?
Yes
No
Both dimensions can be measured accurately?
Long axis in 11-15 mm and short axis > 10 mm?
Thought to be related to the disease?
Long and short axes ≥ 10 mm and can be measured accuretely?
Measurable nodal lesion
Up to 6 nodal lesions
If more than 6 nodal lesions
Non-measurable nodal lesion
Abnormal lymph node
Index nodal lesion
Non-index nodal lesion
Not a lesion (data not recorded on the CRF)
Measurable extranodal lesion
Non-measurable extranodal lesion
Up to 4 lesions for splenic/hepatical lesions
Up to 4 lesions for other extranodal lesions
If more than 4 lesions for splenic/hepatical lesions
If more than 4 lesions for other extranodal lesions
Index extranodal lesion
Non-index extranodal lesion

Appendix B: Calculation of the response for index lesions



Notes:
1. In case of a missing measurement of any of the index lesions, the radiological response for index lesions at that assessment will be "Unknown (UNK)", unless progression was seen.
2. All lesions must have been measured with the same method as the one used at baseline, otherwise the radiological response for index lesions at that assessment will be "Unknown (UNK)".

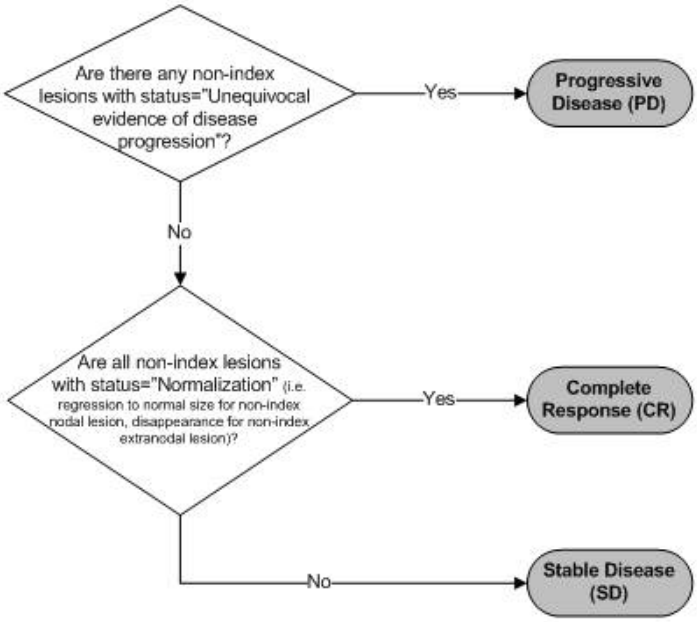
[redacted]



Notes:
1. In case of a missing measurement of any of the index lesions, the radiological response for index lesions at that assessment will be "Unknown (UNK)", unless progression was seen.
2. All lesions must have been measured with the same method as the one used at baseline, otherwise the radiological response for index lesions at that assessment will be "Unknown (UNK)".

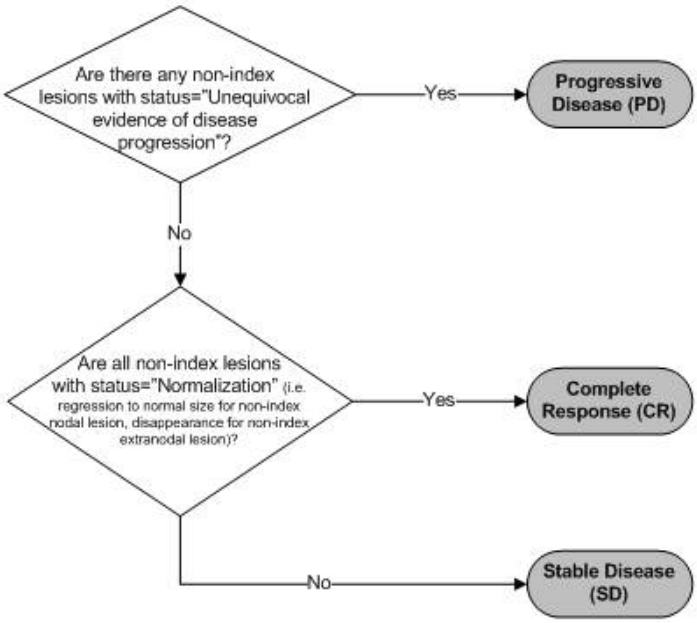
[redacted]

Appendix C: Calculation of the response for non-index lesions



Notes:
1. In case of a missing status of any of the non-index lesions, the radiological response for non-index lesions at that assessment will be "Unknown (UNK)", unless progression was seen.
2. All lesions must have been measured with the same method as the one used at baseline, otherwise the radiological response for non-index lesions at that assessment will be "Unknown (UNK)".

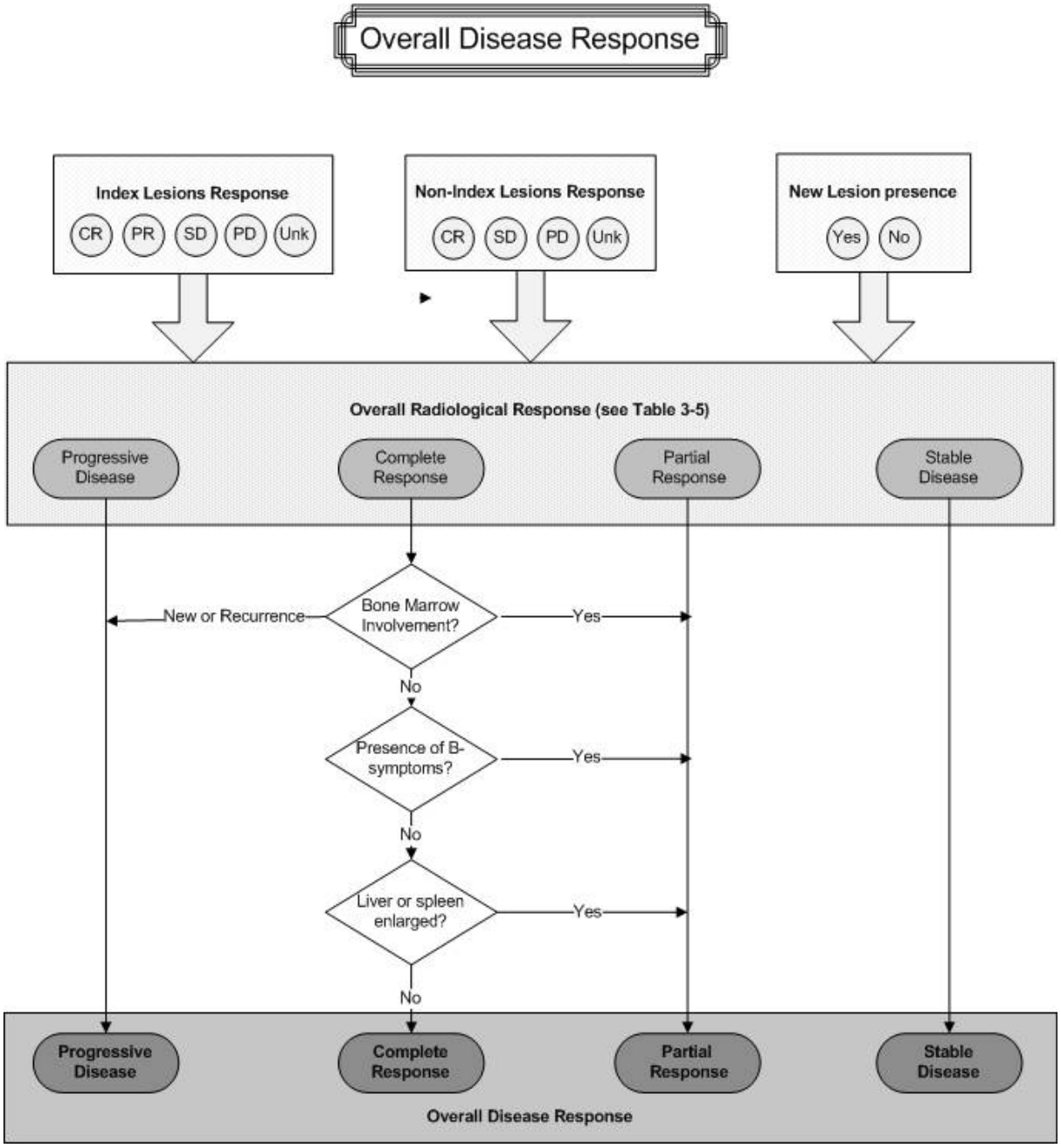
[redacted]



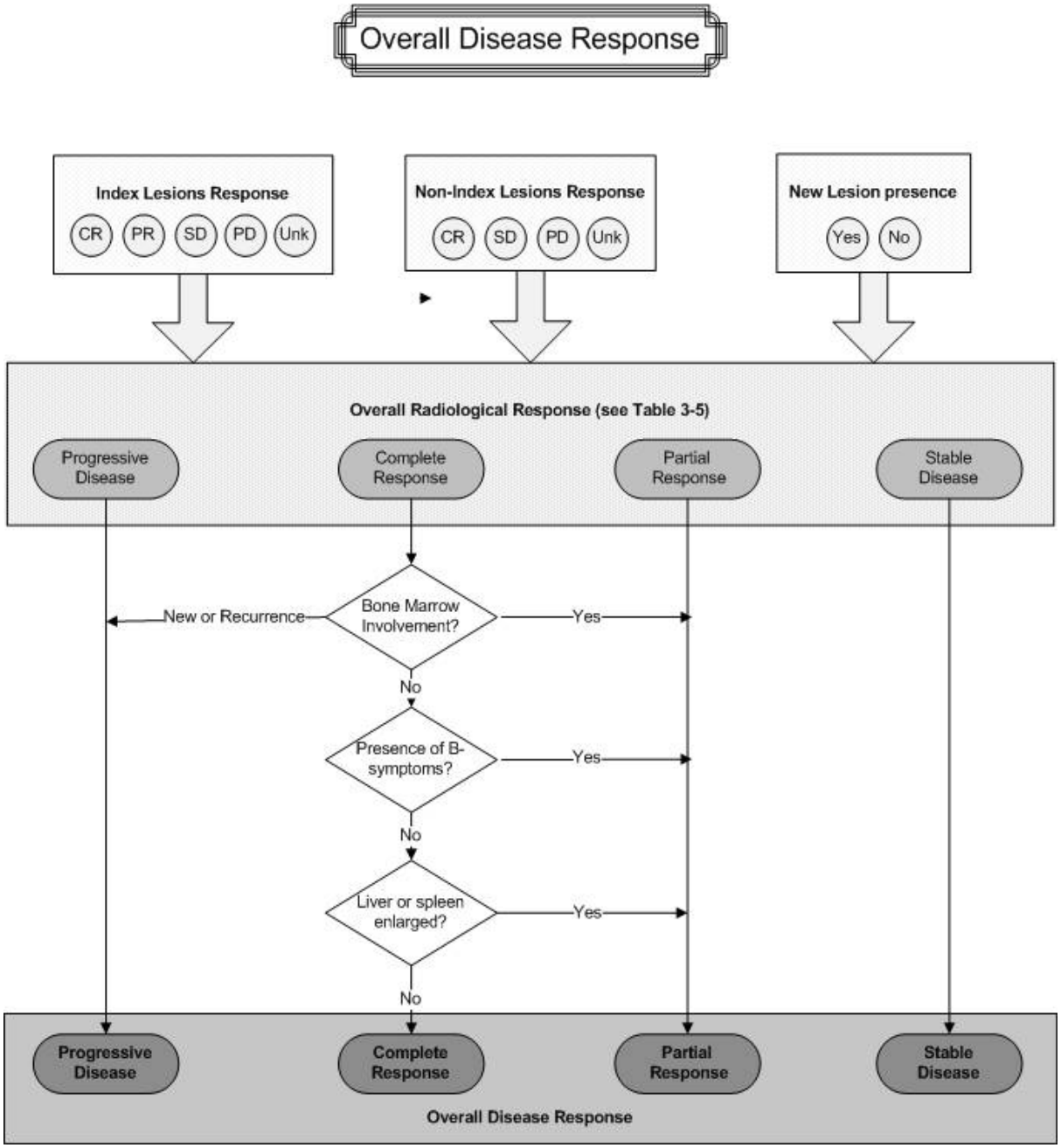
Notes:
1. In case of a missing status of any of the non-index lesions, the radiological response for non-index lesions at that assessment will be "Unknown (UNK)", unless progression was seen.
2. All lesions must have been measured with the same method as the one used at baseline, otherwise the radiological response for non-index lesions at that assessment will be "Unknown (UNK)".

[redacted]

Appendix D: Calculation of the overall disease response



[redacted]


Overall Disease Response
Index Lesions Response
CR
PR
SD
PD
Unk
Non-Index Lesions Response
CR
SD
PD
Unk
New Lesion presence
Yes
No
Overall Radiological Response (see Table 3-5)
Progressive Disease
Complete Response
Partial Response
Stable Disease
Bone Marrow Involvement?
New or Recurrence
Yes
No
Presence of B-symptoms?
Yes
No
Liver or spleen enlarged?
Yes
No
Progressive Disease
Complete Response
Partial Response
Stable Disease
Overall Disease Response

[redacted]

Appendix E: Adaptation for use in maintenance/adjuvant settings

For settings in which no measurable disease is present at baseline (e.g. maintenance), this guideline can be adapted. In such setting, as patients have no more measurable disease at baseline, the event of main interest is no more the Progressive Disease but the Relapsed Disease and the main endpoint is no more the Progression-free survival but the Disease-free survival. The definitions that need to be considered are presented below:

Relapsed disease

The definition of Relapsed Disease can be derived from the definition of New Lesion (see Section 3.4.3) and is as follow:

Appearance of the following will always be considered as **Relapsed Disease (RD)**

- any new nodal lesion > 15 mm in any axis (i.e. previously normal lymph node becoming > 15 mm in any axis) on CT scan or MRI after baseline, or
- any discrete extranodal lesion (including liver or spleen) reliably appearing on CT scan or MRI after baseline, or
- ≥ 50% increase in long axis from baseline of any residual lymph node or mass. A residual lymph node or mass is defined as a previously lymphoma-involved lymph node or mass (>10 mm in short axis (without any upper limit)) that was PET scan negative at baseline and only reliably detected by baseline CT or MRI. **Note**: If a residual lymph node or mass at baseline decreases in size during treatment and becomes normal (i.e. complete disappearance of extranodal mass or ≤ 10 mm in short axis and ≤ 15 mm long axis for nodal mass), then reappearance of an extranodal lesion at the same site or increase of the same nodal mass to > 15 mm in the long axis, will be considered as Relapsed Disease and need to be recorded as a new lesion in the appropriate module of the CRF.

Details on PET scan negative should be provided in the Study Protocol.

Disease-Free Survival

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

Similar censoring rules and reasons as the ones used for PFS can be applied. Full details should be provided in the Study Protocol and in the Report Analysis Plan.

Additional endpoints may be considered for specific lymphoma settings. Full details should be provided in the Study Protocol and in the Report Analysis Plan.

[redacted]